The Chemistry of Functional Groups, Supplement C
Edited by S. Patai and Z. Rappoport

Supplement C

The chemistry of **triple-bonded functional groups** Part 2

Edited by

SAUL PATAI

and

ZVI RAPPOPORT

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Foreword

The present Supplement C contains material on triple-bonded functional groups, such as carbon–carbon triple bonds, cyano and isocyano groups and diazonium groups. These groups have been treated previously in the Chemistry of Functional Groups Series in the following volumes:

The Chemistry of the Carbon–Carbon Triple Bond (2 parts, 1978);
The Chemistry of Diazonium and Diazo Groups (2 parts, 1978).

Arynes, heteroarynes and isocyanides were treated as triple-bonded compounds, and chapters on them are included in this volume.

Some chapters intended for this supplementary volume did not materialize. These should have treated 'photochemistry of the Cyano Group'; Triple bonds in Cycloadditions', 'Compounds Containing $C(CN)_2$ and Related Groups' and 'Metal Triple-bond Complexes'.

We will be very grateful to readers who would call our attention to omissions or mistakes relating to this and other volumes in the series.

SAUL PATAI
ZVI RAPPOPORT

Jerusalem, June 1982

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' is planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. For instance, the volume *The Chemistry of the Ether Linkage* deals with reactions in which the C—O—C group is involved, as well as with the effects of the C—O—C group on the reactions of alkyl or aryl groups connected to the ether oxygen. It is the purpose of the volume to give a complete coverage of all properties and reactions of ethers in as far as these depend on the presence of the ether group but the primary subject matter is not the whole molecule, but the C—O—C functional group.

A further restriction in the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore each of the authors is asked *not* to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced post-graduate level.

With these restrictions, it is realized that no plan can be devised for a volume that would give a *complete* coverage of the subject with *no* overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining *reasonable* coverage with *moderate* overlap, with a minimum of cross-references between the chapters of each volume. In this manner, sufficient freedom is given to each author to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter dealing with the general and theoretical aspects of the group.

(b) One or more chapters dealing with the formation of the functional group in question, either from groups present in the molecule, or by introducing the new group directly or indirectly.

(c) Chapters describing the characterization and characteristics of the functional groups, i.e. a chapter dealing with qualitative and quantitative methods of deter-

mination including chemical and physical methods, ultraviolet, infrared, nuclear magnetic resonance and mass spectra: a chapter dealing with activating and directive effects exerted by the group and/or a chapter on the basicity, acidity or complex-forming ability of the group (if applicable).

(d) Chapters on the reactions, transformations and rearrangements which the functional group can undergo, either alone or in conjunction with other reagents.

(e) Special topics which do not fit any of the above sections, such as photochemistry, radiation chemistry, biochemical formations and reactions. Depending on the nature of each functional group treated, these special topics may include short monographs on related functional groups on which no separate volume is planned (e.g. a chapter on 'Thioketones' is included in the volume *The Chemistry of the Carbonyl Group*, and a chapter on 'Ketenes' is included in the volume *The Chemistry of Alkenes*). In other cases certain compounds, though containing only the functional group of the title, may have special features so as to be best treated in a separate chapter, as e.g. 'Polyethers' in *The Chemistry of the Ether Linkage*, or 'Tetraaminoethylenes' in *The Chemistry of the Amino Group*.

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the author and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, it was decided to publish certain volumes in several parts, without giving consideration to the originally planned logical order of the chapters. If after the appearance of the originally planned parts of a volume it is found that either owing to non-delivery of chapters, or to new developments in the subject, sufficient material has accumulated for publication of a supplementary volume, containing material on related functional groups, this will be done as soon as possible.

The overall plan of the volumes in the series 'The Chemistry of Functional Groups' includes the titles listed below:

The Chemistry of Alkenes (*two volumes*)
The Chemistry of the Carbonyl Group (*two volumes*)
The Chemistry of the Ether Linkage
The Chemistry of the Amino Group
The Chemistry of the Nitro and Nitroso Groups (*two parts*)
The Chemistry of Carboxylic Acids and Esters
The Chemistry of the Carbon–Nitrogen Double Bond
The Chemistry of the Cyano Group
The Chemistry of Amides
The Chemistry of the Hydroxyl Group (*two parts*)
The Chemistry of the Azido Group
The Chemistry of Acyl Halides
The Chemistry of the Carbon–Halogen Bond (*two parts*)
The Chemistry of Quinonoid Compounds (*two parts*)
The Chemistry of the Thiol Group (*two parts*)
The Chemistry of Amidines and Imidates
The Chemistry of the Hydrazo, Azo and Azoxy Groups (*two parts*)
The Chemistry of Cyanates and their Thio Derivatives (*two parts*)
The Chemistry of Diazonium and Diazo Groups (*two parts*)
The Chemistry of the Carbon–Carbon Triple Bond (*two parts*)
Supplement A: The Chemistry of Double-bonded Functional Groups (*two parts*)

Supplement B: The Chemistry of Acid Derivatives (*two parts*)
Supplement C: The Chemistry of Triple-bonded Functional Groups (*two parts*)
The Chemistry of Ketenes, Allenes and Related Compounds (*two parts*)
Supplement E: The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues (*two parts*)
The Chemistry of the Sulphonium Group (*two parts*)
Supplement F: The Chemistry of Amino, Nitroso and Nitro Groups and their Derivatives (*two parts*)

Titles in press:

The Chemistry of Peroxides
The Chemistry of Organometallic Compounds
Supplement D: The Chemistry of Halides and Pseudo-halides

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have started, let alone continued, without the support of many persons. First and foremost among these is Dr Arnold Weissberger, whose reassurance and trust encouraged me to tackle this task, and who continues to help and advise me. The efficient and patient cooperation of several staff-members of the Publisher also rendered me invaluable aid (but unfortunately their code of ethics does not allow me to thank them by name). Many of my friends and colleagues in Israel and overseas helped me in the solution of various major and minor matters, and my thanks are due to all of them, especially to Professor Z. Rappoport. Carrying out such a long-range project would be quite impossible without the non-professional but none the less essential participation and partnership of my wife.

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SAUL PATAI

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CHAPTER **18**

Recent developments on nitrile oxides, nitrile sulphides and nitrile selenides

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I. INTRODUCTION

Much of the work on nitrile oxides has been reviewed previously[1,2]. The first extensive review covering physical properties, syntheses and reactions of nitrile oxides appeared in this series in 1970[3], and a comprehensive book on this 1,3-dipole has been published by Grundmann and Grünanger in 1971[4]. Other reviews dealing with 1,3-dipolar cycloadditions and cycloreversions have appeared recently, some of them in this series[5–8].

This chapter will mainly be concerned with newer chemical aspects of the subject and will also report on the recently discovered 1,3-dipoles nitrile sulphides and nitrile selenides. The primary literature surveyed consists mainly of articles listed in *Chemical Abstracts* from 1970 through 1980.

II. STRUCTURAL DATA ON NITRILE OXIDES

A. Spectroscopic Data

While a wealth of IR and UV data has long been available and reported in the literature[4], more recently the ^{13}C-, ^{15}N- and ^{14}N-NMR spectra[9,10] and mass spectra[11] of nitrile oxides have also been the subject of study.

The mesitonitrile oxide ^{13}C resonance (broadened triplet at 35.4 ppm downfield from TMS in CH_2Cl_2 solution, $|J_{^{13}C,^{14}N}| = 52$ Hz; doublet at 35.2 ppm, $|J_{^{13}C,^{15}N}| = 77.5$, for the ^{15}N derivative) and the ^{14}N absorption (166 ppm downfield from aqueous tetramethylammonium chloride solution; 166.3 ppm for the ^{15}N derivative) both experience a large upfield shift by comparison with the resonances of the corresponding nitriles (mesitonitrile has a carbon shift of 117 ppm and benzonitrile a nitrogen shift of 212 ppm)[9].

Roughly half of the upfield shift of the ^{13}C resonance was accounted for by increased π electron density at the carbon atom of the nitrile oxide in comparison with

the nitrile, while for most of the difference of nitrogen chemical shifts an increase in the diamagnetic shielding term for the nitrile oxide was invoked[9].

The fragments present in the mass spectrum of benzonitrile oxide (70 eV), at *m/e* 103 (4%, $[C_7H_5N]^{\ddagger}$, M − O), 89 (16%, $[C_7H_5]^{\ddagger}$, M − NO) and 91 (20%, $[C_6H_5N]^{\ddagger}$, M − CO) were considered as deriving from the molecular ion (100%, $[C_7H_5NO]^{\ddagger}$) which is made up in part of benzonitrile oxide (to give the first two fragments) and in part of phenylisocyanate formed by isomerization of the nitrile oxide in the radical-ion state (to give the latest fragment)[11].

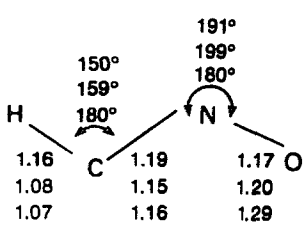
B. Geometry

At the beginning of the last decade the geometry of nitrile oxides was already defined as a linear or almost linear X—C—N—O structure[4] on the basis of infrared and microwave data for fulminic acid (formonitrile oxide) (**2**)[12], acetonitrile oxide (**1**)[13] (Figure 1) and pivalonitrile oxide[14] and X-ray data for 2,6-dimethyl-4-methoxybenzonitrile oxide[15].

Later, further far-infrared and wave millimetre measurements led Winnewisser and associates[12] to reinterpret the structural data for fulminic acid and to conclude that this molecule deviates somewhat from linearity, with the linear form 0.418 kJ mol^{-1} less stable than the bent species **2**. MINDO/3(MINDO/2)MO calculations[16] reproduce well the hump at linear H—C—N—O, and the bent form **3** (Figure 2), where bending is present also in the C—N—O moiety, was calculated to be 0.46 (0.84) kJ mol^{-1} more stable than the linear one. By contrast, the partially or fully optimized geometries (X—C—N—O) of almost all types of nitrile oxides (X = Ar, Cl, F, NH_2, CN, Me etc.), calculated by *ab initio* methods, were linear[17–19]. However, bending is not energetically difficult; in fact the optimized 4-31G HCNO molecule with HCN∠ = 165° is only 5.85 kJ mol^{-1} less stable than the linear one[17] and 5.6 kJ mol^{-1} are required to change the CNO angle from 180° to 170°[221].

(1) (2)

FIGURE 1. Angles and bond lengths (Å) of acetonitrile oxide[13] and fulminic acid[12] from infrared and microwave spectra.



(3)

FIGURE 2. Optimized geometries of fulminic acid. Angles and bond lengths (Å) listed are (top to bottom): MINDO/2, MINDO/3 and STO-3G.

C. Electronic Structure

The vertical ionization potentials (which in terms of Koopmans' theorem, $-\varepsilon_{SCF} = IP_v$, are an experimental measure of orbital energy) of nitrile oxides[20–22] so far determined are gathered in Table 1. For nitrile oxides characterized by a $C_{\infty v}$ (linear HCNO) or C_{3v} (linear *t*-BuCNO) symmetry, the HO (highest occupied) molecular orbitals are a degenerate pair of orbitals localized on the CNO moiety whereas such degeneracy is split for benzonitrile oxides (C_{2v}). In the latter 1,3-dipoles mixing of the out-of-plane π_{CNO} (which is the orbital to be considered in discussing the reactivity in cycloadditions) with the aromatic orbital of appropriate symmetry (Ph_s) gives rise to two new orbitals (Figure 3). The higher energy ($Ph_s - \pi_{CNO}$) is mainly localized on the aromatic ring and the lower one ($\pi_{CNO} + Ph_s$) on the CNO moiety. That is, in the former orbital the highest coefficients are on the ring whereas in the latter the highest coefficients are on the CNO moiety[22]. A weighted account, based on orbital energies and coefficients, of both these orbitals should be taken when discussing the reactivity of nitrile oxides in FO (frontier orbital) interaction terms. The use made by Houk and associates of a HO molecular orbital at −10.0 eV for benzonitrile oxide[23] (see Section VI.B.1) conforms to this need. As a consequence reactions at the CNO moiety will be less affected by ring-substitution than indicated by variation of IP_v: in other words although conjugation will lower IP_v to a large extent, theory foresees a small increase of reactivity[22].

No experimental data have until now been reported for LU (lowest unoccupied) molecular orbital energy values but they can be approximated from IP_v and $\pi-\pi^*$ transition energies (e.g. ε_{LU} (eV) $= -IP_v + E_{\pi\pi^*} + 5.0$)[24]. Both IP_v and electron affinity can be reliably calculated by the MINDO/2 method[16].

The shape and energies of frontier orbitals (FO) of fulminic acid (by MINDO/2[16] and *ab initio* STO-3G[17] methods) and of benzonitrile oxide (by CNDO/2)[24] are reported in Figure 4.

MO calculations for the two nitrile oxides and for acetonitrile oxide have shown that of the two end-atoms the oxygen terminus has the higher coefficient in the HO molecular orbital, while the carbon terminus has the higher coefficient in the LU molecular orbital. Moreover, bending of the molecule increases the relative nucleophilicity (HO coefficient) of the *C*-terminus and to a lesser extent the electrophilicity (LU coefficient) of the *O*-terminus[16,17].

TABLE 1. Vertical ionization potentials (eV) of nitrile oxides RCNO[22]

R	IP_v^1 $Ph_s - \pi_{CNO}$	IP_v^2 Ph_a	IP_v^3 π'_{CNO}	IP_v^4 $\pi_{CNO} + Ph_s$
H[a]	10.83[b]			
t-Bu	9.55[b]			
Ph[c]	8.96	9.80	10.0	10.84
p-$MeOC_6H_4$	8.42	9.71	9.83	10.16
2,4,6-$Me_3C_6H_2$	8.34	9.00	9.46	10.24
2,4,6-$(MeO)_3C_6H_2$	7.95	≈8.7	9.20	9.94
p-ClC_6H_4	8.65	10.02	10.20	10.67
p-$NO_2C_6H_4$	>9.5			

[a]Reference 19.
[b]π_{CNO}.
[c]Reference 21.

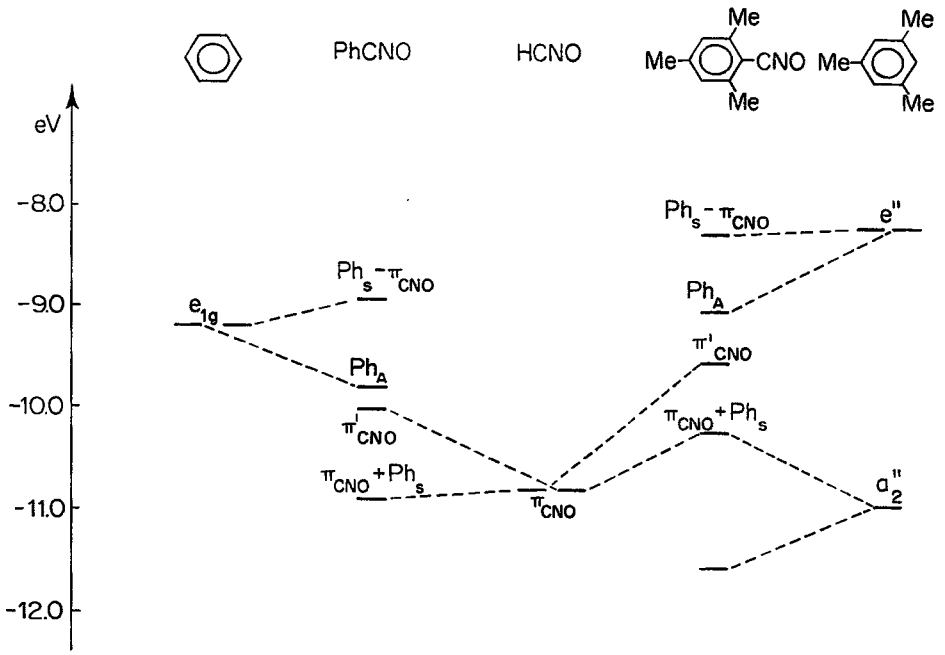


FIGURE 3. Correlations between nitrile oxide ionization potentials.

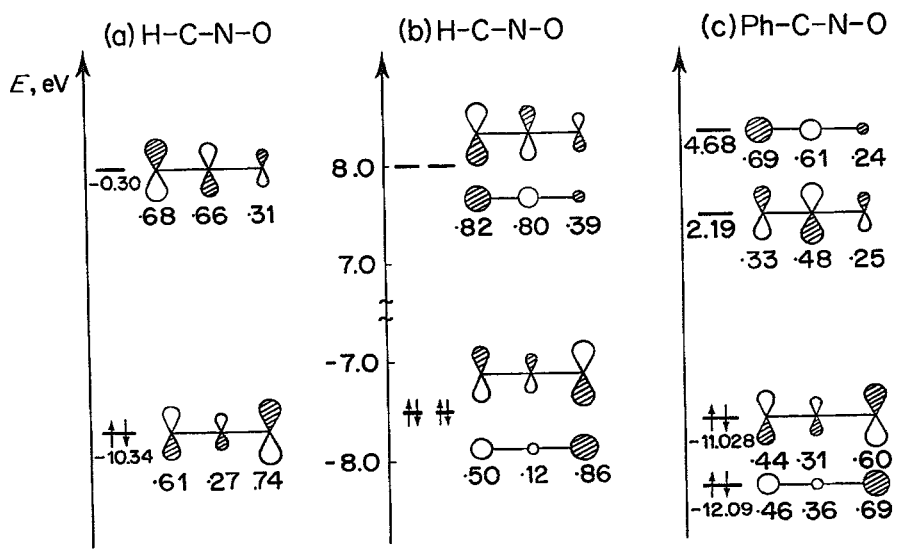
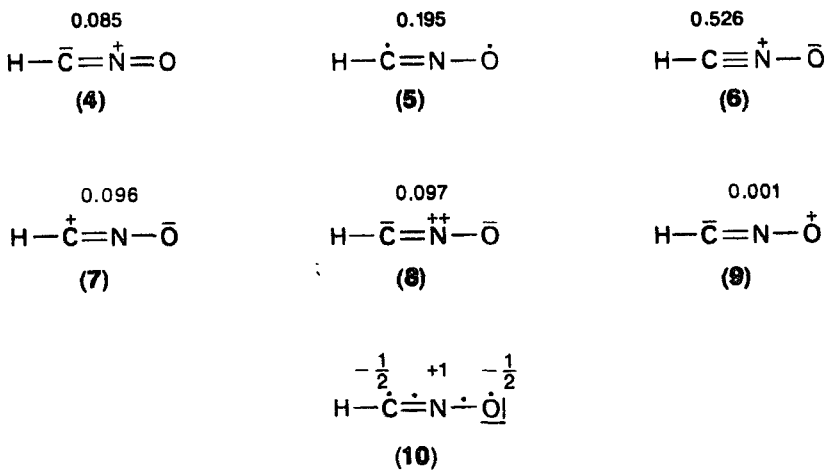


FIGURE 4. Shape and energies of FO of nitrile oxides: (a) MINDO/2[16], (b) STO-3G[17] and (c) CNDO/2[24]. In the latter two cases both the perpendicular π systems are indicated.

We shall consider now the picture of nitrile oxides in valence bond (VB) terminology. A very recent calculation (STO-3G) with geometry optimization (assuming a linear molecule) at CI level (including all excitations among π orbitals) was run by Hiberty on HCNO[25] by a method devised by him which allows the expansion of molecular orbital wave functions into valence bond wave functions[26]. The calculated weights of VB structures **4–9** for HCNO are given in Scheme 1. The values (which



SCHEME 1

refer to the gas phase) are in agreement with previous VB calculations by Hiberty and Le Forestier[26] who found that for parent allenyl–propargyl dipoles one of the zwitterionic octet-stabilized forms (e.g. **6**) is favoured (with the exception of azides where the diradical form is the most stable VB structure) over the diradical structure (e.g. **5**) which in turn may have either a bigger or smaller weight than the other octet zwitterionic structure (e.g. **4**)[27]. Obviously, the relative zwitterionic or diradical character is highly influenced by substituents and the importance of zwitterionic structures becomes enhanced in condensed phases, in particular when the molecule is in a highly polar medium[28].

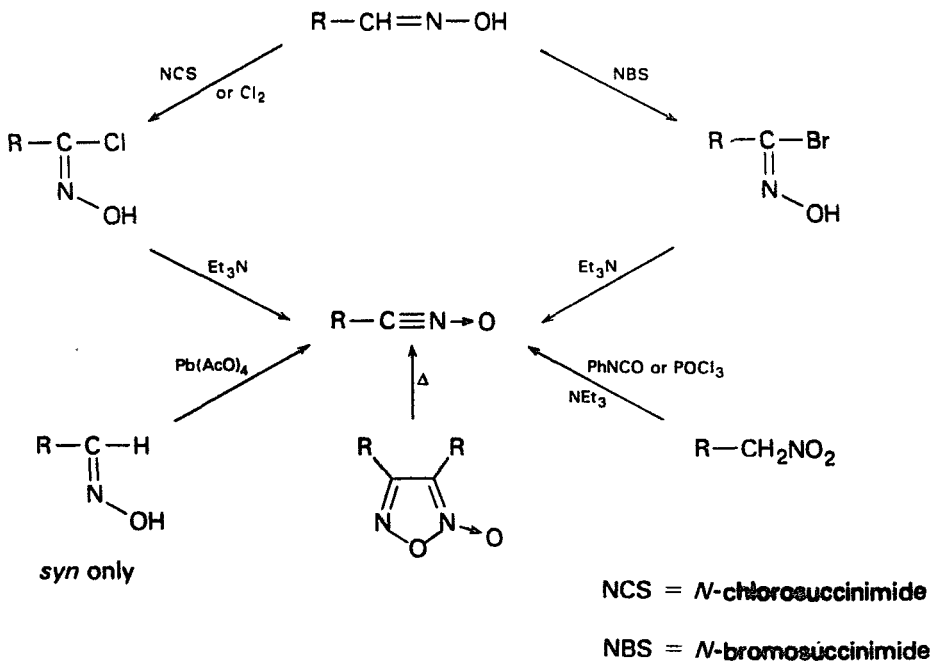
The diradical form emerges as the dominant VB structure (gas phase) in the case of allyl-type dipoles[26–29].

Finally, the wave function for the Linnett structure **10** of nitrile oxides may be expressed as a linear combination of bond eigenfunctions for structures **4**, **5**, **6** and **8**[30].

III. NITRILE-OXIDE-FORMING REACTIONS

A. General

The methods of preparation of nitrile oxides are discussed in detail in Chapter 14 of *The Chemistry of the Cyano Group*[3] and in Grundmann and Grünanger's book[4] on nitrile oxides. For the sake of brevity the most widely used and studied ways to the formation of nitrile oxides are reported schematically in Scheme 2.

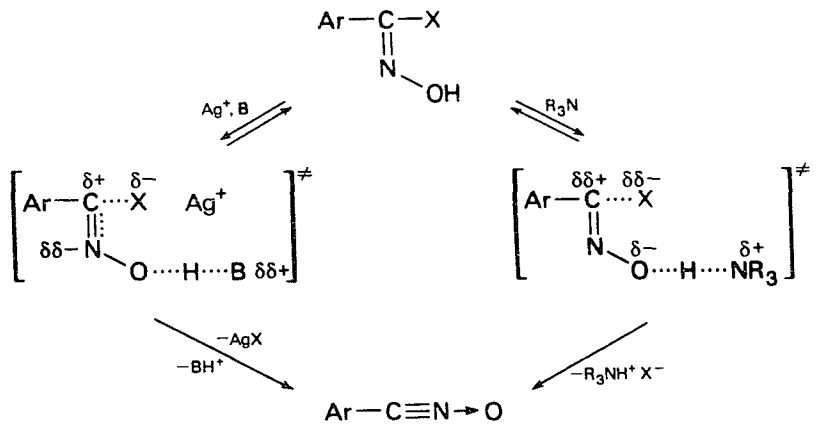


SCHEME 2

B. Dehydrohalogenation of Hydroxamoyl Halides

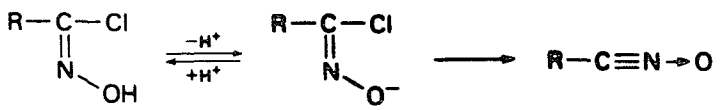
An allegedly improved preparation of hydroxamoyl chlorides from oximes by action of NCS has been reported very recently[31]. Formation of nitrile oxides from hydroxamoyl chlorides by heating in neutral solvent or by treatment with bases are among the commonest synthetic procedures[4]. The mechanism of dehydrohalogenation by bases has been thoroughly investigated in the last decade[32–36].

The substantial kinetic data obtained in the dehydrohalogenation of 3,5-dichloro-2,4,6-trimethylbenzohydroxamoyl chloride and bromide by action of tertiary amines or silver nitrate in acetonitrile as solvent, includes: (*i*) second-order kinetics apart from the reaction of bromide and silver nitrate characterized by an order higher than one in silver ion (anionic assistance by a second molecule of $AgNO_3$); (*ii*) leaving-group effect k_{Br}/k_{Cl} (ca. 10^3 in the case of silver nitrate but 1.6 for *N*-methylmorpholine, Bu_3N, Et_3N in acetonitrile); (*iii*) k_H/k_D (ca. 2 for the reactions of the hydroxamoyl chloride with *N*-methylmorpholine). These results, together with activation parameters (apparent activation parameters for the reaction of the hydroxamoyl chloride: $E_a = 83.8 \pm 1.6$ kJ mol^{-1}, $\Delta S^{\neq} = -8.1 \pm 5.1$ J K^{-1} mol^{-1}), are claimed to accord well with two concerted mechanisms (Scheme 3)[33]. The two mechanisms differ from one another in the degree of breaking of the C—X and O—H bonds, respectively, at the transition state. In the case of silver nitrate, a cation-like transition state has been envisaged with advanced C—X cleavage, while an anionic mechanism is preferred in the reaction with tertiary amines. The elimination of HX by action of tertiary amines occur 10^5–10^7 times faster than with silver nitrate, explaining, therefore, their preferred use for synthetic purposes.



SCHEME 3

It has been reported that hydroxamoyl chlorides in dilute aqueous solution smoothly generate the corresponding nitrile oxides, which are generally fairly stable towards dimerization under those conditions[34,36]. The kinetic study of dehydrohalogenation of benzohydroxamoyl chloride in the presence of sodium chloride at 21°C in water has shown the following salient data: (*i*) the rate of formation of benzonitrile oxide is inversely proportional to hydrogen ion concentration over the pH region 1–3 and (*ii*) the rate is independent of added chloride ion (concentration 0.00–0.28M at pH 2.0). The proposed mechanism postulates rate-determining loss of chloride ion from **12** which is in equilibrium with **11** (equation 1).



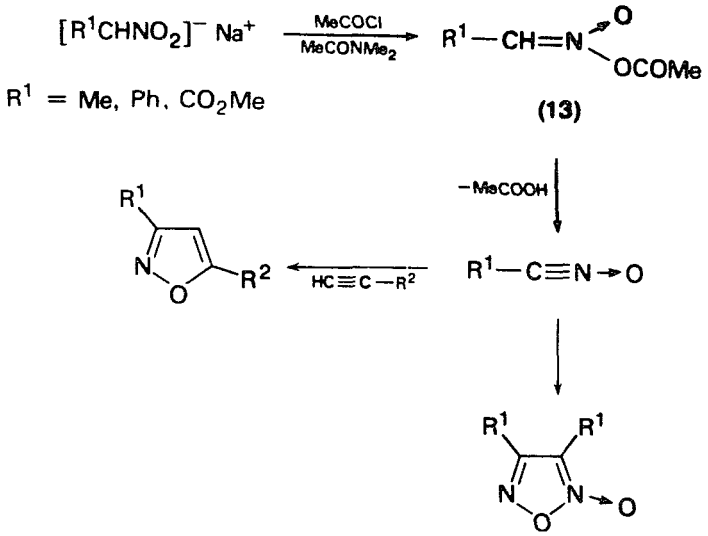
(11) **(12)** (1)

Recently nitrile oxides have been detected (IR) and trapped (with benzaldehyde) in the reaction of benzohydroxamoyl chlorides with iron pentacarbonyl (and also nonacarbonyldiiron)[37].

C. From Nitroalkanes

The dehydration of primary nitroalkanes represents an elegant, mild and very useful method of preparation of nitrile oxides[38]. A detailed procedure of dehydration by action of phosphorus oxychloride has appeared in *Organic Syntheses*[39]. This procedure has the alleged advantage over the commonly used method with phenyl isocyanate that the dehydrating agent and its transformation products are easily removed from the reaction medium by water. It has been claimed that formation of nitrile oxides can also be achieved by treatment of primary nitroalkanes with acetyl chloride (Scheme 4)[40].

Although the formation of a mixed anhydride of the type **13** has also been advanced by McKillop and Kobylecki[41] in the reaction of phenylnitromethane with acetic anhydride–sodium acetate under strictly anhydrous conditions, failure to detect furazan *N*-oxides was considered as evidence that nitrile oxide species were not formed



	R²		
R¹	CO_2Et	Ph	CH_2OAc
Ph	63%	47%	57%
Me	54%	36%	39%

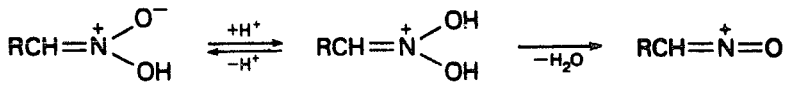
SCHEME 4

and that it was the 1,3-dipole **13** which reacted with added dimethyl acetylenedicarboxylate to give isoxazole derivatives on loss of acetic acid.

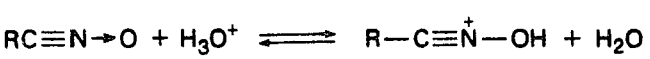
In 1971 Edward and Tremaine reported[36] on the behaviour of arylnitromethanes in acid, resuming an old work by Meyer and Wurster[42], who in 1873 found that primary nitroalkanes in hot concentrated mineral acids gave carboxylic acids and hydroxylamine. (This reaction appears to be less known than the Nef reaction in which primary nitroalkanes are smoothly converted to aldehydes when treated with aqueous mineral acid[43].) On the basis of solvent, substituent and isotopic effects as well as of isolation of nitrile oxides (previously envisaged but not isolated by other authors[43]) the authors[36] advanced a mechanism (Scheme 5) involving a nitrile oxide intermediate **14**.

We are aware of only two cases where secondary nitro compounds may also give rise to nitrile oxides through their *aci* form[44,45]. Isoxazoline **15** was formed in 39% yield together with 37% of 1,1-diphenylethylene by treatment of 1-nitro-1,2,2-triphenylpropane (as its sodium salt) with concentrated hydrochloric acid (Scheme 6)[44].

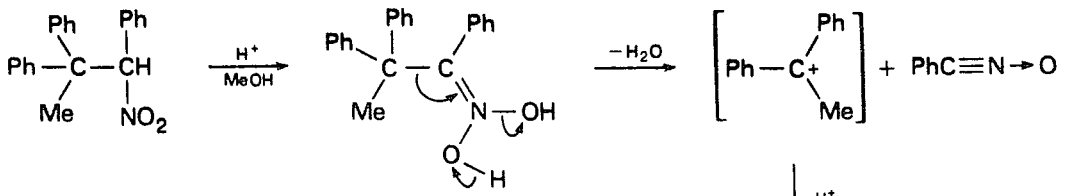
The fragmentation of α-nitro ketones to carboxylic acids and hydroxamic acids by action of mineral acids[46] and the conversion of primary aliphatic and arylaliphatic nitro compounds into nitriles by action of trimethyl(ethyl)amine–sulphur dioxide complexes[47a] and thermal decomposition of the potassium salts of 1,1-dinitroalkanes[47b] has also been considered to involve the formation of nitrile oxides. Finally a curious reaction in which a nitrile oxide is quantitatively formed is that of 1-nitro-3,3-dimethyl-1-butyne with an ynamine (equation 2)[48].



(14)

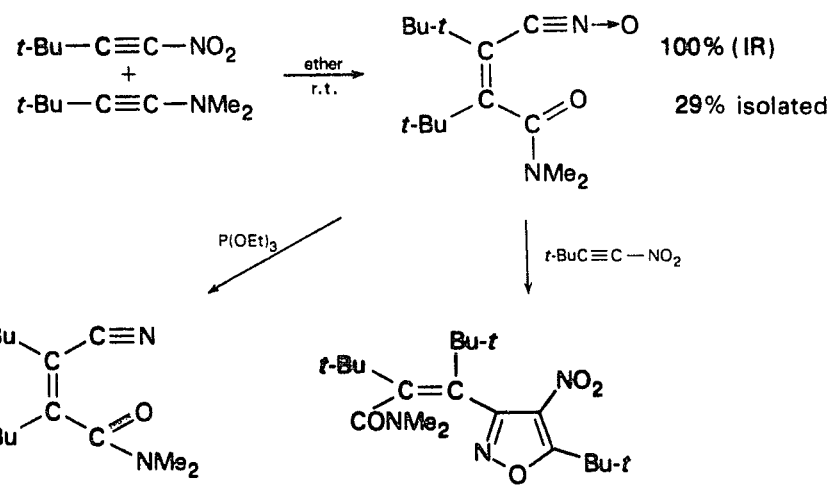


SCHEME 5



(15)

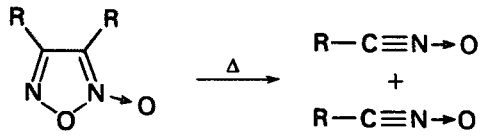
SCHEME 6



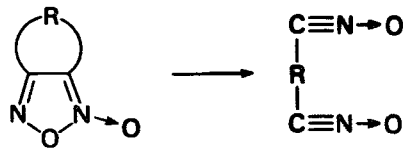
(2)

D. From Furazan *N*-Oxides

Thermally induced cycloreversion of furazan *N*-oxides **16** and **17** appears to be a promising way to obtain nitrile oxides (equations 3 and 4).[5] Flash vacuum pyrolysis has



(16) R = alkyl, Ar, $PhSO_2$ (3)

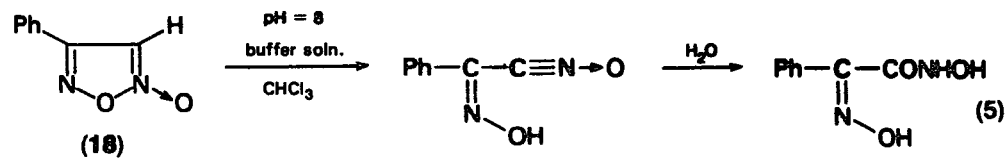


(17) —R— = $-CH_2CH_2CH_2-$, (4)

allowed Paton and associates[49] to prepare aliphatic nitrile oxides otherwise difficult to obtain in the pure state, thus permitting detailed examination of their chemicophysical properties.

Thermolysis of furazan *N*-oxides in the presence of dipolarophiles has been found to be a useful synthetic tool for the preparation of isoxazole derivatives[50,51]. Also diacylfurazan-*N*-oxides with bulky substituents undergo cycloreversion smoothly, while less crowded derivatives (e.g. dibenzoylfurazan-*N*-oxides) follow an internal rearrangement[52].

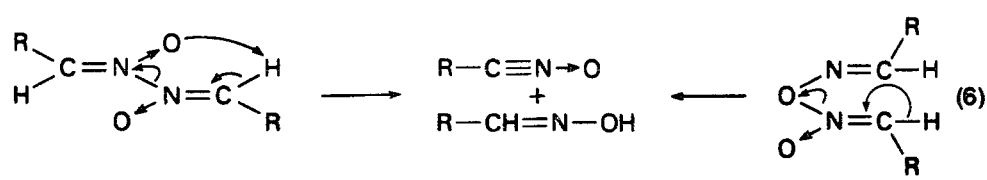
Formation of the nitrile oxide system has also been shown to occur by opening of the ring of a monosubstituted furazan *N*-oxide[53,54]. The reaction of **18** is promoted at room temperature by a slightly basic medium[53] (equation 5).



(18) (5)

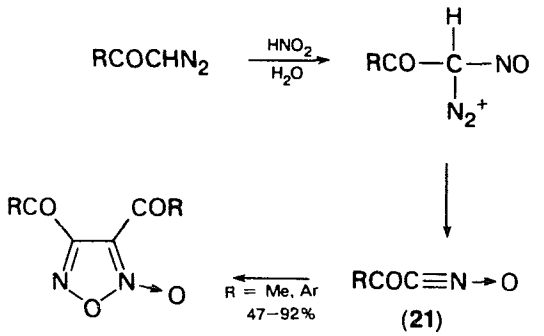
E. Miscellaneous Methods

A promising method for the *in situ* preparation of unstable nitrile oxides has been claimed to be the thermal decomposition under mild conditions of the so-called dehydro dimers of aldoximines[55,56]. More recently Grundmann and Kite[57] checked and tested this reaction with several dehydro dimers of structure **19** or **20** and various dipolarophiles (equation 6).



(19) (20) (6)

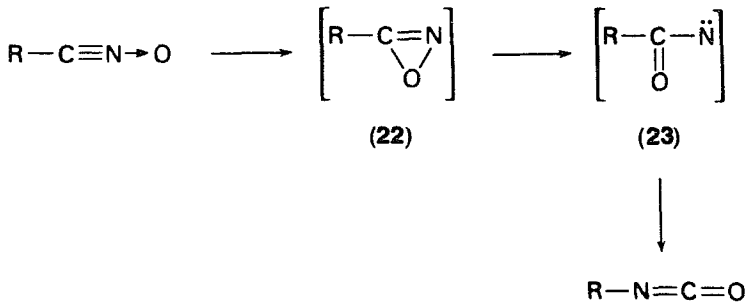
A method for preparation of α-carbonylnitrile oxides (**21**) in good yields from α-diazocarbonyl compounds has been devised by Dahn and coworkers[58a] (equation 7). Nitrile oxides are also formed by oxidation of oximes by Ag_2CO_3 on Celite[58b].



(7)

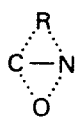
IV. NITRILE-OXIDE–ISOCYANATE REARRANGEMENT

Nitrile oxides, with the exception of simple aliphatic derivatives, have long been known to rearrange to isocyanates on heating[4] and this reaction has been recently the subject of a theoretical study[18,19]. The models examined by *ab initio* MO calculations were the parent compounds formonitrile oxide and acetonitrile oxide. The most relevant results of this study, from our standpoint, is that the rearrangement nitrile oxide → isocyanate involves successive 1,2-migrations of the oxygen and R groups, the former moving first. The most favourable reaction path (equation 8) is predicted to



(8)

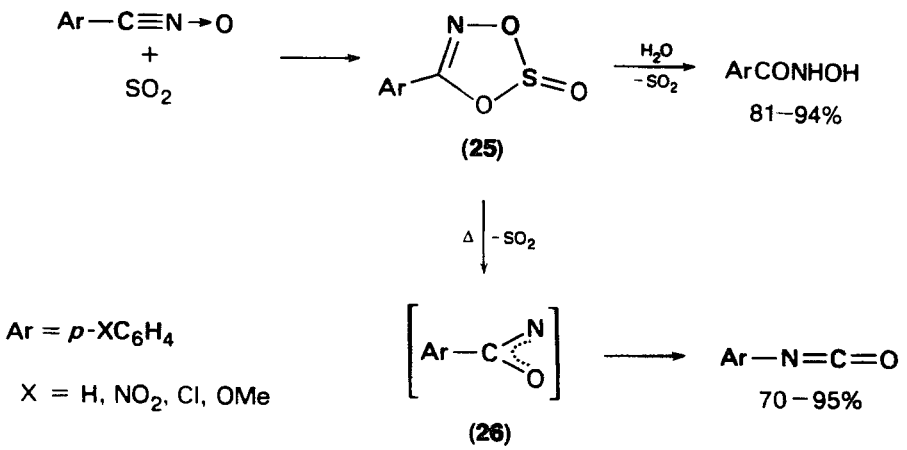
start from a linear 1,3-dipole which then passes through structures corresponding to oxazirine **22** and singlet nitrene **23** neither of which are true intermediates and should not be observable. The calculations seem to rule out a symmetrical transition state of the type **24** for such a reaction.



(24)

Grundmann and associates found[59] that when group R contains a chiral centre at the point of attachment to the nitrile oxide moiety, the rearrangement proceeds with complete retention of stereochemical configuration, this suggesting a concerted bond-breaking and bond-making process in the last step, **23** → isocyanate, of the reaction.

Direct rearrangement of nitrile oxides to isocyanates is generally complicated by the competing reaction of dimerization to furazan *N*-oxides. Of synthetic interest, therefore, is a work by Trickes and Meier[60] who discovered that heating nitrile oxides in anhydrous benzene in the presence of sulphur dioxide gives isocyanates in high yields through **25** as demonstrated by its isolation (Scheme 7)[60,61].

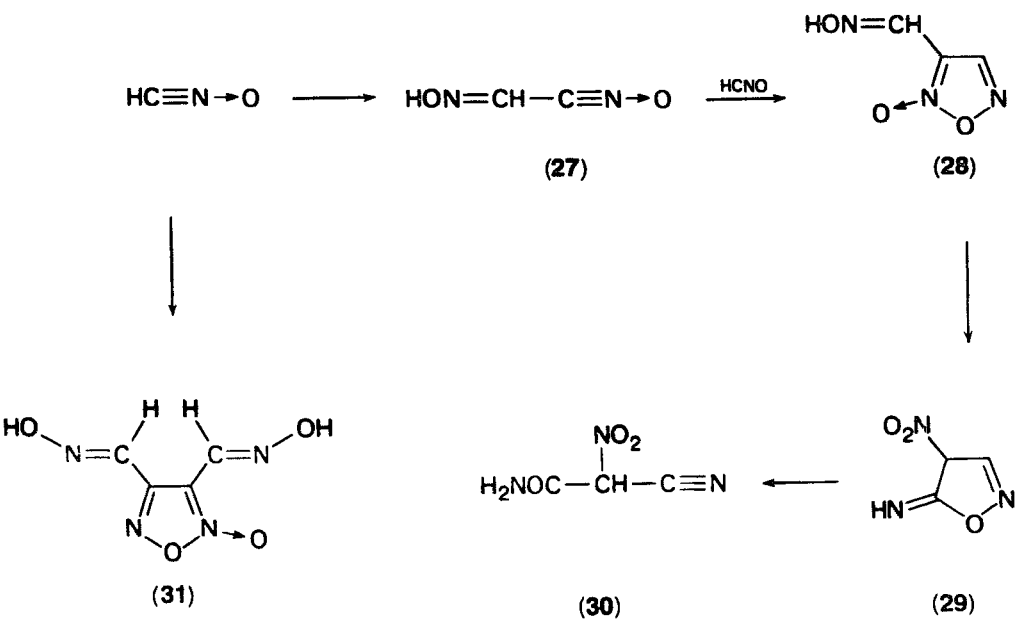


SCHEME 7

V. DIMERIZATION AND POLYMERIZATION OF NITRILE OXIDES

A. Fulminic Acid

Dimerization and polymerization of fulminic acid (formonitrile oxide) has been previously reviewed in detail[3,4]. More recently Grundmann and associates[62,63] have



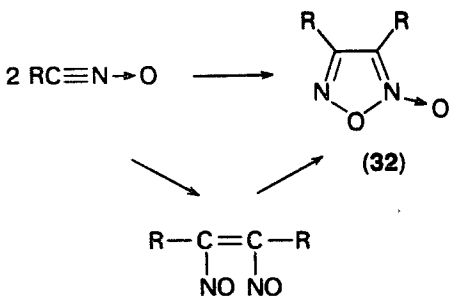
SCHEME 8

thoroughly reinvestigated the process of transformation of fulminic acid into fulminuric acid **30** and determined the stereochemical structure of isocyanilic acid **31**, the formal dimer of **27**. As shown in Scheme 8 fulminic acid dimerizes to hydroxyiminoacetonitrile oxide **27** which undergoes a 1,3-dipolar cycloaddition at the C—N triple bond by another molecule of fulminic acid to give the furazan *N*-oxide **28**. The latter compound rearranges under the existing reaction conditions to **29** which ring-opens to fulminuric acid **30**.

Chemical and spectroscopic evidence allows one to assign to isocyanilic acid the structure of (*E*,*E*)-3,4-bis(hydroxyiminomethyl)furazan *N*-oxide (**31**), thus permitting the correction of previous erroneous data in the literature.

B. Base Catalysis

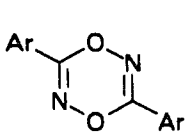
Nitrile oxides, with the exception of highly hindered derivatives[4,64], dimerize readily and the most commonly encountered dimerization product is a 3,4-disubstituted furazan *N*-oxide (**32**). The question whether the reaction leading to **32** is a concerted $[{}_{\pi}4_S + {}_{\pi}2_S]$ or a two-step process (equation 9) has not been definitively answered yet[65].



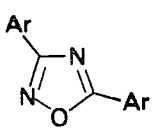
(9)

The action of some organic bases changes the manner of dimerization and reaction products other than **32** are obtained. For example, the action of pyridine on the dimerization of benzonitrile oxide leading to 1,4,2,5-dioxadiazine (**33**) (Ar = Ph) has been known for a long time[4]. This heterocycle is known to form also when nitrile oxides are treated with excess BF_3 in benzene[4].

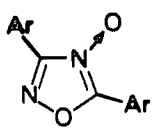
De Sarlo and coworkers have found recently[66] that when variously substituted benzonitrile oxides are treated with excess pyridine, substituted pyridines or 1-methylimidazole in ethanol, high yields of dioxadiazines (**33**) are obtained. Small amounts of 1,2,4-oxadiazoles (**34**), 1,2,4-oxadiazole-4-oxides (**35**) and furazan *N*-oxides (**36**) are generally observed as by-products. The amounts of such compounds increase if the reaction leading to **33** is not fast enough (half-life > 1500 s). The reaction rate for the formation of **33** is increased with increasing nucleophilic character of the base and the electron-withdrawing power of the aryl group of the 1,3-dipole.



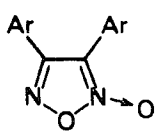
(**33**)



(**34**)



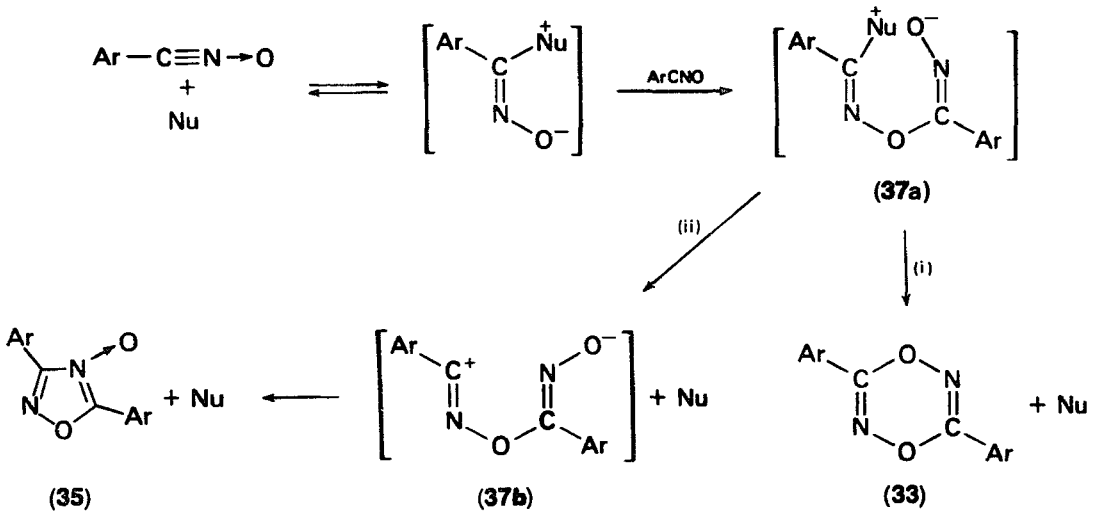
(**35**)



(**36**)

By contrast, when benzonitrile oxides are treated with trimethylamine in ethanol at room temperature or below, the major reaction products are compounds **35**; small amounts of compounds **34** are also obtained, but no oxadiazines have been isolated.

The mechanisms (based on extensive kinetic data), governing the reactions discussed above, are summarized in Scheme 9. The high steric demand by trimethylamine favours **37a** → **37b** isomerization thus preventing **37a** to collapse into **33**.

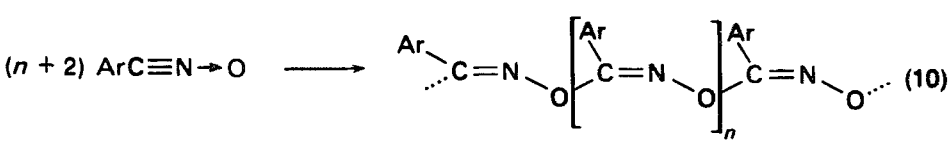


(i) Nu = pyridine, substituted pyridines or *N*-methylimidazole
(ii) Nu = trimethylamine

Ar	35 (%)
Ph	11
4-MeC_6H_4	32
4-$MeOC_6H_4$	49
4-ClC_6H_4	61
4-$NO_2C_6H_4$	36

SCHEME 9

Concentrated solutions of the same aromatic nitrile oxides in dimethyl sulphoxide in the presence of triethylamine give polymer **38** in moderate yields (equation 10).

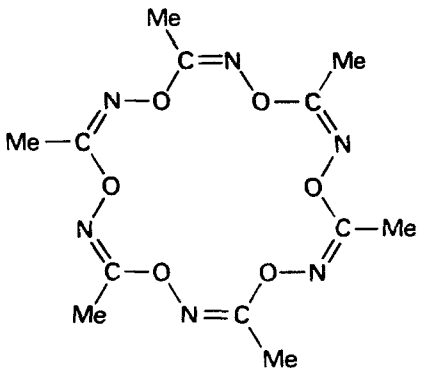


(38)

Such polymers are stated to be relatively stable in the solid state; however in solvents such as ethanol and chloroform they are converted into other products, among them 1,2,4-oxadiazoles (**34**) and the corresponding oxadiazole-4-oxides (**35**).

Attempts to trap any intermediate nitrile oxides have failed as have all the efforts to detect any furazan *N*-oxides (**36**).

The reaction of acetonitrile oxide and other aliphatic nitrile oxides in ethanol in the presence of trimethylamine allowed De Sarlo and coworkers to isolate new types of oligomers[67]. In fact, when solutions ca. 1–3M in acetonitrile oxide and 1–2.5M in nucleophile were reacted at room temperature, the most important products were 3,6-dimethyl-1,4,2,5-dioxadiazine, hexamer **39**, a heptamer and an octamer whose



(39)

structures are related to **39** and also insoluble polymers[67]. In general, in relatively diluted solutions, dimers and cyclic oligomers are favoured, while the yields of insoluble polymers increase with the concentration of acetonitrile oxide. 3,4-Dimethylfurazan *N*-oxide has only been detected by g.l.c. in the reactions described above, although it was the sole identified product for reactions 0.1M in nitrile oxide and 0.2M in trimethylamine.

VI. 1,3-DIPOLAR CYCLOADDITION

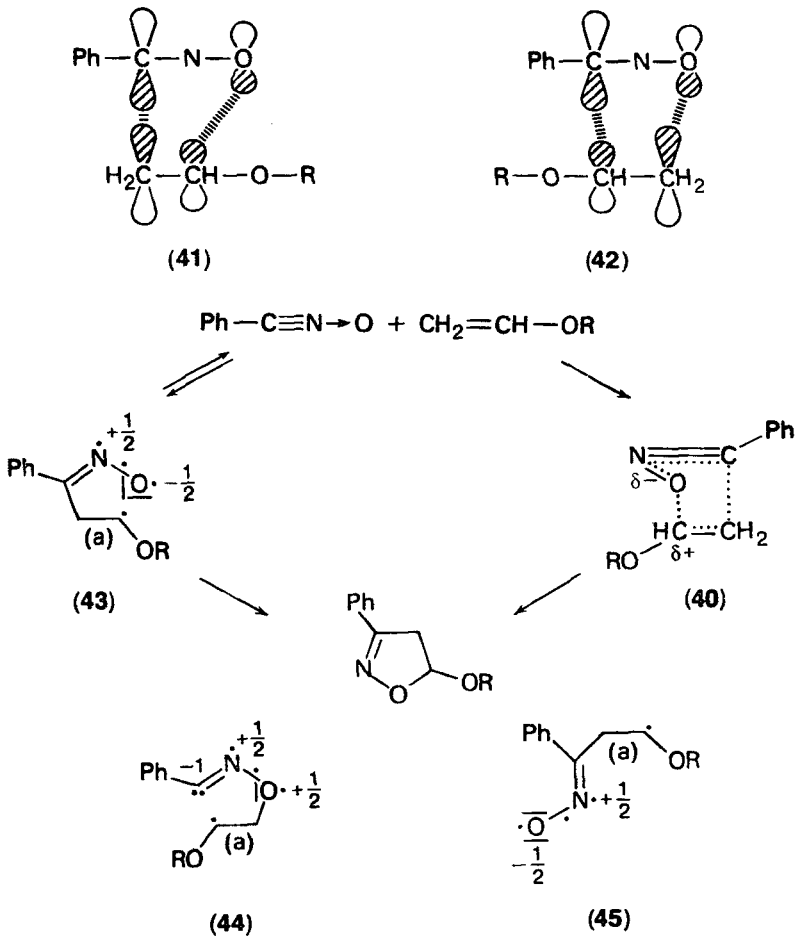
A. Mechanism: Concerted or Stepwise?

The question of concertedness (that is, the timing of the new bonds formation) in 1,3-dipolar cycloadditions has been of outstanding interest for the whole of the last decade.

The more widely accepted Huisgen mechanism, a concerted but not synchronous reaction, entails a two-plane approach of the reactants to give a transition state (TS) **40** which bears partial charges and occurs early along the reaction coordinate (Scheme 10 and Figure 5)[68,69].

Reactivity and selectivity in nitrile oxide cycloadditions were accounted for by Huisgen mostly on the basis of effects such as conjugation, stabilization of partial charges in the TS, maximum gain in σ-bond energy and steric effects[68].

More recently application of MO perturbation theory with special emphasis on interaction between occupied and empty orbitals (in particular HO–LU interactions) has provided a satisfactory explanation of selectivity and reactivity problems. For example in the reaction of benzonitrile oxide with vinyl ether the dominant interaction is $LU_{1,3\text{-dipole}}$–$HO_{dipolarophile}$ and the orientation complex **41** (with large–large and small–small interactions) is more favoured than **42** (two large–small interactions) as proved by the regiospecificity of the reaction[4].



SCHEME 10

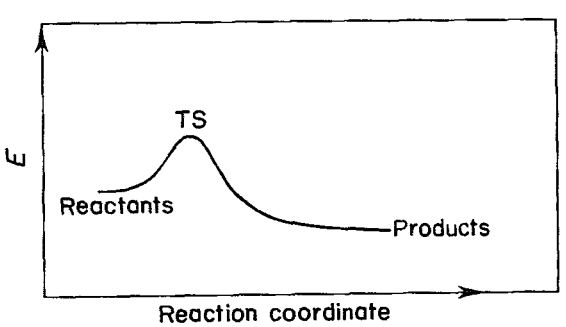


FIGURE 5. Potential energy curve for one-step 1,3-dipolar cycloaddition.

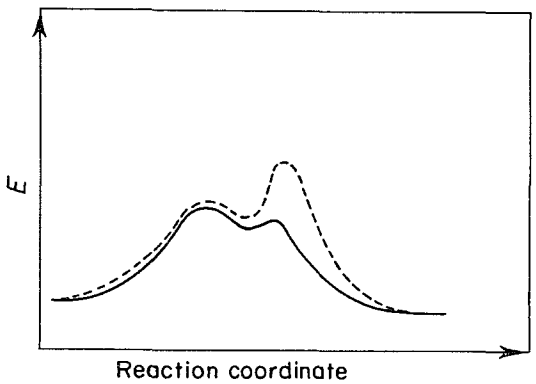
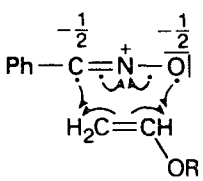


FIGURE 6. Potential energy curves for two-step 1,3-dipolar cycloaddition through a cyclo-diradical (full line) and through an extended diradical (dashed line).

On the other hand the higher stability of spin-paired cyclo diradical **43**, in comparison with **44**, explains the regiospecificity of the reaction in terms of Firestone's mechanism (Scheme 10 and Figure 6)[70]. However, in the latter mechanism, one has to accept that diradicals of the type **43** (even when they occur in the extended conformation **45**) isomerize considerably more slowly by rotation around bond (a) than they revert to the starting addends or collapse to products. This assumption is necessary to account for the experimentally observed strict stereospecificity of nitrile oxide cycloadditions[4]. Moreover, Harcourt, on the basis of quantum-mechanical arguments has pointed out that a concerted diradical mechanism (e.g. **46**) seems more reasonable than a stepwise one, even when one uses Linnett-type electronic structures **10** to represent 1,3-dipoles[30].



(46)

Very interesting are the results of two *ab initio* MO studies on the reaction of fulminic acid plus acetylene by Poppinger[71] (STO-3G) and Schaefer and associates [4-31G and (9s5p/4s2p) double-zeta basis sets][72]. It has been found that the predicted TS resembles more closely the reactants than products; the most relevant change is a marked *trans* bending of the HCNO skeleton (Figure 7). In contrast with Huisgen's two-planes approach, all the atoms in the TS lie in one plane. Even if this atomic array were to be correct, Poppinger suggested that conjugative stabilization should be very small in such an early TS and consequently does not entail an appreciable increase in reactivity of alkyne dipolarophiles compared with alkenes.

Moreover, although the TS looks relatively symmetric on geometrical grounds, this does not necessarily mean that the process is a synchronous one. In fact the force constants calculated by Schaefer for the C···C and C···O bonds in the TS are 3.07 and 0.31 mdyn/Å, respectively, implying that the C···C bond is about ten times

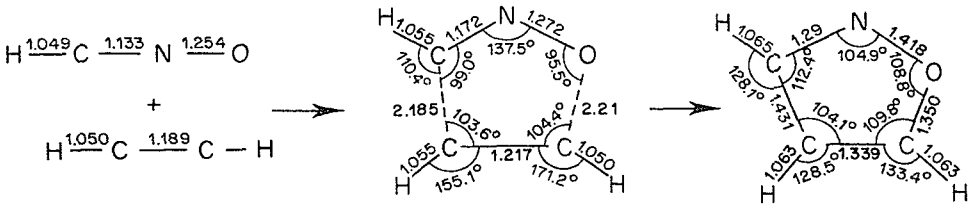


FIGURE 7. Theoretical (4-31G SCF) structures for reactants, transition state and product for the acetylene plus fulminic acid reaction. The TS is 118.7 kJ higher in energy than the reactants[72].

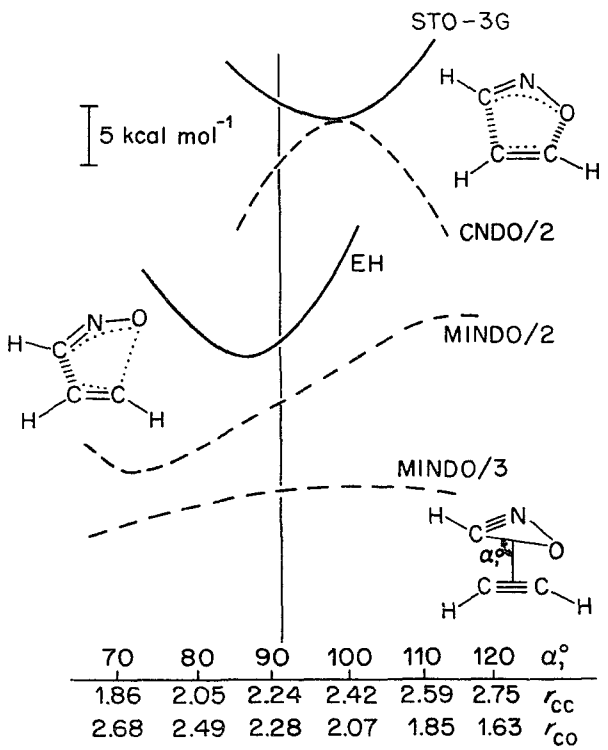


FIGURE 8. Energies of unsymmetrical 'one-bond' and symmetrical 'two-bond' transition-state geometries for fulminic acid–acetylene by various calculation techniques; $\alpha = 60°$ and $\alpha = 120°$ correspond roughly to biradicaloids with the CC and CO bond formed, respectively; $\alpha = 90°$ corresponds to a geometrically synchronous transition state. Reprinted with permission from P. Caramella, K. N. Houk and L. N. Domelsmith, *J. Amer. Chem. Soc.*, **99**, 4511 (1977). Copyright (1977) American Chemical Society.

stronger than the C···O bond. The similarity between the bond lengths is simply due to the fact that C—O is shorter than C—C (see isoxazole structure), so when both bonds are stretched to ca. 2.20 Å C···C is still strong while C···O has almost vanished. MNDO calculations magnify the extent of this asynchronism indicating the possibility of a zwitterionic intermediate in the reaction[73]. It should be remembered, however, that MNDO (and also MINDO/3) tends to exaggerate interatomic repulsion around van der Waals' distances and consequently fails to reproduce very weak bonds[74] (such as C···O in the TS).

A study by Houk and associates has evidenced that calculations which include overlap (EH, *ab initio*) favour a two-bond symmetrical TS for fulminic acid plus acetylene, whereas semiempirical calculations which neglect overlap (MINDO/2, MINDO/3 and CNDO/2) favour one-bond unsymmetrical geometry (biradical-like) for the TS (Figure 8)[75]. This systematic discrepancy was attributed by the authors to an inherent defect (neglect of overlap) of the latter methods which leads to an underestimation of closed-shell repulsion in a highly asynchronous TS.

As a conclusion on the mechanistic discussion, we wish to point out that: (*i*) a diradical intermediate may not be excluded *a priori* in the reaction of nitrile oxides with dipolarophiles of very similar FO energies (that is in the case of large HO–LU separations) when dipolarophiles bear a good radical stabilizer, (*ii*) the possibility of a dipolar intermediate must be considered when an electron-poor nitrile oxide reacts with an electron-rich dipolarophile bearing also a good cation stabilizer and (*iii*) all experimental and theoretical data make, at present, the 1,3-dipolar cycloadditions of nitrile oxides one of the best examples of 'concerted but not synchronous' cycloadditions[76].

B. Reactions with Carbon–Carbon Double and Triple bonds

1. *Reactivity and regioselectivity*

The reactivity and regioselectivity in the most simple PMO treatment, which takes into account only the interactions between empty (LU) and occupied (HO) frontier orbitals (FO), are governed by equations (11) and (12), respectively[7]. These second-order perturbation expressions permit the calculation of change of energy following the interaction of nitrile oxides with dipolarophiles (Figure 9). Q ($\simeq$4–6 eV) is a correction factor which takes into account the narrowing of FO energy gaps during the approach of the molecules to one another[77]. The other symbols have the usual meanings[5,7,23,24,77].

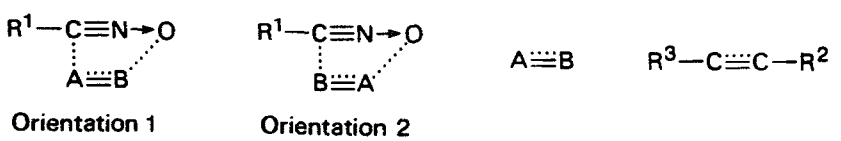


FIGURE 9.

$$\Delta E_1 = 2\,\frac{[c_{O,HO}c_{B,LU}\beta_{CO} + c_{C,HO}c_{A,LU}\beta_{CC}]^2}{E_{HO(N)} - E_{LU(D)} + Q} + 2\,\frac{[c_{O,LU}c_{B,HO}\beta_{CO} + c_{C,LU}c_{A,HO}\beta_{CC}]^2}{E_{HO(D)} - E_{LU(N)} + Q} \qquad (11)$$

$$\Delta E_2 - \Delta E_1 = 2\,\frac{[(c^2_{A,LU} - c^2_{B,LU})(c^2_{O,HO}\beta^2_{CO} - c^2_{C,HO}\beta^2_{CC})]}{E_{HO(N)} - E_{LU(D)} + Q} + 2\,\frac{[(c^2_{A,HO} - c^2_{B,HO})(c^2_{O,LU}\beta^2_{CO} - c^2_{C,LU}\beta^2_{CC})]}{E_{HO(D)} - E_{LU(N)} + Q} \quad (12)$$

N = nitrile oxide, D = dipolarophile

The importance of the contribution of coefficients in equation (11), which are very often overlooked, is understood if one compares, for example, the reactivity of ethylene with that of conjugated systems. In fact, the expected increase of reactivity of the latter dipolarophiles as a result of higher HO and lower LU energy levels, is somewhat tempered by the decrease of their FO coefficient values at the reaction sites.

Equation (12), in turn, shows that the regioselectivity is a function of $c^2\beta^2$ values. The relative nucleophilicity of the two end-atoms of nitrile oxides, predicted on the basis of coefficients ($c^2_{O,HO} > c^2_{C,HO}$), may be reversed when one considers both coefficients and resonance integrals[7,23,78]. In fact $c^2_{O,HO}\beta^2_{CO}$ is higher than $c^2_{C,HO}\beta^2_{CC}$ when the interacting centres are 1.75 Å apart, while $c^2_{C,HO}\beta^2_{CC} > c^2_{O,HO}\beta_{CO}$ holds at a distance of 2.20 A. The latter value corresponds to the calculated TS distance between fulminic acid and acetylene[72]. Moreover, it should be remembered that bending of the nitrile oxide in approaching the transition state lowers the difference in the HO coefficients[16,17].

Table 2 shows relative rate constants of the reactions of benzonitrile oxide with several double- and triple-bond dipolarophiles[79]. For the sake of a direct comparison of experimental results with those expected theoretically, the FO energies of nitrile oxides and several classes of dipolarophiles are reported in Figure 10[23].

The higher reactivity of *trans* than *cis* double bonds, of alkenes than alkynes, the greater rate-retarding effect of a β-methyl (e.g. methyl crotonate) than α-methyl substituent (e.g. methyl methacrylate) and the low reactivity of double bonds bearing substituents of opposite electronic effect (e.g. methyl 3-pyrrolidinoacrylate), are all characteristic features of nitrile oxide cycloadditions and are apparent in Table 2.

The generally lower reactivity of alkynes in comparison with alkenes[6,79,80] could be explained in FO interaction terms. Nitrile oxides are moderately electron-deficient 1,3-dipoles[81] for which LU-dipole control is often dominant in the 1,3-dipolar cycloaddition (Figure 10)[23]: consequently the higher IP_v (lower HO energy) of the

TABLE 2. Relative rates of the cycloadditions of benzonitrile oxide with double and triple carbon–carbon bonds[79]

Dipolarophile	k_{rel}	Dipolarophile	k_{rel}
β-Pyrrolidinostyrene	25.2	Ethylene	1.0
Norbornene	15.3	Cyclopentadiene	0.44
Methyl acrylate	8.3	Acetylene	0.40
Dimethyl fumarate	6.1	1-Hexene	0.31
Methyl methacrylate	3.6	Cyclopentene	0.21
Dimethyl acetylenedicarboxylate	3.1	Dimethyl maleate	0.21
Butyl vinyl ether	2.1	Phenylacetylene	0.112
Methyl 3-pyrrolidinoacrylate	1.88	Methyl crotonate	0.082
Methyl propiolate	1.24	Methyl 3,3-dimethylacrylate	0.0062
Styrene	1.15	Cyclohexene	0.0025

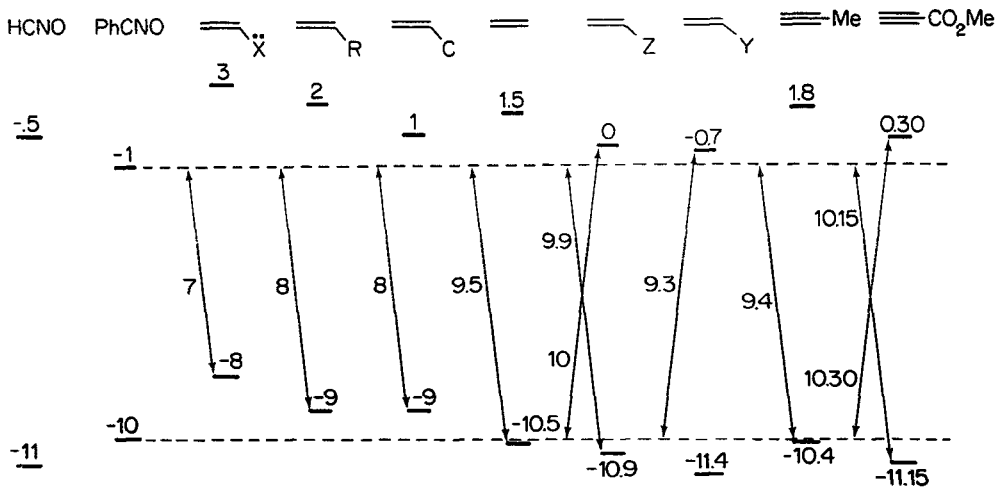
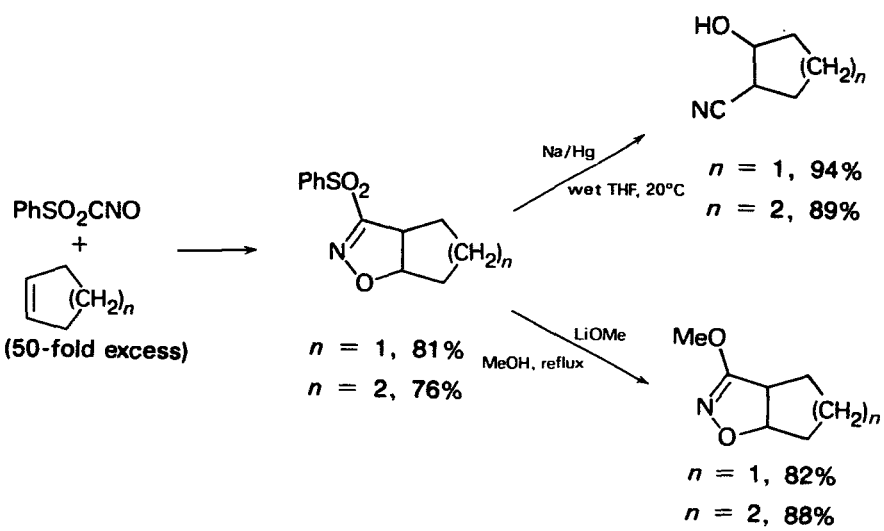


FIGURE 10. Frontier orbital energies (eV) for nitrile oxides and dipolarophiles. X = OR, NR_2; R = alkyl; C = C=C, Ph; Z = COR, CO_2R, CN; Y = NO_2, SO_2R.

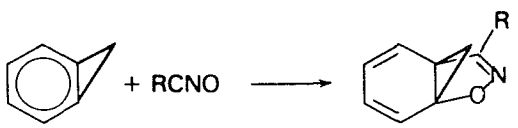
triple bond (e.g. phenylacetylene IP_v = 8.82 eV)[82] with respect to the corresponding double-bond dipolarophiles (e.g. styrene IP_v = 8.55 eV)[83] are mostly responsible for the difference in reactivity found for the two classes of compounds.

Noteworthy also is the high reactivity of methyl acrylate which, on the basis of Houk's model (Figure 10), should be found at the bottom end of the reactivity scale. This expectation is not fulfilled even in the case of the electron-poor benzenesulphonylnitrile oxide for which the following k_{rel} were found: cyclopentene = 0.83, 1-hexene = 1.0, methyl acrylate = 1.22, styrene = 4.17, *n*-butyl vinyl ether = 12.9, norbornene = 36.7[84]. Interestingly enough, benzenesulphonylnitrile oxide reacts readily with alkyl-substituted alkenes (even with tetramethylethylene) to give high yields of isoxazolines which are useful synthons (Scheme 11)[85].



SCHEME 11

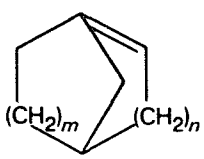
Table 2 also shows that factors (e.g. strain and steric factors) other than FO interactions are important in determining reaction rates. In fact the well-known high reactivity of strained double bonds has been recently further documented by a number of reactions of cyclopropenes[86,87], benzvalene[88], hexamethyldecarbenzene[88], benzocyclopropene **47** (equation 13)[89], methylenecyclobutane[90], benzocyclobutene[91], *E*-cyclooctenes[92,93] and compounds with a double bond at the bridgehead position (Bredt alkenes)[93]. In particular Bredt alkenes **48** reacted with mesitonitrile oxide quantitatively in a few minutes at room temperature to give a mixture of regioisomers **49** and **50**, whereas a single less-hindered adduct (e.g. **51** in the case of 1-methyl-*E*-cyclooctene) was isolated from the reactions of 1-methyl-substituted cycloalkenes[93].



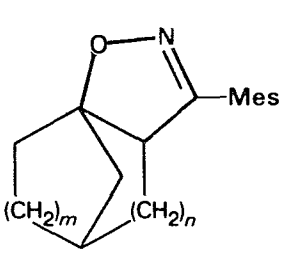
(13)

(47)

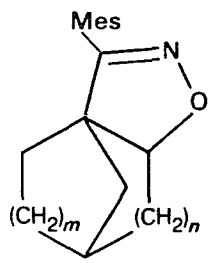
R = Mes, CH_2Cl_2, reflux	27%	48%
R = Ph Et_2O, 0°C	10%	53%



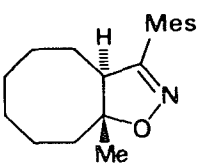
(48)



(49)



(50)

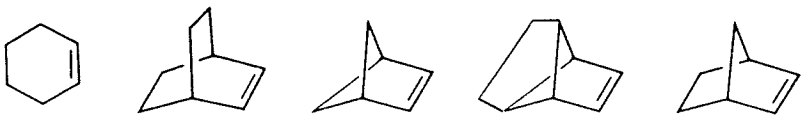


(51)

m = *n* = 2	90%	10%	Mes = mesityl
m = 3, *n* = 1	77%	23%	
m = 1, *n* = 3	64%	36%	

The high reactivity of strained alkenes (k_E/k_Z = 7320[92] and 6100[79] for the reactions of *E*- and *Z*-cyclooctenes with mesitonitrile oxide and benzonitrile oxide respectively) does not find a completely satisfactory explanation either in the release of strain energy in the TS or in FO energies. This was conclusively proved for norbornene by Huisgen who studied the relative rates of the reactions of conjugated dienes and 1,3-dipoles with several cycloalkenes (see in Scheme 12 the data for mesitonitrile oxide)[94].

In particular even if one assumes that the rate enhancement found for **54** and **55** compared with **53** fully originates from strain release in the transition state, such an effect can only be partially responsible (≤50%) for the high rate constant of norbornene **56**. The '*x*' electronic factor which, in addition to strain, operates in norbornene was tentatively attributed by Huisgen to the 'Fukui effect', that is the nonequivalent orbital extension (e.g. **57**) which results from a mixing between $\pi_{2,3}$ and $\sigma_{2,3}$ bonds through the interaction of both with the methano bridge[95a]. Thus the higher



(52) (53) (54) (55) (56)

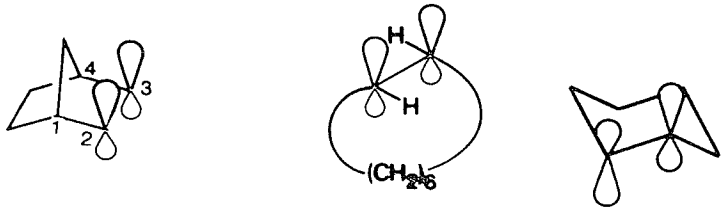
	(52)	(53)	(54)	(55)	(56)
k^a	1.2	5.7	2,280	2,300	3,150
IP_v(eV)	9.18	9.05	—	8.63	8.97
ΔStrain^b	−0.63	−2.13	−41.6	−37.24	−19.81

^{a}Rate constant (l mol^{-1} s^{-1} × 10^6, in CCl_4 at 25°C) for the reaction with mesitonitrile oxide. ^{b}Cycloalkane strain − cycloalkene strain (kJ mol^{-1}) evaluated by force field for molecular mechanics calculations (MM2).

SCHEME 12

π-electron density on the *syn* methano bridge side allows a better orbital interaction between nitrile oxides and norbornene in comparison with that experienced by the 1,3-dipole with the symmetric dipolarophiles **53–55**. Since this orbital picture finds confirmation neither in MINDO/3 nor in MNDO calculations of norbornene, this rate-accelerating effect was interpreted by Huisgen as operative in the TS[94]. Very recent *ab initio* calculations support this suggestion[95b].

Geometrical distortions affecting the lobe size (e.g. **58** and **59**)[96] which consequently bring about accelerating or reducing reaction rate effects were also invoked to explain both the high reactivity of *E*-cyclooctenes[92,93] and the surprisingly low reactivity of cyclohexene towards nitrile oxides.



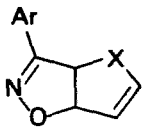
(57) (58) (59)

A factor which decreases the reactivity of double bonds is the aromaticity loss on going from reactants to TS. This has been found with furan, thiophene and their benzo derivatives which are very little reactive (k_{rel} cyclopentadiene/k_{rel} furan = 9,300 and k_{rel} indene/k_{rel} benzofuran = 180) with nitrile oxides[97–100] (Scheme 13 and Table 3) in spite of their low ionization potentials [compare the IP_v (from π orbitals) of furan (8.88 eV), thiophene (8.90 eV), benzothiophene (8.2 eV) and benzofuran (8.66 eV) with those of cyclopentadiene (8.6 eV) and indene (8.20 eV)][97–99].

The cycloaddition with thiophene is regiospecific with the formation of adducts of type **60**[99,100], while, besides compound **60** (X = O), minor amounts of regioisomer **61** and trace amounts of the oxime **62** are isolated from the reaction of benzonitrile oxide with furan[97]. The reactions of these latter dipolarophiles are complicated by further reactions of the primary cycloadducts[97,99,100].

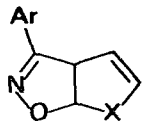
More reactive and regiospecific are benzothiophen-5-oxide and benzothiophen-5,5-dioxide which give adducts of the type **63**[102,103].

As expected for a LU-dipole control, *p*-nitrobenzonitrile oxide reacts faster with monosubstituted alkylethylenes than the *p*-methoxy derivative; both give only

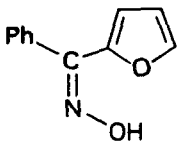


(60)

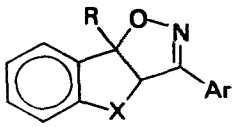
X = O, S



(61)



(62)



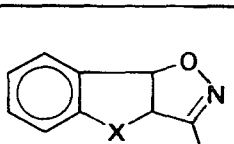
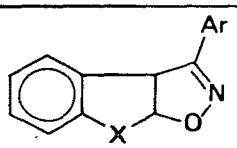
(63)

Ar = Mes; R = Me; X = SO, SO_2

Ar = Ph; R = H, Me; X = SO_2

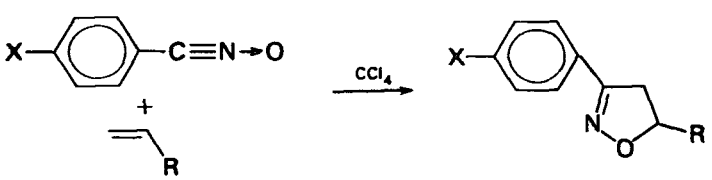
SCHEME 13

TABLE 3. Regioisomer ratios and total yields of the reactions of benzonitrile oxide and mesitonitrile oxide (values in parentheses for the latter 1,3-dipole) with indene[101], benzofuran[98] and benzothiophene[99] in ether or benzene at room temperature

X	Regioisomer ratios 		Dipolarophile excess (equivalents)	Total yield (%)[a]
O	70(26)	30(74)	100(4.2)	24(89)
S	78(26)	22(74)	10(5)	1.9(89)
CH_2	98(74)	2(26)	2(2)	91(76)

[a]Reaction times for mesitonitrile oxide: fifteen days with indene, four months with benzofuran and benzothiophene.

5-substituted isoxazolines as a consequence of the regiochemical orbital size control (Scheme 14)[104]. The lower reactivity of the *t*-butyl derivative is easily accounted for by steric effects.

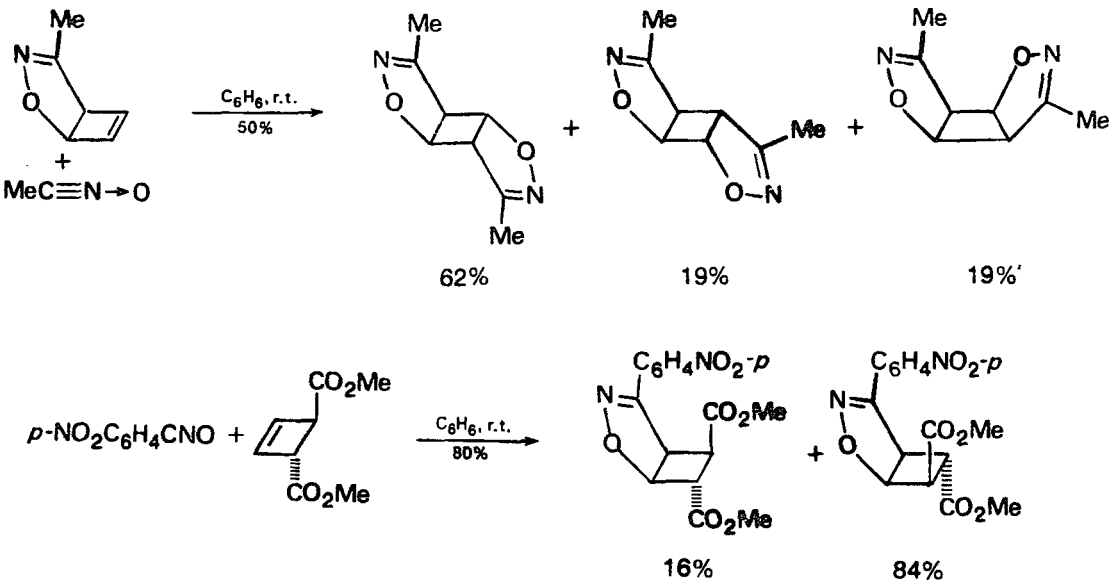


R	IP_v	k(1 mol^{-1} s^{-1}) × 10^3	
		p-NO_2[a]	*p*-MeO[b]
Me	9.90	13.4	2.41
n-Pr	9.68	12.6	2.38
t-Bu	9.61	7.26	1.44

[a]25°C.
[b]20°C.

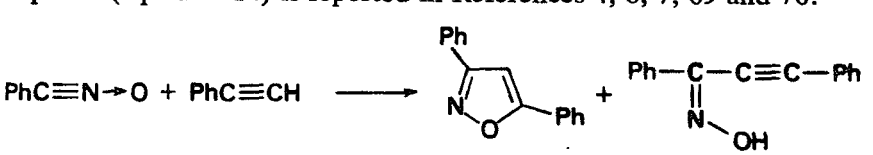
SCHEME 14

As far as regiochemistry is concerned the only known exception to regiospecificity of alkyl- and aryl-monosubstituted and 1,1-disubstituted ethylenes (which give 5-substituted isoxazolines)[4,5,105] is represented by the reaction of styrene with benzonitrile oxide where trace amounts (≈0.5%) of 3,4-diphenyl-2-isoxazoline have been isolated[106]. By contrast, mixtures of regioisomers are as a rule obtained from the reactions of 1,2-disubstituted alkenes[107–113] [indene[101], dihydronaphthalene[101], asymmetrically substituted cyclopentenes[107,108] and cyclobutenes[109,110] (e.g. Scheme 15)].



SCHEME 15

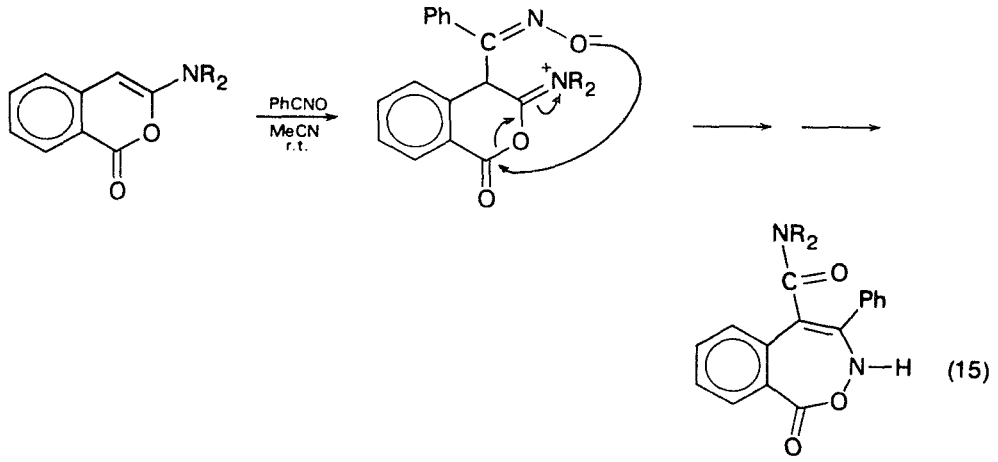
The reactions of monosubstituted alkyl- or aryl-acetylenes give exclusively 5-substituted isoxazoles[4,6,7,114–118] (see also Section VI.C). A detailed discussion concerning the competition between 1,3-addition and cycloaddition for this type of dipolarophiles (equation 14) is reported in References 4, 6, 7, 69 and 70.

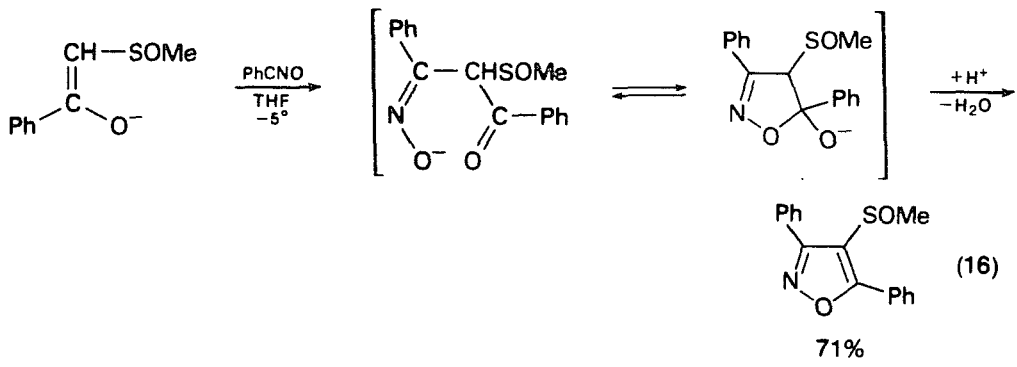


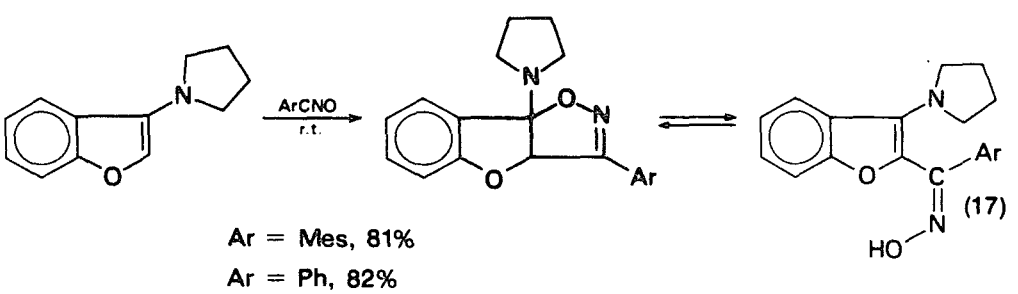
(14)

The LU nitrile oxide controlled reactions of enamine-, enol-ether- and enolate-type compounds always give adducts where the carbon atom of the nitrile oxide is attached to the β position with respect to the most powerful electron-donating group of the dipolarophile[119–130] (equations 15[130], 16[123] and 17[121]). In some instances the possibility of a nonconcerted attack has been advanced.

Regarding regioselectivity, the data reported in Tables 4a and 4b clearly show that the behaviour of moderately electron-poor (e.g. methyl acrylate, $IP_v = 10.72$[135] and acrylonitrile, $IP_v = 10.92$[136]) and strongly electron-poor (e.g. nitroethylene and methyl vinyl sulphone, $IP_v \simeq 11.4$ for both)[137] conjugated monosubstituted alkenes (to give 5-substituted 2-isoxazolines as dominant adducts) is similar[84,110,131–134]. These results are true, in spite of a change from the situation of the former dipolarophiles, in which the two FO interactions are in competition with one another, into the



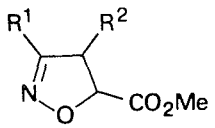




situation of the latter dipolarophiles, which is characterized by $LU_{dipolarophile}$ control (Figure 10). Moreover, a sharp increase in the percentage yield of 4-substituted derivatives is observable on passing to monosubstituted alkynes (cyanoacetylene, $IP_v = 11.60$ eV[138] and methyl propiolate, $IP_v = 11.15$ eV[139]) related to the alkenes mentioned above.

A partial plausible explanation for these findings lies in the following (*i*) $c_\beta > c_\alpha$ in both HO and LU of these dipolarophiles, and $c_C^2\beta_{CC}^2 > c_O^2\beta_{CO}^2$ in both HO and LU of

TABLE 4(a). Ratios of regioisomers from the reactions[a] of nitrile oxides with α,β-unsaturated esters[84,131]



R^2 = H (**65**) (**66**) (**67**) (**68**)

R^2 = Me (**69**) (**70**)

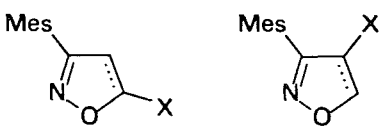
R^2 = Ph (**71**) (**72**)

	R^1						
	H	CN	Me	Ph	Mes	*t*-Bu	$PhSO_2$
65:66	100:0	99:1	95:5	96:4[b]	93.4:6.6	100:0	—
67:68	84:16	66:34	69:31	72:28	28:72	91:9	94:6
69:70	62:38	44.5:55.5	36:64	34:66	27:73	18:82[b]	62:38
71:72	24:76	15:85	30:70	30:70	36:64	22:78	12:88

[a]The reactions of benzonitrile oxide with all the esters studied as well as the reactions of all the nitrile oxides with methyl propiolate were carried out in ether. In the other cases neat dipolarophiles were used as solvent. The reactions were carried out at temperatures in the range 5–80°C. Total yields: **65** + **66** = 72–99%, **67** + **68** = 36–97%, **69** + **70** = 5–93%, **71** + **72** = 52–97%.

[b]The regioisomer ratios were practically independent of reaction temperature (5°C and 80°C).

TABLE 4(b). Ratios of regioisomers from the reactions[a] of mesitonitrile oxide with double and triple bonds conjugated with electron-withdrawing groups[110,132,134]

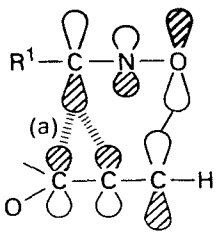


(**73**) (**74**)

Dipolarophile	Ratio **73**:**74**
CH_2=CHCN	>98:2
CH_2=CHCOMe	100:0
CH_2=$CHNO_2$	100:0
CH_2=$CHSO_2Me$	94:6
CH_2=$CHCF_3$	97:3
CH≡CCN	57:43
CH≡CCOMe	80:20
CH≡CCF_3	57:43

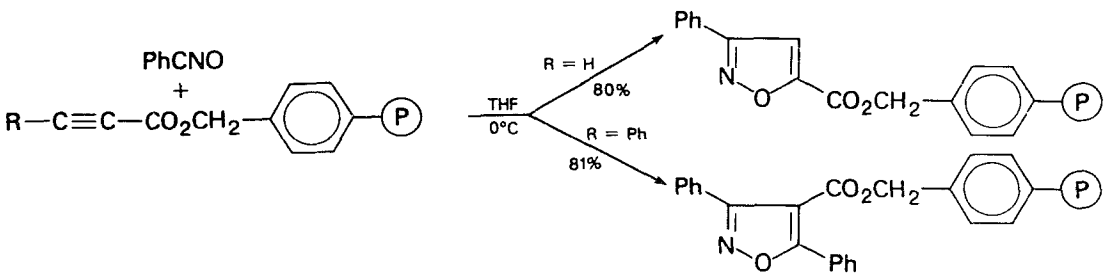
[a]In carbon tetrachloride or benzene.

the dipole, (*ii*) neither the difference between c_β and c_α nor that between $c_C^2\beta_{CC}^2$ and $c_O^2\beta_{CO}^2$ in the HO-dipolarophile and, respectively, in the HO-dipole are large, (*iii*) so, it is no matter which FO interaction is dominant as both FO interactions slightly favour 5-substituted regioisomers, and (*iv*) the secondary orbital interaction (a) depicted in **64**, which favours the 4-substituted product, is important for linear alkynes while it is of little relevance for alkenes[140].



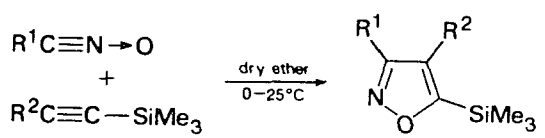
(64)

In contrast with what has been found for the couple methyl acrylate/methyl crotonate (Table 4a) is the observation that benzonitrile oxide reacts with nitroethylene



(P) = cross-linked divinylbenzene-styrene copolymer

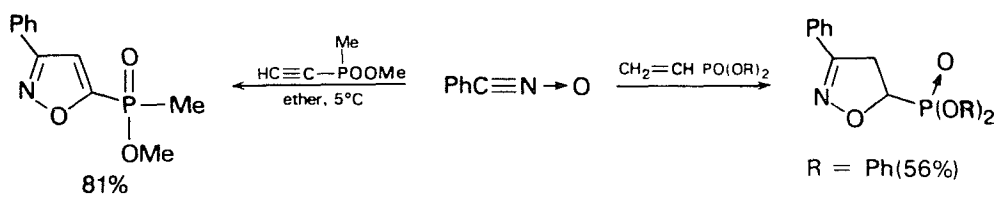
SCHEME 16



R^1 = Mes, R^2 = H or $SiMe_3$ (98%)

R^1 = Me, R^2 = H(69%) or $SiMe_3$ (46%)

R^1 = Ph, R^2 = H (62%) or $SiMe_3$ (44%)



R = Ph(56%)

R = H(88%)

SCHEME 17

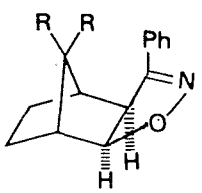
to give only 3-phenyl-5-nitro-2-isoxazoline, whereas with 1-nitropropene the sole 3-phenyl-4-nitro-5-methyl-2-isoxazoline is isolated[133].

Mixtures of regioisomers are often isolated from the reactions of β-substituted α,β-unsaturated esters[131] (see Table 4), ketones[134,141–3], sulphoxides[106], sulphones[106] and with perfluoroalkyl monosubstituted alkynes and alkenes[132,144]. It has also been observed that the regioselectivity of the reactions between nitrile oxides and α,β-unsaturated esters and ketones is influenced by solvent polarity[131,141]. Some triple-bond-conjugated esters bound to insoluble polymers (Scheme 16)[145] have very recently been found to be unexpectedly good dipolarophiles.

Finally some examples of reactions of nitrile oxides with triple bonds bearing silicon group[146] and double and triple bonds bearing phosphorus derivatives[147,148] as substituents have been reported (Scheme 17).

2. Syn–anti *selectivity*[5,*]

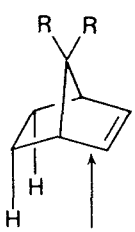
Benzonitrile oxide reacts with 7,7-dimethylnorbornene in a 100% selective manner to give the sole *syn* adduct **75**[149] and again a *syn* adduct is found dominant with norbornadiene[150].



(75)

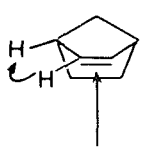
(a) R = H (99%)

(b) R = Me(34%)



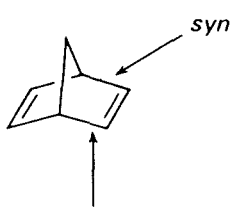
anti

(76)



anti

(77)



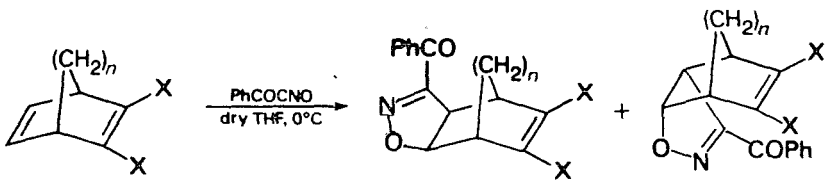
anti

These results cast some doubt both on the steric hindrance by ethano bridge hydrogens to *anti* attack (e.g. **76**) and on the torsional effect between the bridgehead and olefinic hydrogens (e.g. **77**) as dominant factors in a rationalization of the strict *syn* specificity observed for 1,3-dipolar cycloadditions on norbornene derivatives[5]. The nonequivalent orbital extension (see **57**, Section VI.B.1) is an attractive alternative explanation to steric effects.

This type of electronic effect was also invoked to explain the *syn–anti* selectivity of the LU nitrile oxide controlled reactions of compounds **78**[151,152]. In norbornadienes **78a–c** the effect of the methano bridge prevails, while in **78d** and **78e** the dominant conjugative entity was suggested to be the tetrasubstituted double bond with a consequent larger HO extension (higher π-electron density) *anti* to the ethano and propano bridge, respectively, in agreement with experimental results.

Syn–anti ratio values for adducts **79** and **80** have been shown to be dependent on reaction conditions. For instance the ratio **79c**:**80c** decreases with increasing solvent polarity, dropping from a value of 3 in tetrahydrofuran to 0.725 in methanol/water (1:1)[153a]. Moreover the same authors, studying the temperature dependence of this

*In a recent paper the use of an alternative nomenclature has been proposed to describe addition reactions on two diastereotopic faces of a double bond: π-facial stereoselectivity for *syn–anti* selectivity and the symbols z_f and e_f instead of *syn* and *anti*. The z_f (f denotes facial) isomer is the product from the attack of a reactant on the double-bond site of the molecule nearer to the out-of-plane group of highest Cahn–Ingold–Prelog priority scale, e_f is for the other isomer[158].

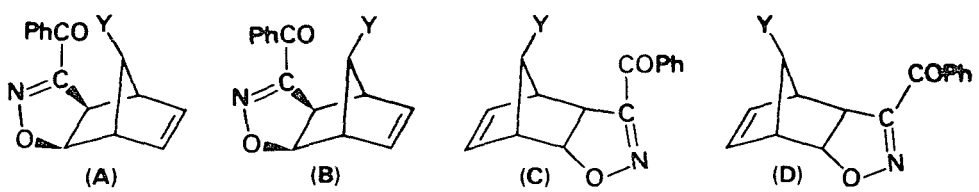


(78) (79) (80)

	79(%)	80(%)	Total yield (%)
(a) X = H, n = 1	81	19	76
(b) X = CN, n = 1	68	32	90
(c) X = CO_2Me, n = 1	75	25	95
(d) X = CO_2Me, n = 2	0	100	98
(e) X = CO_2Me, n = 3	0	100	76

reaction showed that compound **80c** is favoured over **79c** by enthalpic factors albeit disfavoured by entropy, whereas both factors favour **79a** over **80a**[153a]. We reckon, therefore, that an explanation of *syn–anti* selectivity wholly based on orbital interactions is insufficient.

Of relevance is the influence of substituents on the methano bridge of norbornadiene in determining the *syn–anti* ratio of cycloadducts. In Scheme 18 are reported the results of the LU-dipole controlled reactions of benzoylnitrile oxide with norbornadienes substituted at position 7 with electron-withdrawing lone-pair-bearing groups.[153b]. The *anti* methano bridge adducts are always dominant but also worth noting is the ratio between the two isomeric *syn* adducts. In fact, the most hindered of the two possible *syn* attacks is the only or the preferred reaction path chosen by the 1,3-dipole.



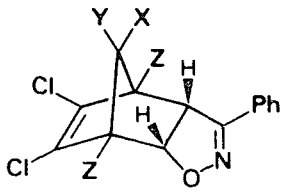
(A) (B) (C) (D)

syn adducts *anti* adducts

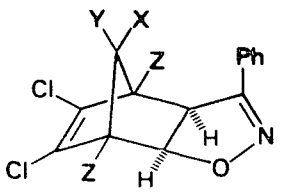
Y	A(%)	B(%)	C(%)	D(%)	Total yield (%)
PhCOO	13	6	41	40	76
t-BuO	23	0	37	40	75
OH	12	0	29	59	66

SCHEME 18

Further examples of dominant *anti* methano bridge addition to norbornadiene systems are found in the HO-dipole controlled reactions of benzonitrile oxide with electron-poor polychloronorbornadienes which give *anti* (**81**) and *syn* (**82**) adducts[154]. The electronic factor which should favour *anti* addition was indicated in the



(81)

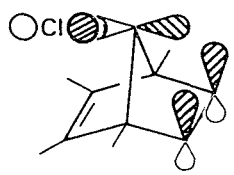


(82)

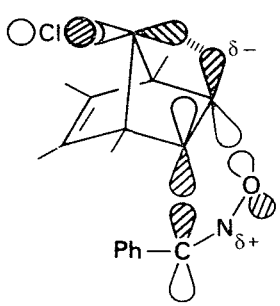
	X	Y	Z	81:82
a	Cl	Cl	Cl	100:0
b	Cl	H	Cl	100:0
c	H	Cl	Cl	80:20
d	H	H	Cl	17:83
e	H	H	H	16.5:83.5

Franck–Neumann $\sigma^*-\pi$ effect[155], which not only decreases *anti* π-electron density (e.g. **83**), but also aids in stabilizing the partial negative charge present on the dipolarophile in the TS (e.g. **84**). Moreover, in 7-substituted 1,2,3,4-polychloronorbornadienes the *syn* attack is also disfavoured by steric effects such as shielding of the *syn* side by the chlorine atom (when X = Y = Cl and X = Cl, Y = H) or by the tilting of the methano bridge towards the reacting double bond (when X = H, Y = Cl) due to repulsion between the 7-chlorine atom and the dichloro-substituted double bond.

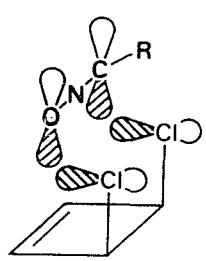
Examples of reactions of 7-azabenzonorbornadienes[156] and benzonorbornadienes[153b] with nitrile oxides have also been reported; the attack occurred only *syn* to the aza and methano bridge[156]. An even more complex picture of effects determining *syn–anti* selectivity is found for other dipolarophiles studied.



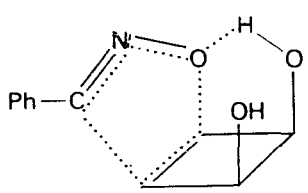
(83)



(84)



(85)



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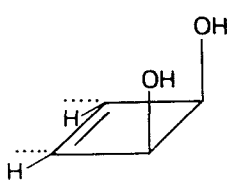
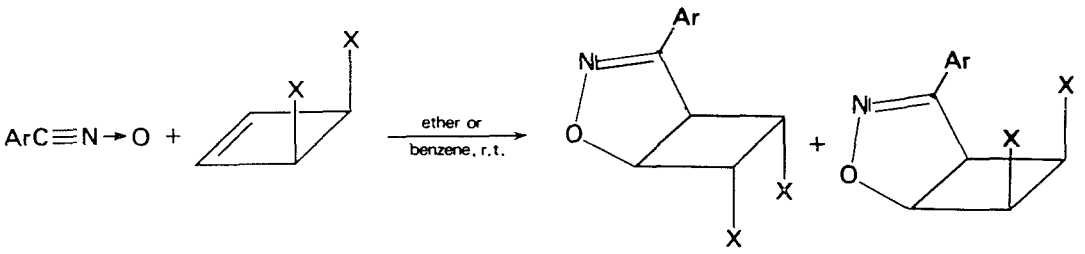


(87)



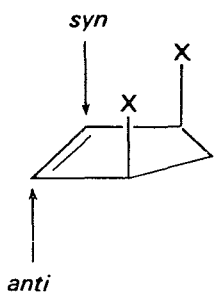
X	Ar = Ph *syn*:*anti*	Ar = Mes *syn*:*anti*	Ar = *p*-$NO_2C_6H_4$ *syn*:*anti*
CO_2Me	5:95	0:100	12:88
Cl	48:52[a]	27.5:72.5	69:31[a]
OAc	90:10	89:11	—
OH	≥95:≤5	89:11[b]	—

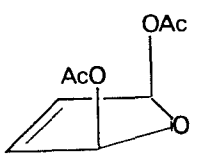
[a]In acetonitrile the following *syn*:*anti* ratios were found: Ph, 71:29; *p*-$NO_2C_6H_4$, 81:19.
[b]In methanol *syn*:*anti* ≈50:50.

SCHEME 19

Thus, the σ^*–π effect together with steric factors, hydrogen bonding (e.g. **86**) and an interaction between LU nitrile oxide and the lone pairs of the substituent (e.g. **85**) were taken into account when rationalizing the formation of *syn* and *anti* adducts in the reactions of *cis*-3,4-disubstituted cyclobutenes with nitrile oxides (Scheme 19)[110,157]. *Syn* attack was highly favoured by the presence of electron-attracting substituents which also bear lone pairs.

In striking contrast with the data of Scheme 19 for cyclobutenes, the *cis*-3,5-disubstituted cyclopentenes react with nitrile oxides to give *anti* adducts as dominant products (Scheme 20)[106].





syn : *anti*[a] = 0 : 100

X	*syn*:*anti*[a]	X	*syn*:*anti*[a]
OH	40:60	AcO	10:90
Br	0:100	MeO	20:80

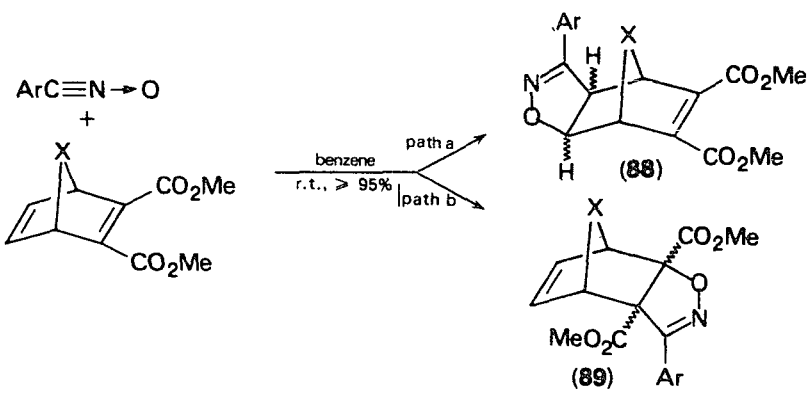
[a]For reactions with benzonitrile oxide in ether at room temperature.

SCHEME 20

In order to explain the contrasting results reported above, structural *ab initio* calculations were carried out which indicated the existence in the molecule of a slight ($\leq 5°$) geometrical distortion of the hydrogens of the double bonds of cyclopentenes, cyclobutenes (e.g. **87**), norbornadiene and norbornene towards the opposite side of the preferred 1,3-dipole attack[95b,158]. Further recent *ab initio* MO studies on energies of transition states led Houk and associates to advance a general rule of stereoselectivity which states: attack of a reagent (1,3-dipole) at an unsatured site occurs such as to minimize antibonding secondary orbital interactions between the critical FO of the reagent and those of the vicinal bonds[158]. However, in spite of the numerous studies on this topic, the interesting *syn–anti* selectivity is far from being satisfactorily understood.

3. *Site selectivity*[159] *and periselectivity*[5]

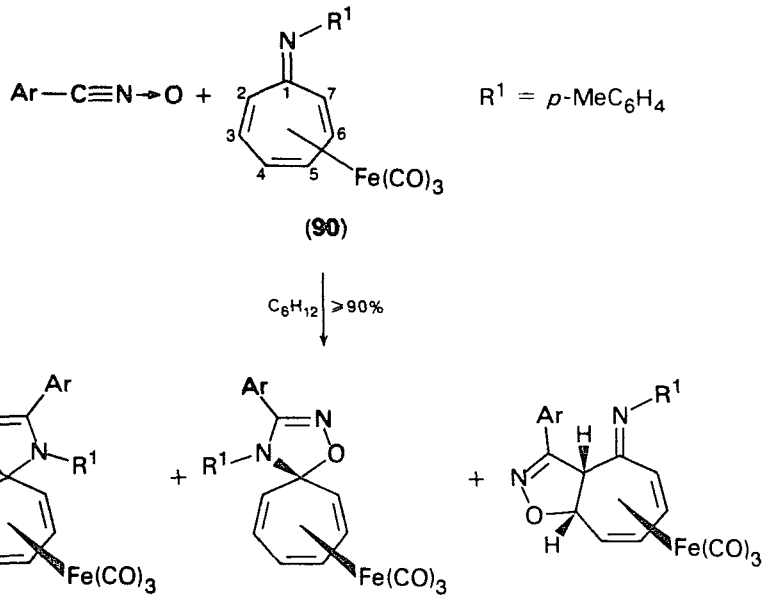
Scheme 21 gathers the salient results of a recent site selectivity study on the reaction of nitrile oxides with norbornadienes[160]. The adducts **88** and **89** for X = O were neither isolated nor detected since they fragmented to the corresponding isoxazole and furan derivatives. The path (a):path (b) ratios found are nicely rationalized on the basis of the FO interaction approach if one considers that HO and LU in norbornadienes are mainly localized on the disubstituted and tetrasubstituted double bond, respectively, and that the attack at the tetrasubstituted double bond is the more hindered. Moreover, one should take into account that $LU_{dipolarophile}$–HO_{dipole} interaction is dominant for X = O, while for X = CH_2 the other interaction prevails. Path a:path b ratio results are dependent on solvent polarity.



	X = O		X = CH_2	
Ar	Path a (%)	Path b (%)	Path a (%)	Path b (%)
Ph	25	75	86.5	13.5
p-$NO_2C_6H_4$	44	56	96	4
Mes	43	57	—	—

SCHEME 21

An unusually high solvent effect on site selectivity was observed in the reaction of 2,6-dichlorobenzonitrile oxide with 8-*p*-tolyl-8-azaheptafulvene–irontricarbonyl (**90**) (Scheme 22)[110]. When the reaction was carried out in cyclohexane the preferred

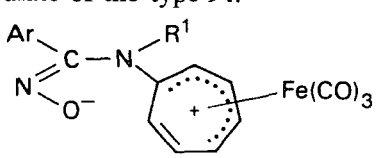


Ar = Ph	≤10	≥90	—
Ar = 2,6-$Cl_2C_6H_3$	3.0	20.5	76.5
Ar = 2,6-$Cl_2C_6H_3$	27.0[a]	69.4[a]	3.6[a]

[a]In MeOH; $\left[\frac{91(\%) + 92(\%)}{93(\%)}\right]_{MeOH} : \left[\frac{91(\%) + 92(\%)}{93(\%)}\right]_{C_6H_{12}} = 87.2$

SCHEME 22

site of attack by the 1,3-dipole was the free 2,3-double bond whereas in methanol the dominant attack resulted at the carbon nitrogen double bond. This finding raises the mechanistically interesting possibility that along the reaction path leading to **91** and **92** there is a dipolar intermediate of the type **94**.

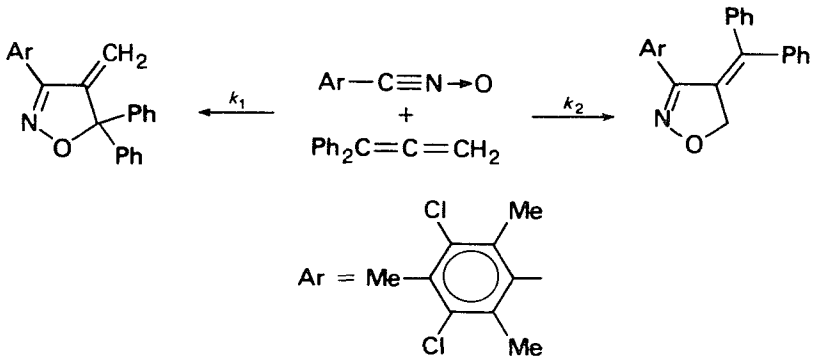


(94)

Another noteworthy aspect of the reactions of Scheme 22 is the site selectivity change induced by the irontricarbonyl group. In fact 8-substituted 8-azaheptafulvenes react with all types of nitrile oxides at the carbon–nitrogen double bond irrespective of the solvent used as reaction medium (see Section VI.D.3). A similar behaviour was observed previously for tropone and tropone–irontricarbonyl[161].

Site selectivity (and regioselectivity) in the reactions of allenes with nitrile oxides has also attracted the interest of researchers[162,163,164a]. The salient data obtained for 1,1-diphenylallene are shown in Scheme 23[163].

The sole examples of [6 + 4]cycloadditions of nitrile oxides until now discovered are the perispecific reaction of 6-dimethylaminofulvene with benzonitrile oxide to give

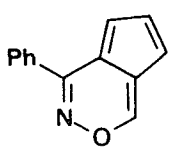


	$k_1{}^a$	$E_a{}^b$	$\Delta S^{\neq c}$	$k_2{}^a$	$E_a{}^b$	$\Delta S^{\neq c}$
CCl_4	9.4	63.1	−129.6	4.36	77.3	− 92.0
CCl_4/EtOH(1.4)	11.5	56.8	−142.1	7.30	64.3	−125.4

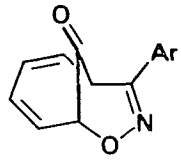
[a] l mol^{-1} s^{-1} × 10^4 at 70°C.
[b] kJ mol^{-1}.
[c] J mol^{-1} K^{-1}.

SCHEME 23

95a as final adduct[164b] and the reactions of arylnitrile oxides with tropone to give **95b** as minor product of a reaction in which [4 + 2]adducts are dominant[161].



(95a)

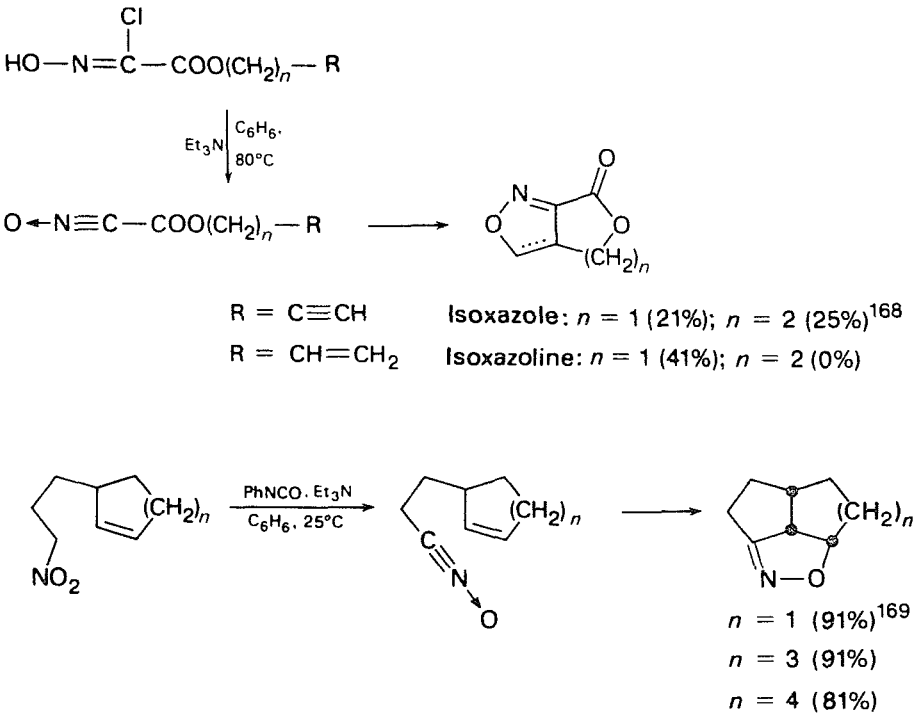


(95b)

The [8 + 4]adducts isolated from the reactions of nitrile oxides with 8-azaheptafulvenes (see Section VI.D.3) are most seemingly formed through a zwitterionic intermediate; alternatively they may be the isomerization products of [4 + 2] primary adducts[110].

4. Intramolecular cycloadditions

Intramolecular cycloadditions of nitrile oxides to carbon–carbon double and triple bonds (Scheme 24) proceed generally easily even when the reaction will afford compounds characterized by considerable geometrical strain[165–169]. This reaction is very useful in synthesis (see Section VI.C) owing to its regiospecificity and stereospecificity. Electronic effects are not controlling and are generally outweighed by strain factors. Obviously, by increasing the distance between the reacting groups there is a parallel decrease in the propensity to intramolecular reaction with a consequent overall enhancement of the intermolecular type of cycloaddition[165].



SCHEME 24

5. Solvent effects, activation parameters and Hammett ρ values

The solvent polarity effect on reaction rates [e.g. mesitonitrile oxide plus acrylonitrile, $k^{35°}$ (l mol^{-1} s^{-1}) × 10^5:79(CCl_4), 78(C_6D_6), 87(CD_3COCD_3) and 89(DMSO-d_6)][170], the Hammett ρ values [e.g. ρ = +0.36 for the reaction of *para*-substituted benzonitrile oxides with acrylonitrile][35] and the activation parameters [e.g. mesitonitrile oxide plus *Z*-cyclooctene, E_a = 77.75 kJ mol^{-1} and $\Delta S^{\neq}$ = −69.4 J K^{-1} mol^{-1}][92] reported in papers of the last decade, have confirmed the previously well-known trends for these parameters. A discussion of ρ values on the basis of FO interactions is found in References 5 and 6[171].

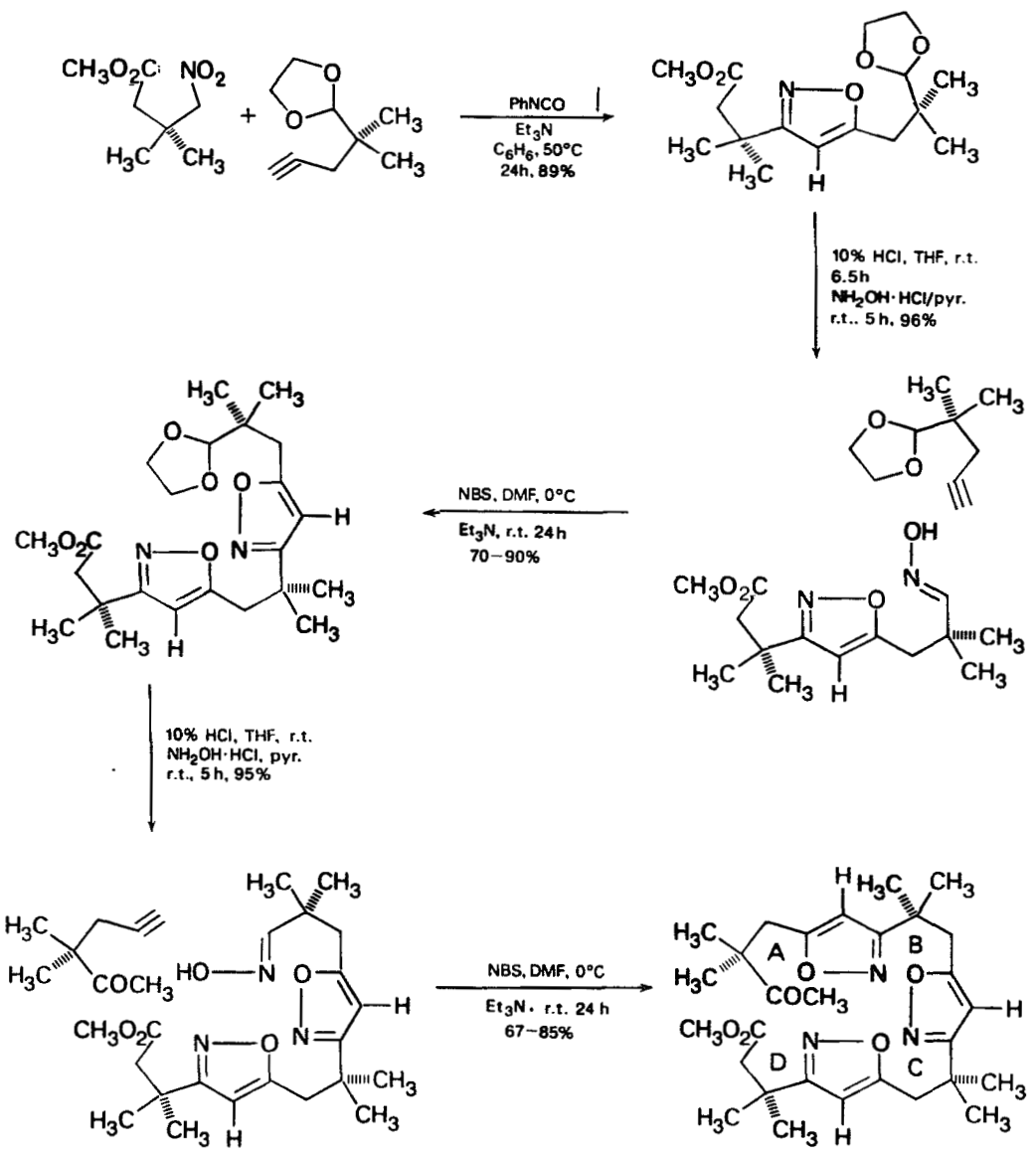
C. Nitrile Oxides as Synthons for Natural Products

The application of 1,3-dipoles to the synthesis of natural products has been a very recent development in this topic with particular emphasis on the use of nitrones[172] and nitrile oxides.

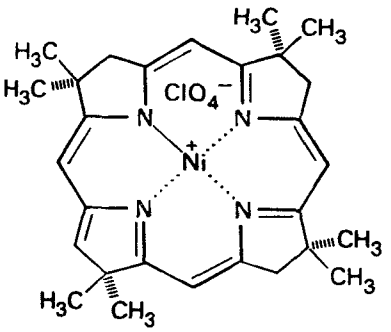
An outstanding application of the latter class by Stevens and coworkers led to the preparation of several polyisoxazoles, e.g. **96** (Scheme 25), which are latent synthons for the preparation of corrinoid compounds. In fact the authors have achieved the multistep synthesis, from **96**, of metal complexes **97** and **98** of octamethylcorphin and octamethylcorrin, respectively[173].

The preparation of compound **96**, which results from the so-called 'counterclockwise' synthetic scheme **99**, is an excellent example of the versatility and potential of this class of 1,3-dipoles as synthons, especially if one considers (*i*) the

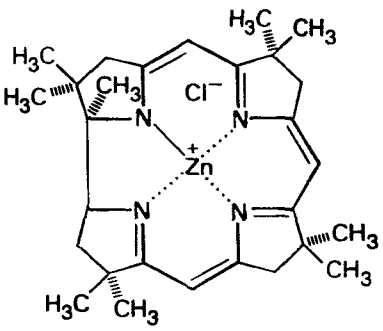
reaction conditions (in which nitrile oxides are obtained both from nitroalkanes and oximes) which are so mild that functional groups like esters, ketones and nitriles perfectly withstand the chemical operations, (*ii*) the still high reactivity of these heavily substituted nitrile oxides as a consequence, at least in part, of a reduced dimerization rate, (*iii*) the strict regiospecificity found in the reactions with monosubstituted acetylenes to give 3,5-disubstituted isoxazole systems (due, at least in part, to the bulky groups on both nitrile oxides and dipolarophiles) and (*iv*) the higher reactivity of the carbon–carbon triple bond compared to those of cyano and carbonyl groups.



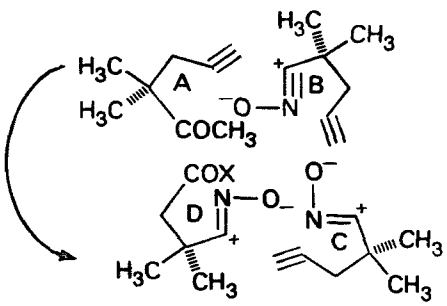
(96)



(97)



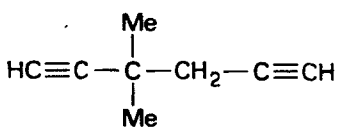
(98)



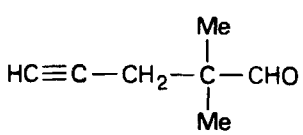
(99)

SCHEME 25. Reproduced by permission of Pergamon Press Ltd. from R. V. Stevens, *Tetrahedron*, **32**, 1599 (1976).

Two examples of lack of selectivity, noted by Stevens and coworkers, were the equal reactivity of the two triple bonds with different steric environments present in **100**[174] and the similar activity of the triple bond and the unactivated aldehyde group in **101**[173].



(100)

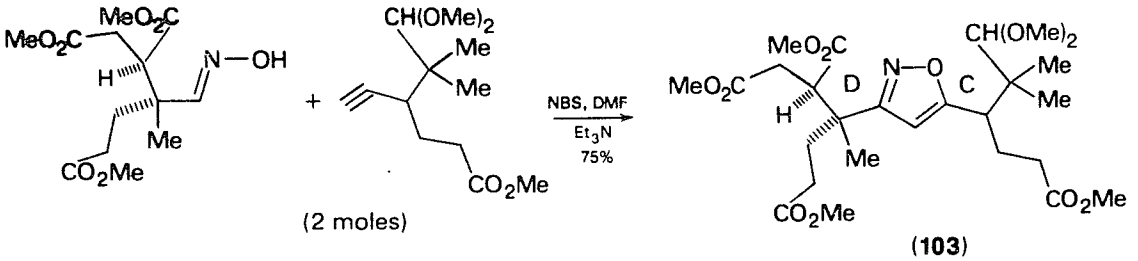


(101)

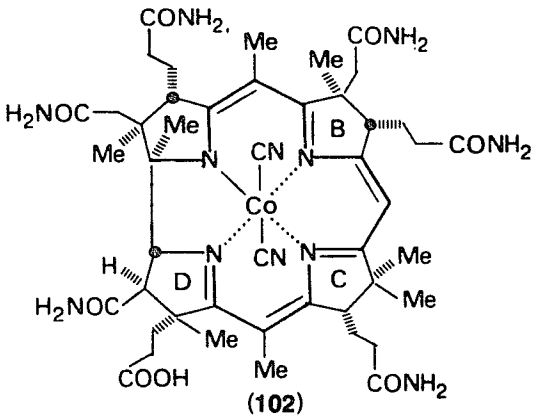
Success in the total synthesis of cobyric acid **102** via nitrile oxides appears now at hand considering that the cited authors have been able to prepare a latent form **103** of the 'southern half' of that vitamin (equation 18)[175].

Reactions between acetylenes and nitrile oxides to give isoxazoles as source of masked functionalities, e.g. β-enamino ketones, β-diketones and α,β-unsaturated ketones, have also been used for the synthesis of prostaglandin analogues[176] and of natural hentriacontane-14,16-dione[177]. In this latter case $Me-(CH_2)_{14}-CNO$ was reacted with $Me-(CH_2)_{12}-C\equiv CH$ to give only the corresponding 3,5-disubstituted isoxazole in 35% yield.

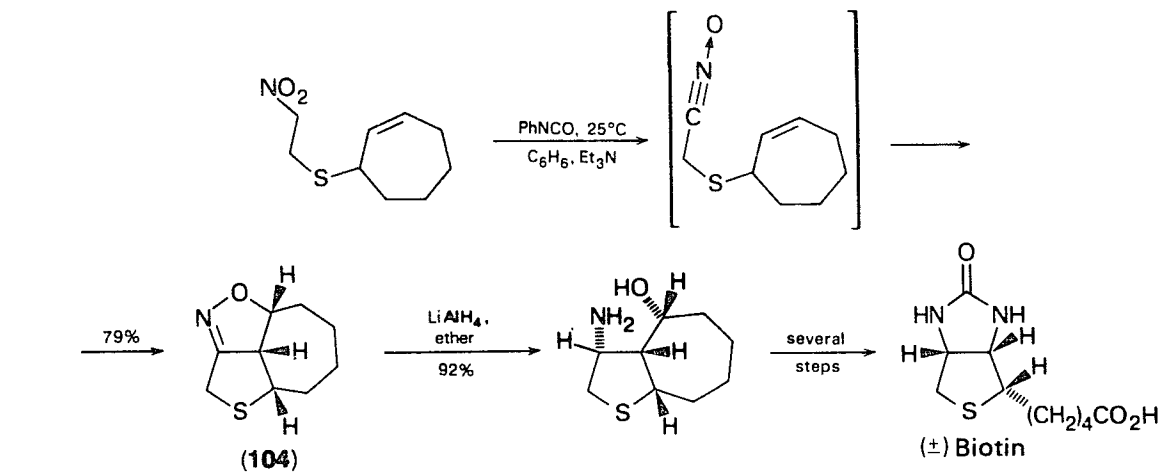
Intramolecular cycloaddition to give isoxazoline **104**[178] and furazan *N*-oxide **105b** (two isomers)[179] serve admirably to construct suitable skeletons for facile syntheses of (±)biotin (Scheme 26).



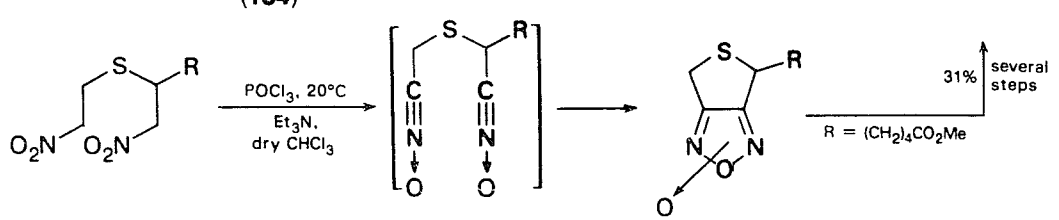
(103)



(102) (18)



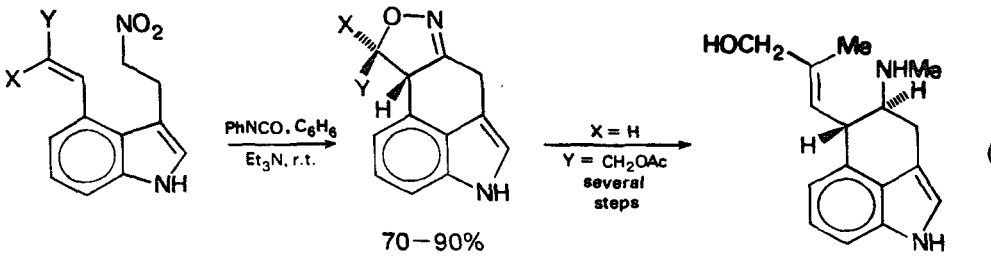
(104)



(**105a**) R = H (10%)

(**105b**) R = $(CH_2)_4CO_2Me$ (81%)

SCHEME 26



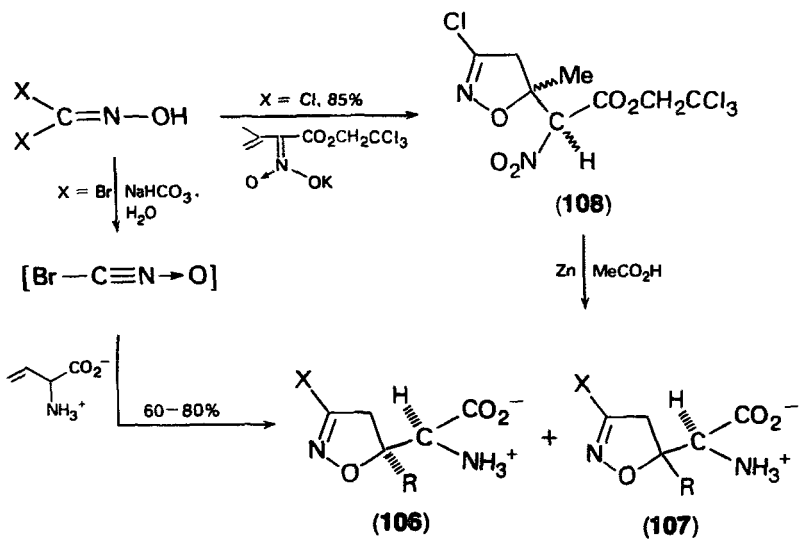
(19)

X = Y = H

X = OMe; Y = H

X = H; Y = CH_2OAc

Other outstanding examples of reactive capacities of nitrile oxides are well represented by the synthesis of numerous other compounds such as the antibiotics (−)-vermiculine[180] and (±)-thienamycin[181], ergot alkaloid chanoclavin I (equation 19)[182], analogues of glutarimide antibiotics[183] and a fungal metabolite of *Streptomyces sviceus* **106a** (with antitumoural activity) (Scheme 27)[184,185].



(a) X = Cl, R = H

(b) X = Br, R = H

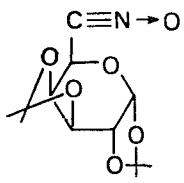
(c) X = Cl, R = Me

SCHEME 27

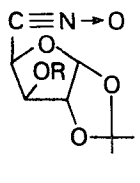
Chloronitrile oxide failed to react with vinylglycine itself to give amino acids **106a** and **107a**[184]. By contrast a mixture of isoxazolinylglycines **106b** and **107b** (**106b**:**107b** ≈ 1:3) was obtained in good yields by cycloaddition of the highly reactive (70% yield with styrene) bromonitrile oxide with vinylglycine[185]. The synthesis of **106c** and **107c** was achieved from the sluggish reactive chloronitrile oxide (only 6% yield in the reaction with styrene; most probably as a consequence of the easy dimerization of the dipole)

with an α,β-unsaturated nitronate in water salt to give **108** which was easily reduced to give a mixture of the diastereoisomers **106c** and **107c**[184].

Tronchet and coworkers[186] and other groups[187] have investigated the use of nitrile oxides for the synthesis of analogues of natural *C*-glycosylnucleosides many of which show antiviral and antitumoural activity. The synthesis of such compounds was achieved following two pathways: (*i*) by cycloaddition of aromatic nitrile oxides to double and triple bonds bearing the glycosyl group and (*ii*) by reaction of glycosylnitrile oxides with appropriate alkenes and alkynes. Glycosylnitrile oxides **109–115** were prepared according to the usual transformations aldehyde → oxime →

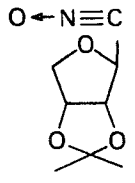


(109)

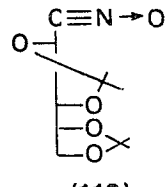


(110)

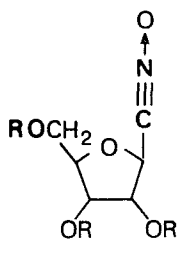
R = Me, CH_2Ph



(111)

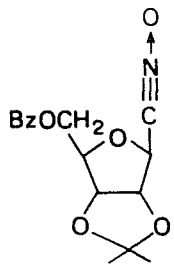


(112)

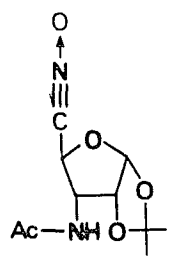


(113)

R = Ac, Bz



(114)



(115)

hydroxamoyl chloride → treatment with base; there resulted unstable compounds which dimerized to furazan *N*-oxides in the absence of dipolarophiles or nucleophiles. They present no relevant peculiarity as regards dipolarophilic reactivity.

Finally 1,3-dipolar cycloaddition of nitrile oxides was profitably used in the synthesis of heterocyclic derivatives of steroids[188].

Several procedures for the preparation of semisynthetic penicillins have been patented which have made use of nitrile oxides; however, the subject is outside the scope of the review and will not be covered.

D. Reactions with Hetero Double and Triple Bonds

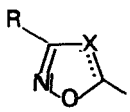
1. General

The following scale of reactivity of hetero double bonds with nitrile oxides has been found: carbon–sulphur > carbon–nitrogen > carbon–oxygen. The carbon–sulphur double bond is an excellent dipolarophile, the carbon–nitrogen double bond still compares favourably with the carbon–carbon double bond while the carbon–oxygen

double bond and carbon–nitrogen triple bonds are poor dipolarophiles characterized by much lower reaction rates[4].

By way of illustration, benzylidenemethylamine reacts with benzonitrile oxide four times faster than styrene whose reactivity is 479 times that of benzaldehyde. Moreover, phenylacetylene reacts with the same 1,3-dipole 49 times faster than benzonitrile and methyl propiolate is ten times more reactive than methyl cyanoformate[79].

The reaction rates of all types of heterodipolarophiles with nitrile oxides are, as a rule, enhanced by conjugating and electron-attracting substituents as expected for HO-dipole controlled reactions. Also BF_3 is an efficient catalyst[4]. These reactions are generally regiospecific and give adducts of type **116**.



(116)

HO

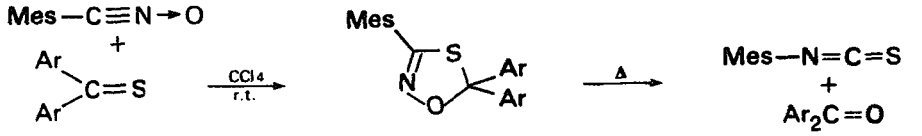
LU

X = N, O, S

A key factor which explains the sequence of dipolarophilic activity as well as the regioselectivity found for hetero multiple bonds was indicated by Huisgen[68] in the 'maximum gain in σ-bond energy of the new σ bonds'. In FO terms the reactivity and regioselectivity are well rationalized by equations of the type (11) and (12). In particular, at a distance between the interacting centres higher than 1.75 Å the resonance integral values are in the order $\beta_{CC} > \beta_{CN} > \beta_{CO} > \beta_{NO} > \beta_{OO}$.

2. *Carbon–sulphur double bond*

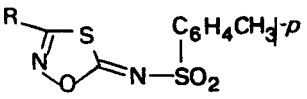
Nitrile oxides react very easily with carbon–sulphur double bonds to give high yields of 1,4,2-oxathiazoles which spontaneously or by heating decompose to isothiocyanates and carbonyl compounds[4] [equation (20); Hammett $\rho = 1.02$; Ar = Ph, k(25°C, CCl_4,



(20)

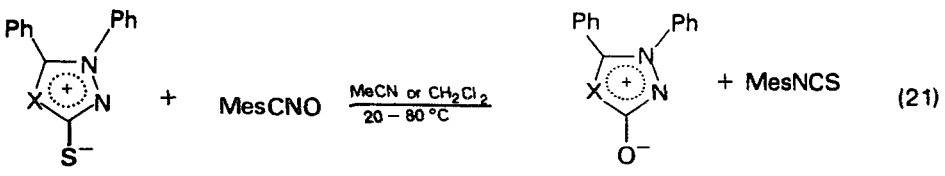
1 $mol^{-1}\,s^{-1}$) = 20.6, E_a = 33.0 kJ mol^{-1}, $\Delta S^{\neq} = -116.2$ J $mol^{-1}\,K^{-1}$; Ar = Ph, k(25°C) = 4.89(CH_2Cl_2), 9.05(MeCN) and 17.8(EtOH)][189]. Further examples reported recently concern cyanothioformamides[190], trithiocarbonate *S,S*-dioxides[191], sulphonyl isothiocyanates (to give good yields of adducts **117**)[192], thiohydrazides, thioamides and azolium thiolates[193,226]. This reaction sometimes represents an elegant method of synthesis of carbonyl derivatives from thiocarbonyl analogues as shown by the synthesis of **119** from **118** (equation 21)[193].

Benzonitrile oxide reacts smoothly and stereospecifically with diaryl sulphines to give in all cases studied a single 1,4,2-oxathiazole-4-oxide derivative (**120**)[194]. With thiofluorenone *S*-oxide a mixture of two regioisomers **121** and **122** was obtained in 75% yield. Unexpectedly, the 'wrong' isomer **122** was the dominant product (ratio **122**:**121** ≃ 11).



(117)

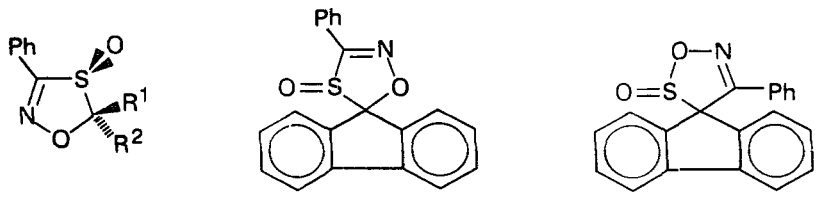
R = Me, *t*-Bu, CO_2Et, Ph, Mes



(118) (119)

X = O (63%)

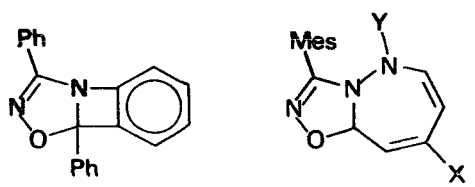
X = S (97%)



(120) (121) (122)

3. *Carbon–nitrogen double bond*

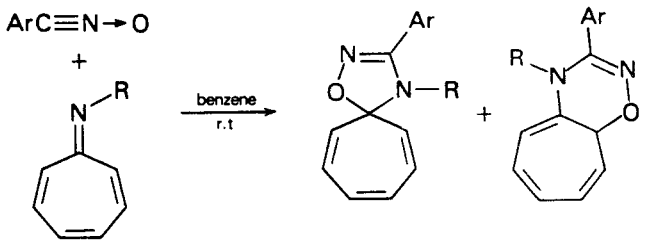
The well-known high reactivity of azomethines with nitrile oxides has been further confirmed[195] and the dipolarophilic reactivity of other types of carbon–nitrogen double bond has been documented by several reactions performed in the last decade[196–209]. Benzonitrile oxide reacts smoothly with a benzazete derivative (at −30°C) to give the unstable adduct **123** (≥65%)[197] and shows site-specific attack at the carbon–nitrogen double bond of 1,4-diaryl-1-aza-1,3-butadienes[198]. Site-specific were also the reactions of mesitonitrile oxide with 1,2-diazepines to give adducts **124** in good yields[199] and of aromatic nitrile oxides with 8-azaheptafulvenes (**125**) affording in good yields adducts **126** and **127** (equation 22)[110]. Compounds **126** and **127**



(123) (124)

X = H, Y = CO_2Et

X = Me, Y = CO_2Et, COPh



(22)

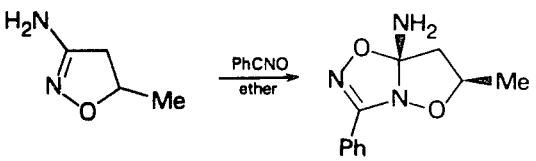
(125) (126) (127)

Ar	R	Yield %	126	Ratio	127
Ph	*p*-MeC_6H_4	91	≥95[a]		≤5
Ph	Me	47	33		67
2,6-$Cl_2C_6H_3$	*p*-MeC_6H_4	57	≤5		≥95

[a]The **126:127** ratios are for solutions in $CDCl_3$.

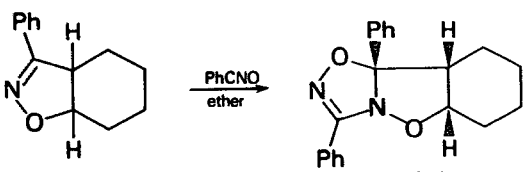
interconvert readily into each other at room temperature and the equilibrium is dependent on solvent polarity[110].

While oximes are poor dipolarophiles[4,200], although their reactivity is enhanced by BF_3 catalysis[4], the oxime-like double bond of 2-isoxazolines is a fairly good dipolarophile[97,99,201–204] and its reactivity is increased by electron-donor substituents at position 3 (equation 23)[202] or when the heterocycle is condensed at positions 4 and 5 with a carbocyclic ring (equation 24)[201]. Noteworthy also is the activation on the *syn* face of the isoxazoline **128** by the unsubstituted carbamate group, which was attributed to a hydrogen bond between the nitrile oxide oxygen and the NH hydrogen in the TS (equation 25)[204].



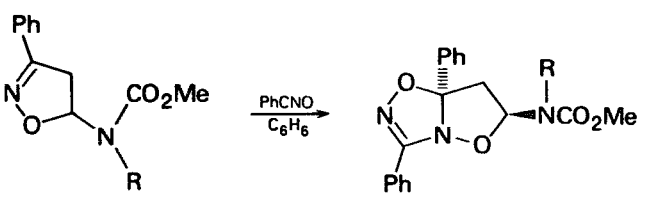
80%

(23)



53%

(24)



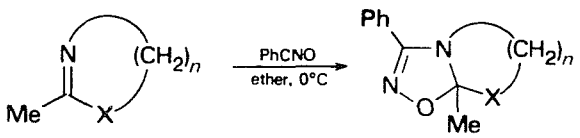
(128)

R = Me, 0%

R = H, 66%

(25)

Other types of reactive carbon–nitrogen double bonds have been found in 2-pyrazolines[205], in the enol form of urazoles[206], in amidoximes[207] and in cyclic imidic esters and amidines (e.g. adducts **129**) (equation 26)[207].



(26)

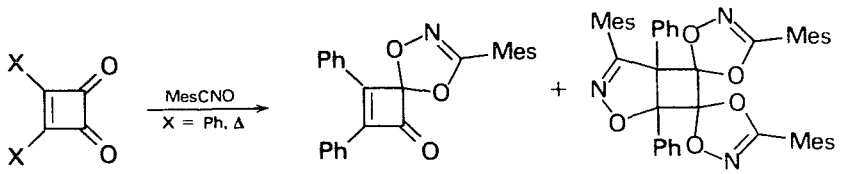
(**129**)

n	*X*	Yield (%)
2	O	87
3	O	26
3	NMe	32

Phenyl isocyanate reacted with the stable mesitonitrile oxide to give after 15 months at 20°C a 76% yield of 1,2,4-oxadiazolin-5-one derivative[195]. Finally, a BF_3-promoted reaction of aromatic nitrile oxides with 1,3,5-triazine has been reported recently[209].

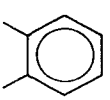
4. Carbon–oxygen double bond

The carbon–oxygen double bond is in general a very sluggish dipolarophile towards nitrile oxides[4]. However, there are examples of competition between carbon–carbon and carbon–oxygen double bonds as found for α-azidovinyl ketones[210], for a nonconjugated aldehyde (see Section VI.C) and for the very slightly reactive cyclobutenediones **130** (equation 27)[211].



(**130**) 25% 3%

X = Me, Ph, Cl,

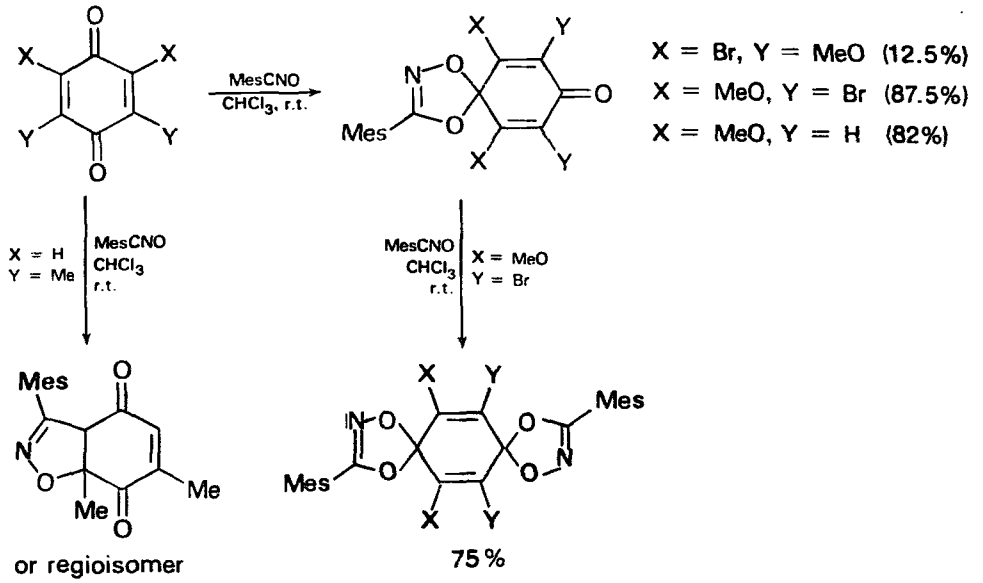


(27)

Moreover site-specific attacks of mesitonitrile oxide on carbon–oxygen double bonds have been found for tetrasubstituted (e.g. chloranil and iodanil) and 2,6- and 2,5-disubstituted benzoquinones (Scheme 28)[212]. The only exception was found for 2,5- and 2,6-dimethyl derivatives where only the product derived from the attack of the nitrile oxide on the carbon–carbon double bond was detected (Scheme 28)[212].

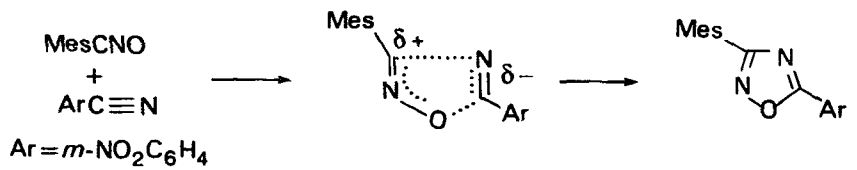
5. Carbon–nitrogen triple bond

Aromatic nitriles have long been known to show some dipolarophilic activity towards nitrile oxides[4,195]. A kinetic study[213] of the reaction of mesitonitrile oxide with benzonitriles (equation 28) has revealed that the cycloaddition is characterized by a ρ



SCHEME 28

value of +1.32 for derivatives with electron-withdrawing substituents and a ρ of +0.43 for electron-donating substituents. This result is in agreement with a HO-dipole controlled cycloaddition.

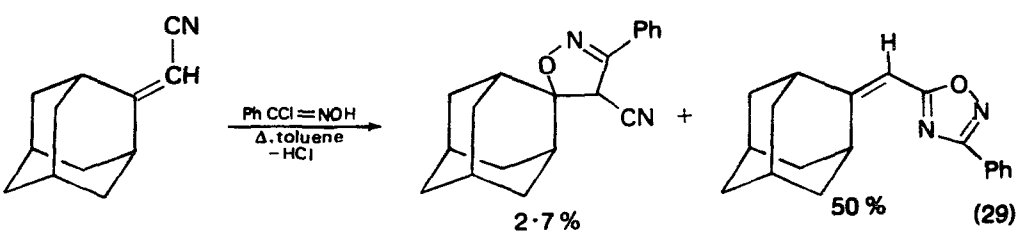


(28)

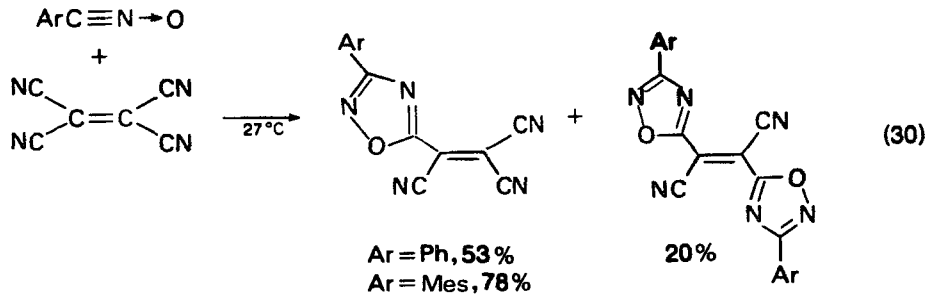
Solvent	k(l mol^{-1} s^{-1})[a]	E_a(kJ mol^{-1})	S(J mol^{-1} K^{-1})
CCl_4	209×10^{-5}	69.8	−100.3
$MeNO_2$	12.6×10^{-5}	75.2	−108.7

[a]At 70°C.

Examples of reactions where the carbon–nitrogen triple bond competes favourably with a carbon–carbon double bond[214–216] are shown in equations (29)[214] and (30)[215].



(29)

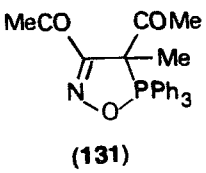


(30)

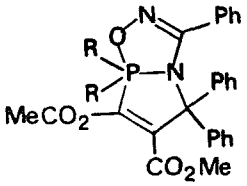
Aliphatic nitriles have been reported to add to nitrile oxides only when bearing electron withdrawing substituents or upon Lewis acid catalysis[4]. The use of acetonitrile as solvent for nitrile oxide cycloadditions led casually to the discovery that simple aliphatic nitriles also react, albeit very slowly, with nitrile oxides[33,141,157]. A kinetic study of this reaction has been published recently[217].

6. *Miscellaneous*

The reactivity of nitrile oxides has been tested on molecules with double bonds such as C=P[218], P=N[219] and S=O[220] with production of the respective adducts **131**, **132** and **133**.

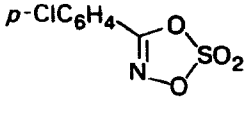


(131)



(132)

R = Me, Ph



(133)

VII. REACTION OF NITRILE OXIDES WITH OXYGEN, NITROGEN AND CARBON NUCLEOPHILES

A. General

A previous chapter of a volume in this series[3] deals in detail with the addition of nucleophiles to nitrile oxides and the subject was also reviewed in 1971 in a book[4].

The reactions of nucleophiles with nitrile oxides occur exclusively at the carbon atom of the 1,3-dipole. From a structural point of view it is of interest to note that all the additions studied were kinetically controlled, 100% stereoselective, leading to single *Z* isomers even when this isomer was the thermodynamically less stable product.

The reaction of fulminic acid with OH^- has been studied by *ab initio* methods (4-31G basis set) determining the potential energy hypersurface (Figure 11)[221]. The calculations have shown that formation of one of the two geometrical isomers is predetermined by a preferential bending of the oxygen of the 1,3-dipole in the transition state towards the incoming nucleophile. The authors have claimed that a key factor which determines the stereochemistry of the easy bending of fulminic acid

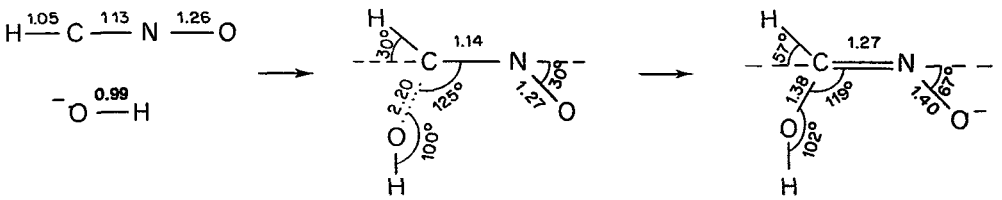
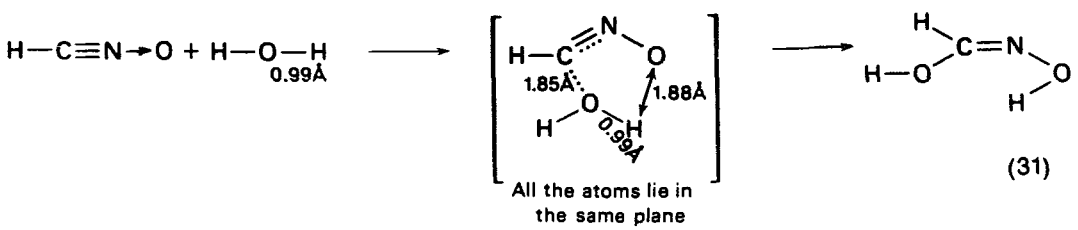


FIGURE 11. Theoretical structures (4-31G SCF) for reactants, transition state and product for the fulminic acid plus OH^- reaction. The TS is 136 kJ higher in energy than an initial HO · · · HCNO complex[221].

approaching the TS is the preference of the forming lone pair to develop *trans* to the attacking nucleophile. Moreover, comparing their results with *ab initio* calculations concerning transition states in 1,3-dipolar cycloadditions, they put in evidence the surprisingly similar geometries of the activated complexes of the two reactions. They have outlined in particular that the *E* (*trans*) bending observed in the 1,3-dipole (*i*) occurs very early in the reaction coordinate. (*ii*) it is the result of C···nucleophile (or dipolarophile) bonding and, (*iii*) most important from a reaction mechanism point of view, there is no need of any bonding between the oxygen end of the 1,3-dipole and the nucleophile (or dipolarophile) at this reaction stage.

On the basis of theoretical calculations (*ab initio*, STO-3G basis set) it has been shown by the same group that a similar mechanism governs the reaction of acetonitrile oxide and formonitrile oxide with water[221]. It has also been predicted that as the transition state **134** is being reached (equation 31), the proton shift from one oxygen to the other occurs without an energy barrier. As there are no intermediates on the reaction pathway the authors classified the process a $[_{\pi}4 + _{\sigma}2]$ concerted but asynchronous addition[221].



All the atoms lie in the same plane

(134)

(31)

B. Reaction with Water

Nitrile oxides react with water to give hydroxamic acids, RCONHOH. It was found by Hegarty and coworkers[34,35] that below pH ca. 8 the reaction was slow (R = *p*-$MeOC_6H_4$, $t_{1/2}$ > 100 min) and pH-independent as expected for H_2O as nucleophile.

For pH ≥ 9.5 the nucleophilic species was OH^- as proved by the proportionality of log k_{obs} versus pH in the region. In Figure 12 is shown the pH–rate profile for the conversion of *p*-methoxybenzonitrile oxide into the corresponding benzohydroxamic acid. For the arylnitrile oxides examined, both the reactivities with H_2O and OH^- are only slightly enhanced by electron-withdrawing substituents, as indicated by the ρ values found which were +0.80 and +0.57 for OH^- and H_2O attacks, respectively. In Table 5 are reported the rate constants for the hydrolysis of arylnitrile oxides in various conditions.

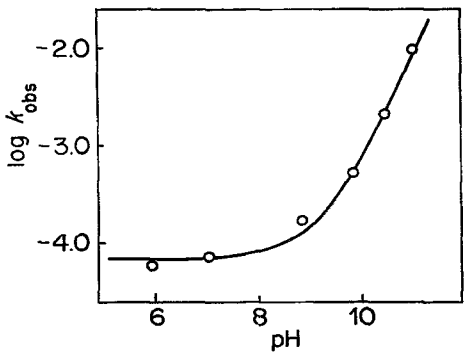


FIGURE 12. Plot of $\log k_{obs}$ versus pH for the hydrolysis of *p*-methoxybenzonitrile oxide in water at 30°C. Reproduced by permission of the Royal Society of Chemistry from K. J. Digman, A. F. Hegarty and P. L. Quain, *J. Chem. Soc., Perkin Trans. 2*, 1457 (1977).

TABLE 5. Observed rate constants for the hydrolysis of benzonitrile oxides in water[35]

Substituent	$10^4 k_{H2O}(s^{-1})$ (at pH 4.65 and 61°C)	$10^3 k_{obs}(s^{-1})$ (at pH 11.15 and 25°C)
p-MeO	2.25	4.89
H	3.10	7.37
p-Cl	4.52	11.8
m-Cl	4.98	14.4
m-NO_2	7.83	40.7
p-NO_2	8.98	33.2
o-Cl	1.45	—

The finding, in an acid-catalysed hydrolysis experiment, that the logarithm of the rate of hydrolysis is inversely proportional to pH over the range1.0–0.0, was claimed to represent the first good evidence for the existence of the nitrilium ion species **135** in the repeatedly advanced mechanism for the reaction leading to hydroxamic acid (equation 32)[35].

$$RC{\equiv}N{\rightarrow}O \xrightleftharpoons{+H^+} R{-}C{\equiv}\overset{+}{N}{-}OH \xrightarrow{H_2O} RCONHOH \qquad (32)$$

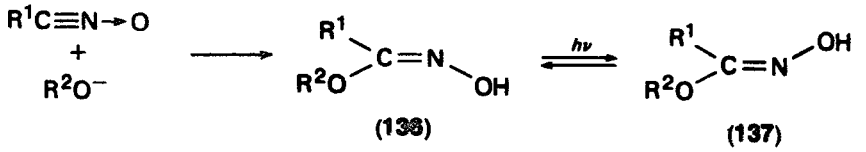
(135)

A kinetic experiment on *p*-nitrobenzonitrile oxide has revealed also the existence of a general-base-catalysed hydration of nitrile oxides to hydroxamic acid by *N*-ethylmorpholine ($k = 1.32 \times 10^{-2}$ l mol^{-1} s^{-1} at 25°C)[34].

C. Reaction with Alkoxides and Acetate Ions

The reaction of nitrile oxides with sodium alkoxides in absolute alcohol allowed the isolation of compound **136** to which the *Z* configuration was assigned and which

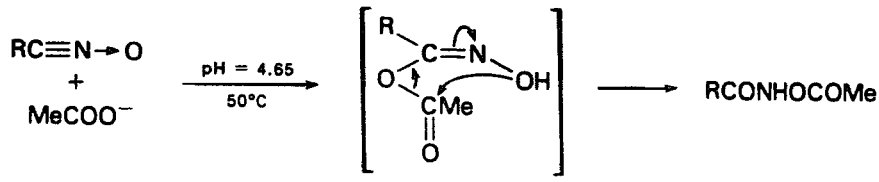
represents a fixed enolic model of hydroxamic acid. Irradiation of **136** at 70°C for 2 h in benzene caused isomerization to the *E* isomer **137** (equation 33)[35].



(33)

(138) **(137)**

A kinetic experiment with *p*-nitrobenzonitrile oxide and sodium ethoxide showed that the reaction rate was second order, first order each in ethoxide ion and nitrile oxide. A second-order rate constant and a ρ value of +0.75 close to that for OH^- was also found for the reaction of nitrile oxides with acetate ion which gives **139** through the not isolated **138** (equation 34)[35].

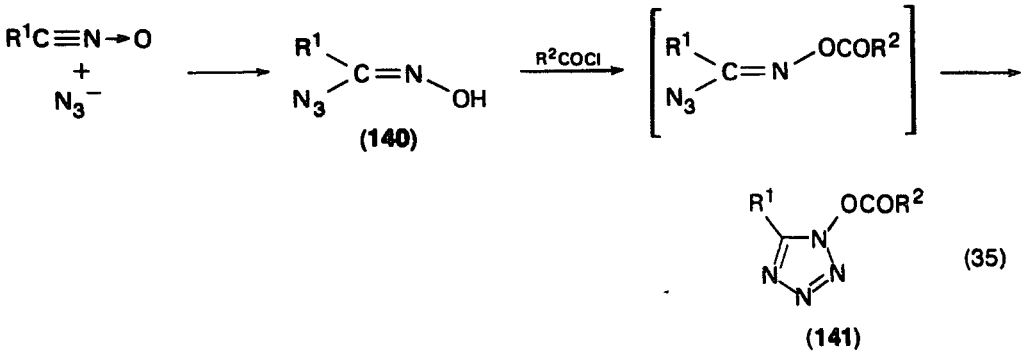


(34)

(138) **(139)**

D. Reaction with Azide Ions

This long-known reaction[3,4,222] has been recently reconsidered by Hegarty[35] who attributed at the final product **140** the *Z* configuration. *Z*-Azidoximes, which are generally stable compounds, can be readily converted into tetrazoles **141** by action of acyl chlorides (equation 35)[223].

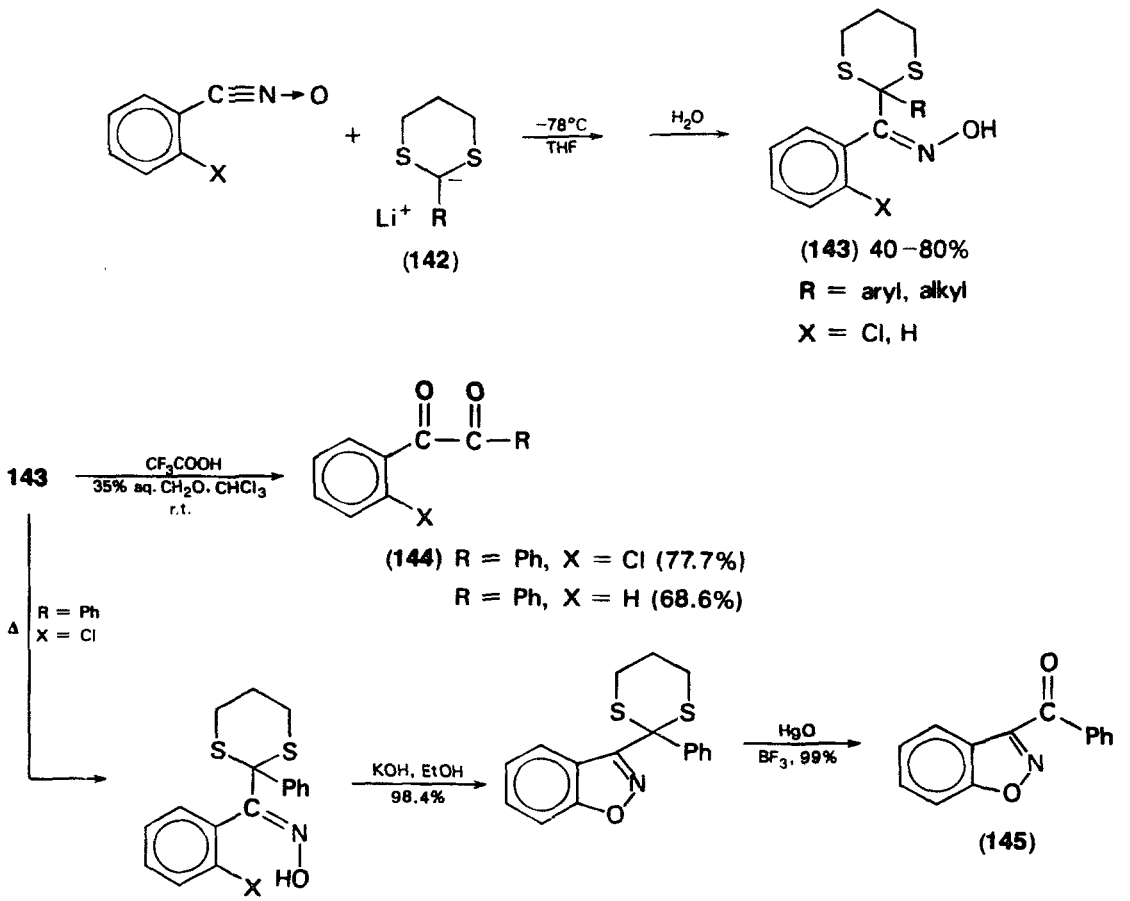


(35)

(140) **(141)**

E. Reaction with Carbanions

Numerous literature data regarding reactions of nitrile oxides or hydroxamoyl chlorides with Grignard compounds and acetylide ions have been previously reviewed[3,4]. The reaction with hydroxamoyl chlorides proceeds, most probably, through the preliminary formation of nitrile oxides which then undergo attack by excess nucleophile. Formation of acetylenic oximes was obtained both by reaction of hydroxamoyl chlorides with acetylenic Grignard reagents (sole product) and directly from nitrile oxides and acetylenic compounds (in mixture with the cyclic 3,5-disubstituted isoxazoles)[3,4].

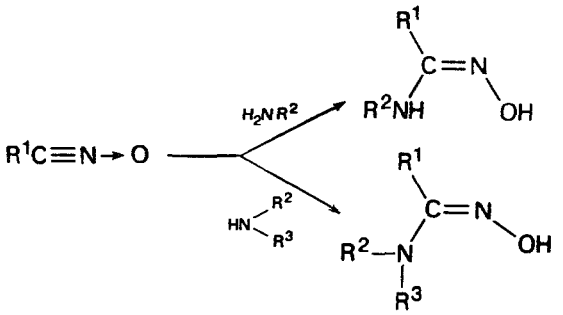


SCHEME 29

Two recent examples of reactions of nitrile oxides with carbanions are that with 2-lithio-1,3-dithianes (**142**)[224a] to give ketoximes (**143**) (Scheme 29) and that with α-metalated isocyanides (R—$\bar{C}$H—N=C; R = H, Ph) which affords 4-imidazolin-2-ones in good yields[224b]. The former reaction also represents a good synthetic route to α-diketones **144** and to 3-acylindoxazenes **145**.

F. Reaction with Primary and Secondary Amines

The overall reactions are shown in equation (36); various solvents can be used. Hegarty and coworkers have studied the kinetics of these reactions in water[34]. In the addition of primary and secondary amines to nitrile oxides, the pseudo-first-order rate constant k_{obs} at a given pH is directly proportional to the total amine concentration as shown in Figure 13 for *p*-nitrobenzonitrile oxide and morpholine. The experimental curves show no upward curvature indicative of catalysis by a second mole of amine. Furthermore, as shown by the graph, the rate of reaction of the nitrile oxide with water in these conditions, is negligible. The second-order rate constants k_B, which can be calculated from the slope of the plot of k_{obs} against amine concentration, are reported in Table 6. These show the low sensitivity of the reaction toward the nature of the amine. The low Brønsted coefficients +0.48 and +0.37 for primary and secondary



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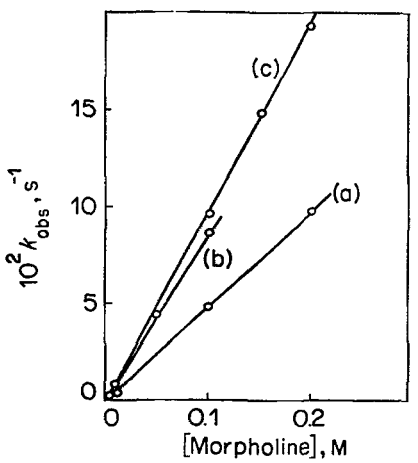
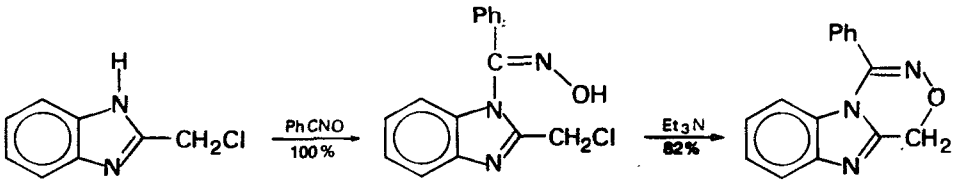


FIGURE 13. Plots of the observed rate constants versus total morpholine concentration at (a) pH 8.04, (b) pH 8.33 and (c) pH 8.82 for the reaction with *p*-nitrobenzonitrile oxide at 25°C. Reproduced by permission of the Royal Society of Chemistry from K. J. Digman, A. F. Hegarty and P. L. Quain, *J. Chem. Soc., Perkin Trans. 2*, 1457 (1977).

TABLE 6. Reaction of amines with *p*-nitrobenzonitrile oxide at 25°C in water

Amine	pK_a	k_B(l mol^{-1} s^{-1})
Methoxyamine	4.75	0.053
Hydroxylamine	6.00	0.250
Hydrazine	8.27	3.59
Imidazole	6.95	0.340
Morpholine	8.32	1.97
Piperazine	9.84	5.61
Piperidine	11.35	18.90
Trifluoroethylamine	5.84	0.038
Cyclohexylamine	10.63	11.34
Ethylamine	10.88	13.20

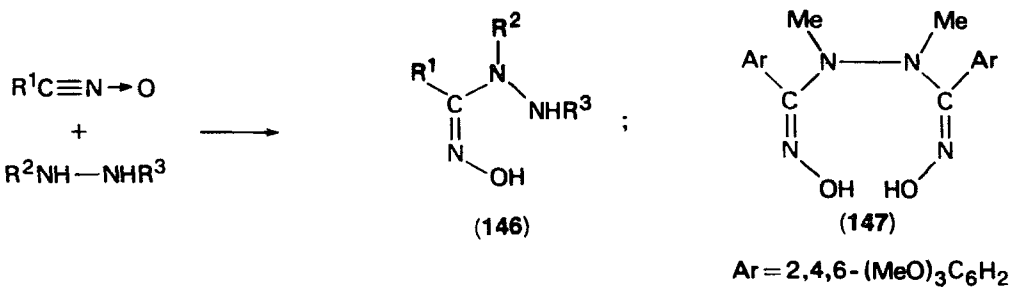


(37)

amines, respectively, confirm this and are also indicative of a reactant-like transition state for amidoxime formation. Further support for this mechanism is represented by the small ρ value found, +0.53, for the Hammet plot of the log of the second-order rate constants versus σ for the reactions of several benzonitrile oxides with morpholine. In some cases the initially formed oxime can undergo cyclization with an electrophilic centre on the original nucleophile (e.g. equation 37)[225].

G. Reaction with Hydrazines

Preparation of hydrazide oximes **146** from nitrile oxides and hydrazines has been reported to be complicated by side-reactions[3,4]. However, Grashey and Weidner[226] found that *p*-nitrobenzonitrile oxide and 2,4,6-trisubstituted benzonitrile oxides reacted with hydrazines to give **146** in high yields (Scheme 30). In the reaction of 2,4,6-trimethoxybenzonitrile oxide with *N.N'*-dimethylhydrazine, some (bis)hydrazide oxime **147** was isolated in mixture with the corresponding monoadduct **146**.

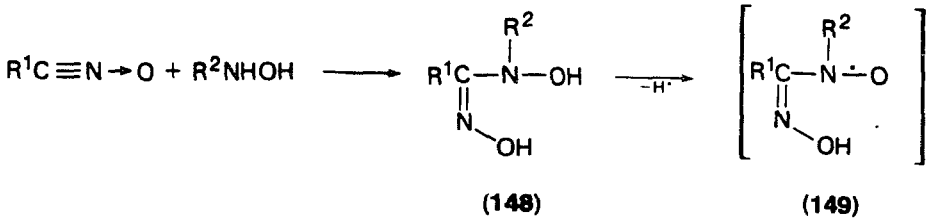


R^1	R^2	R^3	Yield (%)
p-$NO_2C_6H_4$	Me	H	58
2,4,6-$Me_3C_6H_2$	Me	H	87
2,4,6-$(MeO)_3C_6H_2$	Me	H	86
2,4,6-$(MeO)_3C_6H_2$	Me	Me	56

SCHEME 30

H. Reaction with Hydroxylamines

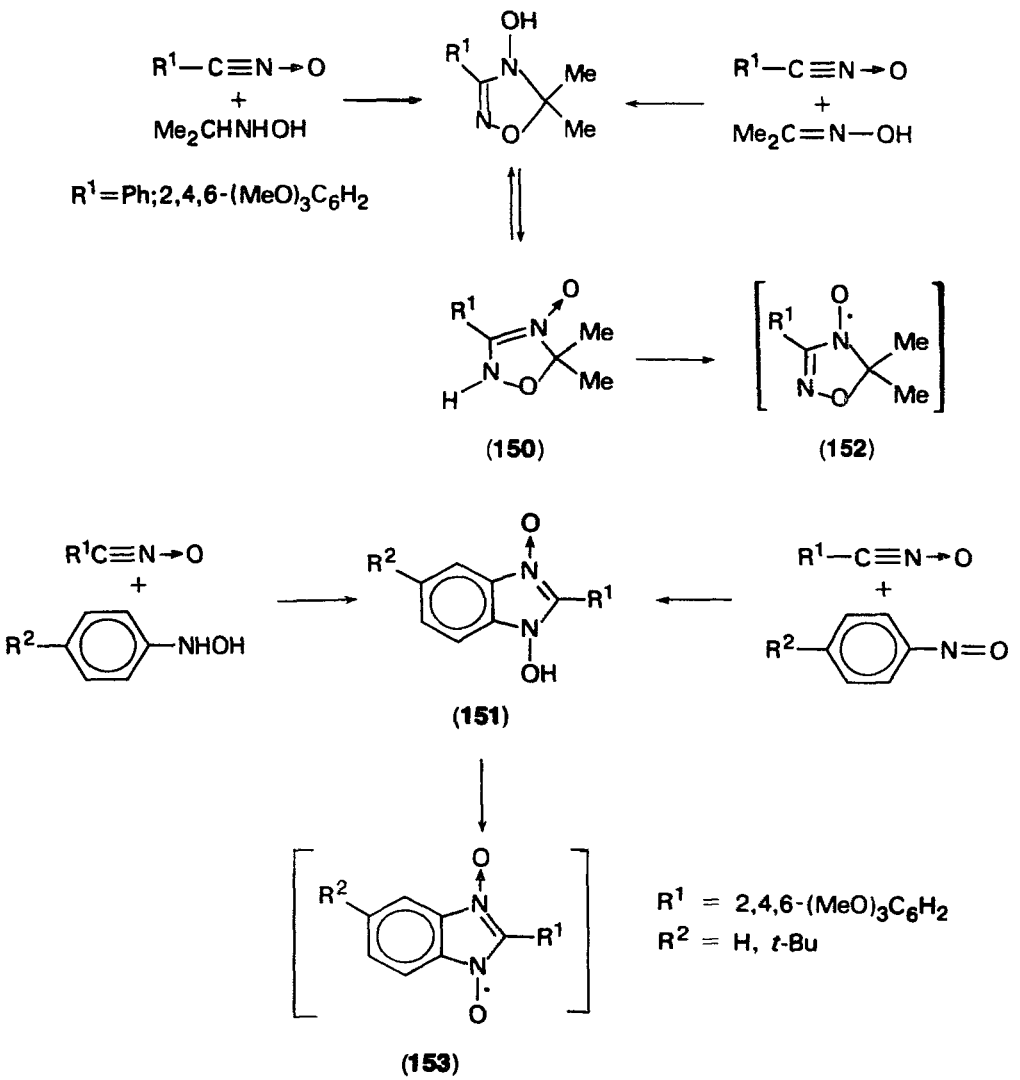
Aliphatic and aromatic nitrile oxides react with unsubstituted and substituted hydroxylamines in chloroform, ether or benzene, to give rise to N^2-hydroxyamidinyl N^1-oxide radicals **149**, detected by ESR spectroscopy, through **148** (equation 38)[4,200]. The intermediate N^1,N^2-dihydroxyamidines **148** were isolable only in a few cases. For example, *N*-isopropylhydroxylamine as well as *N*-arylhydroxylamines reacted with nitrile oxides to give as final isolable products **150** and **151**, respectively, which could be oxidized by action of nitrile oxides and also by PbO_2 to radicals **152** and **153**[200].



(38)

(148) (149)

Compounds **150** and **151** were also obtainable by 1,3-dipolar cycloaddition of nitrile oxides to the suitable oximes or nitrosobenzene (Scheme 31)[200].

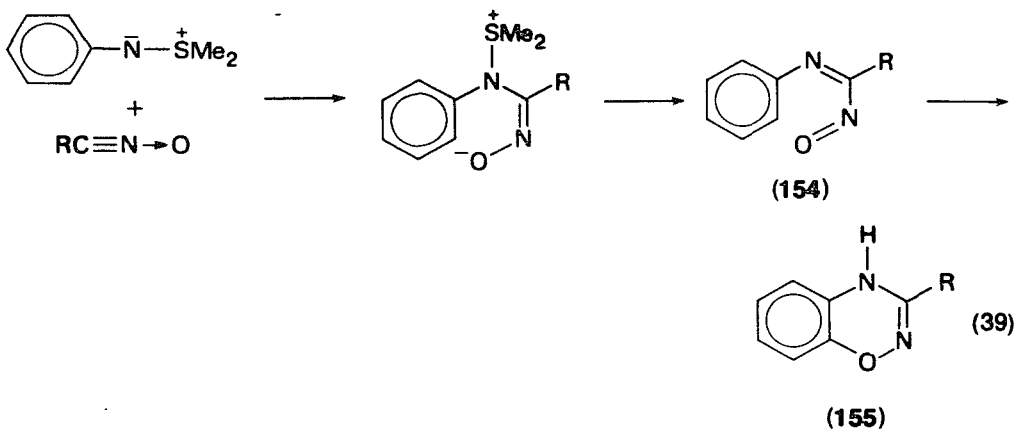


SCHEME 31

I. Reaction with the Betainic Nitrogen of Sulphimides

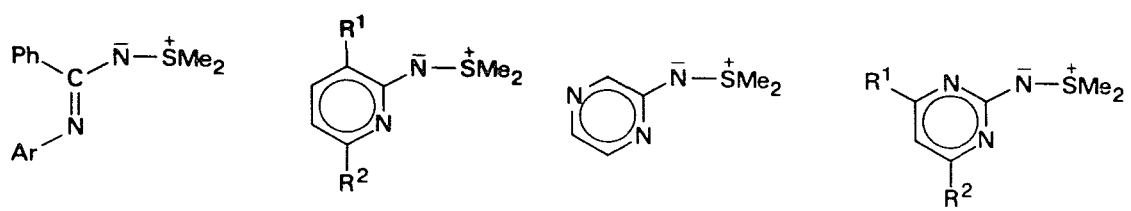
Sulphimides $R_2S{=}NR$, which contain a nucleophilic nitrogen, react with substituted nitrile oxides to give annelation reactions.

N-Aryl-*S*,*S*-dimethylsulphimides react with equimolar amounts of 4-tolunitrile oxide in dichloromethane at room temperature to yield, in 1–3 h, 1,2,4-benzooxadiazines (**155**) according to the mechanism shown in equation (39)[227]. Evidence in favour of the intermediacy of a nitrosoimine **154** was provided by the isolation of its Diels–Alder adduct with thebaine.

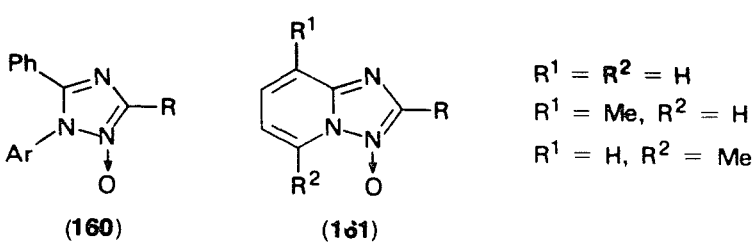


Sulphimides containing imidoyl and heterocyclic groups, **156–159**, react with nitrile oxides at room temperature or below to give 1*H*-1,2,4-triazole 2-oxides **160** and annelated derivatives, e.g. **161**[228].

This manner of ring-closure has been interpreted as being favoured by the greater nucleophilicity of the suitably placed nitrogen atom and/or of the greater aromatic character of the final compounds.



Ar = Ph, *p*-MeC_6H_4

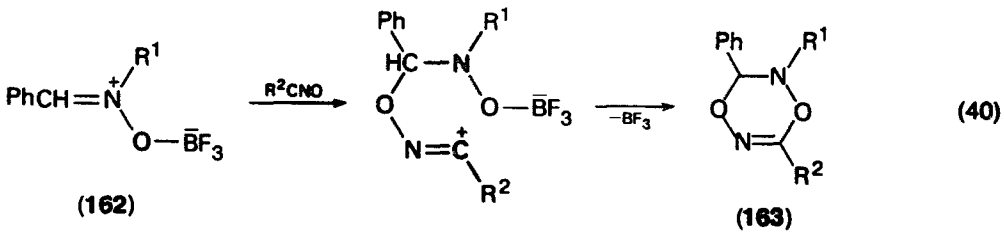


J. Miscellaneous

E-Hydroxamoyl chlorides are formed when nitrile oxides are treated at pH < 2 with Cl^- ion[229]. The reaction is stereospecific[230] and is thought to involve initial nucleophilic attack by Cl^-. The reduction of nitrile oxides to *E*-oximes by treatment with BH_4^- or AlH_4^- is also stereospecific[221].

VIII. REACTION OF NITRILE OXIDES WITH ELECTROPHILES

A probably electrophilic reaction of a betaine on aromatic or aliphatic nitrile oxides has been described[231]. Betaines **162** which are obtained by action of boron trifluoride on nitrones, react with nitrile oxides to give 2,3-dihydro-1,4,2,5-dioxadiazines (**163**) (equation 40). This reaction is reminiscent of the boron-trifluoride-catalysed reaction of oximes with nitrile oxides[4]:



(162) (163) (40)

(a) R^1 = Me, R^2 = Ph; 20%

(b) $R^1 = C_6H_{11}$, R^2 = *t*-Bu; 45%

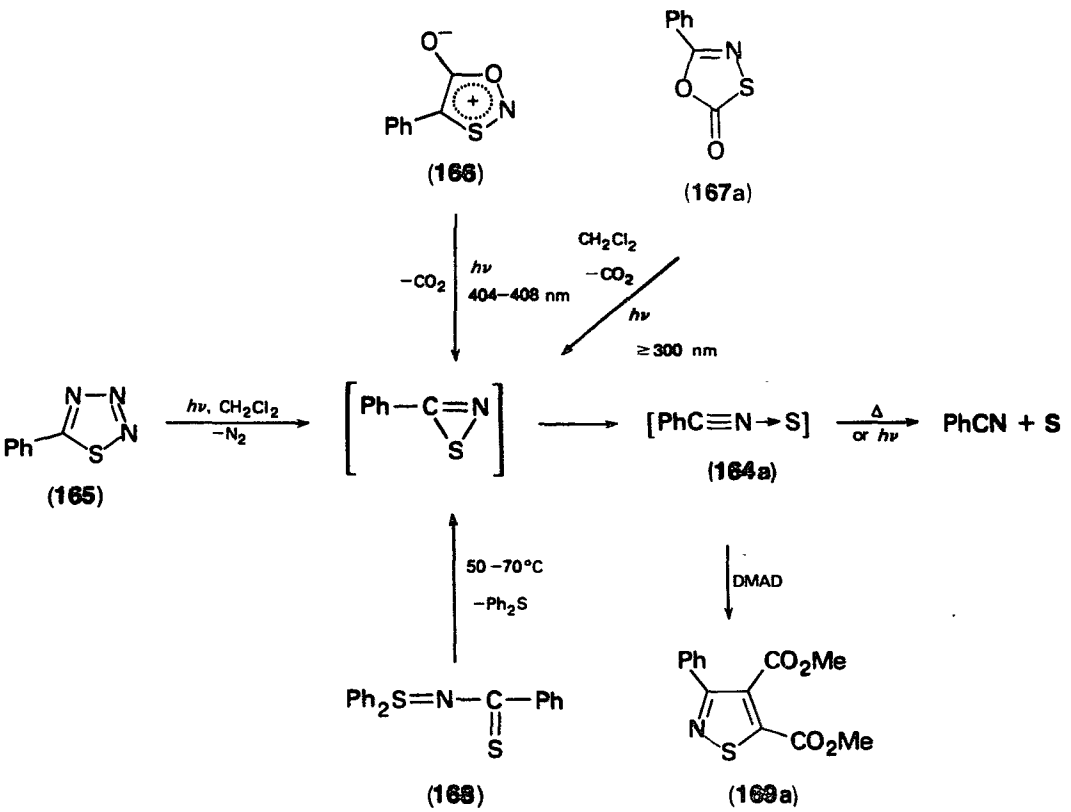
IX. NITRILE SULPHIDES

Nitrile sulphides **164** are unstable nonisolable compounds which decompose quantitatively to give nitriles and sulphur. The N—S bond of **164** is therefore weaker than the N—O bond of nitrile oxides. According to CNDO/2 calculations this difference is due to a smaller coulombic stabilization of the N—S bond compared to N—O, even though the former bond should involve π bonding between $3p_y$ and $3p_z$ orbitals of sulphur and $2p_y$ and $2p_z$ orbitals of nitrogen[232].

Benzonitrile sulphide (**164a**) has been generated in a number of ways (Scheme 32): (*i*) as the main product in the photolysis of 5-phenyl-1,2,3,4-thiatriazole (**165**)[233,235], of 4-phenyl-1,3,2-oxathiazolylio-5-oxide (**166**) (in CH_2Cl_2/Et_2O)[233–235] and of 5-phenyl-1,3,4-oxathiazol-2-one (**167a**)[233,235] and (*ii*) by thermolysis of *N*-thiocarbonyldiphenylsulphimide (**168**)[236]. In all these reactions, benzonitrile and sulphur were formed in high yields. When dimethyl acetylenedicarboxylate (DMAD) was used as trapping dipolarophile, thiazole **169a** was obtained, generally in low yields. Benzonitrile sulphide could be formed and detected (λ_{max} = 240, 295, 313 and 335 nm) in the free state in solid matrix by means of the photolysis of **165–167a** at 85 K in EPA [diethyl ether–isopentane–ethanol (5:5:2)] glass[233]. The thiazirine (Scheme 32) was detected by carrying out the photolysis in PVC matrix at 10–15 K[235b].

From a mechanistic point of view it may be of interest to note that formation of benzonitrile sulphide from **165** is a cycloreversion process which takes place with the molecule in the excited singlet state. In fact population of the triplet state of **165** by energy transfer from excited triplet state of benzophenone leads to quantitative recovery of **165**[233]; this finding rules out any triplet intermediate as the initiating state of the reaction.

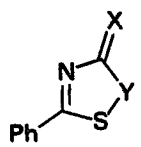
A systematic study of the photolytic behaviour of phenyl-substituted five-membered heterocyclic compounds led Holm and Toubro to discover that formation of



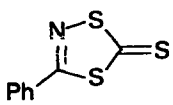
SCHEME 32

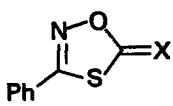
benzonitrile sulphide in variable yield takes place also from all the heterocycles of Scheme 33[235]. The authors concluded that a ready photolytic fragmentation of the heterocyclic compounds with formation of nitrile sulphides occurs when extrusion of a small inorganic fragment (CO, CO_2, N_2, etc.) is possible[235].

Up to date, the most convenient method of preparation of nitrile sulphides **164** is the thermally allowed $[_{\omega}2_s + {}_{\sigma}2_s + {}_{\sigma}2_s]$ 1,3-dipolar cycloreversion of oxathiazolones **167**

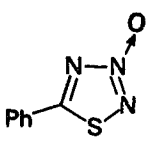


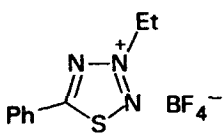
X, Y = O, S; O, CO; S, S





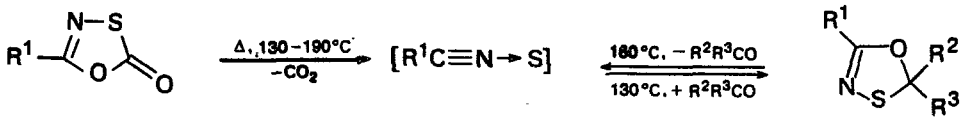
X = S, NH, O





SCHEME 33

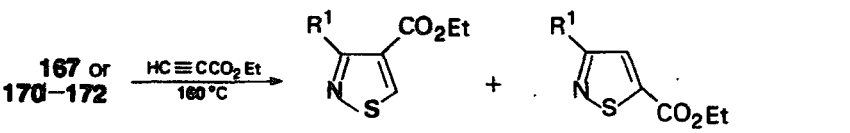
(Scheme 34)[237–241]. The rate of decarboxylation of **167** is **167d** ⩾ **167e** > **167f**, thus indicating a development of a partial positive charge on the nitrile sulphide moiety of the molecule in the transition state of the cycloreversion. The rate of thermolytic fragmentation of compounds **167** is first order and independent of concentration of added dipolarophile[239]. Moreover the same regioisomer ratio **173:174** has been obtained from the reaction of ethyl propiolate with both **167** and 1,3,4-oxathiazoles **170–172** (Scheme 34) in agreement with the intermediacy of free nitrile sulphide in both processes[241].



(167) **(168)**

(a) R^1=Ph; (b) R^1=*p*-ClC_6H_4;
(c) R^1=*p*-$MeOC_6H_4$; (d) R^1=Me;
(e) R^1=CH_2Cl; (f) R^1=CO_2Et

(170) R^2=CCl_3, R^3=CCl_3
(171) R^2=H, R^3=CCl_3
(172) R^2=Ph, R^3=CF_3



(173) **(174)**

R^1=*p*-$MeOC_6H_4$	1·33	: 1·0	
R^1=Ph	1·0	: 1·1	(from **167**)

SCHEME 34

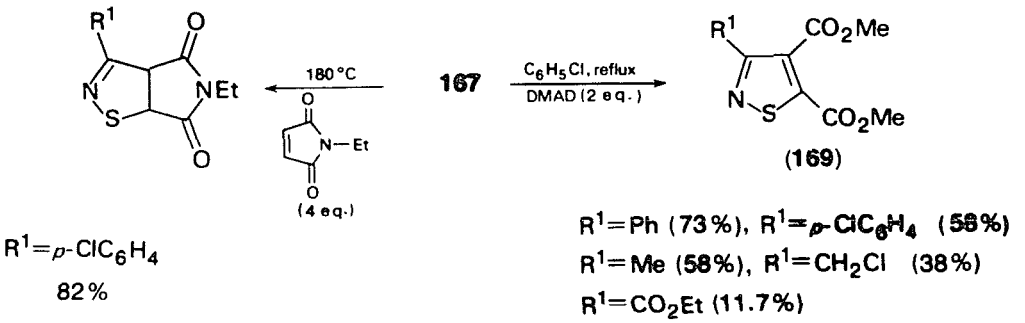
As previously stated, the facile decomposition of nitrile sulphide to sulphur and nitrile[235c,238] represents a severe drawback for the usefulness of this 1,3-dipole in synthesis. A way to limit this disadvantage is to carry out the cycloadditions in the presence of a large excess of dipolarophile in a solution of lower polarity and at high dilution.

Good yields of cycloadducts have been found only when double and triple carbon–carbon bonds bear electron-withdrawing substituents such as carboalkoxy and acyl groups[232,239,240,243] (Schemes 34–36).

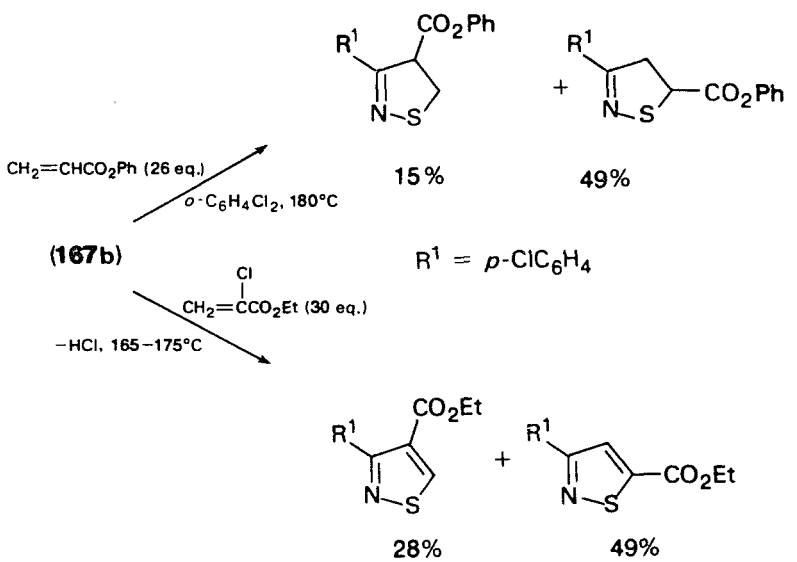
Although the number of reactions explored are by far less than those of nitrile oxides, the cycloadditions of nitrile sulphides appear characterized by a low regioselectivity; the adduct with the electron-withdrawing group in position 5 is, however, often dominant over the other regioisomer in the reactions with monosubstituted derivatives (Schemes 34 and 36).

The carbonyl groups activated by electron-withdrawing substituents are good dipolarophiles towards nitrile sulphides, with which they react in a regiospecific fashion to give in high yields 1,3,4-oxathiazoles **170–172**. The reaction is reversible (Scheme 34)[241,242].

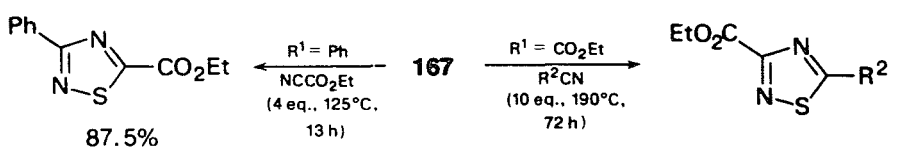
Nitriles which add to nitrile sulphides to give 1,2,4-thiadiazoles (Scheme 37)[215,237,238] are also reactive dipolarophiles.



SCHEME 35

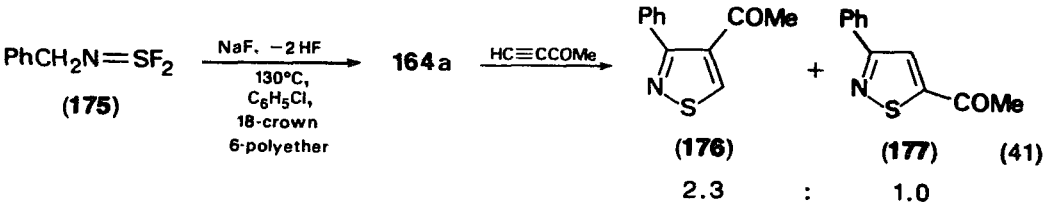


SCHEME 36



SCHEME 37

Another method of preparation of benzonitrile sulphides is the formal 1,3-elimination of HF on heating (*N*-benzylimino)sulphur difluoride **175** in the presence of NaF[232,243] (equation 41). The HF formed greatly influences the regiochemistry of the cycloaddition as shown in the case of 3-butyn 2-one. In fact the ratio **176**:**177** is 2.3 and 0.6 when the 1,3-dipole is generated from iminosulphur



difluoride **175** and oxathiazolone **167a**, respectively. This change in regiochemistry has been explained as being due to the formation of a coordination compound [3-butyn-2-one HF] with consequent change in the electronic nature of the dipolarophile[232].

The data related to reaction rates of 1,3-dipolar cycloadditions of nitrile sulphides suit well a pericyclic reaction governed by the dominant interaction HO_{dipole}–$LU_{dipolarophile}$. The relatively high-lying energy level of the HO of nitrile sulphides is due to the low electronegativity of sulphur (2.5) compared to that of oxygen (3.5). The nucleophilic character of the sulphur centre of the 1,3-dipole (see CNDO/2 data of Table 7) strongly favours the interaction of this end with the more electrophilic (higher LU coefficient) site of the dipolarophile[232]. However this assumption is fully implemented only by results in the case of cycloaddition to nitriles (Scheme 37) and to carbon–oxygen double bonds (Scheme 34), whereas the 'wrong' 5-substituted regioisomer has often been found to be dominant in the reactions of monosubstituted carbon–carbon double- and triple-bond dipolarophiles (Schemes 34 and 36).

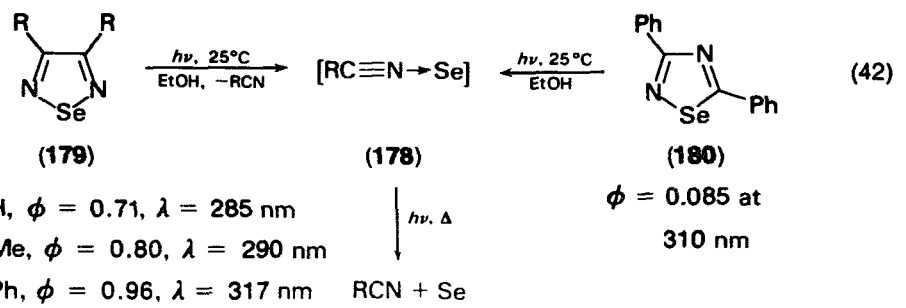
TABLE 7. FO parameters (CNDO/2) of benzonitrile sulphide[232]

	c_C	c_N	c_S	E(eV)	$(c_S\gamma_{CS})^2/15^a$	$(c_C\gamma_{CC})^2/15^b$
HO	−0.289	−0.079	0.950	−9.75	1.05	0.135
LU	0.348	−0.408	0.130	1.26	0.02	0.312

[a]For a carbon–sulphur distance of 2.30 Å; γ_{CS} = 4.17.
[b]For a carbon–carbon distance of 1.75 Å; γ_{CC} = 6.22.

X. NITRILE SELENIDES

Nitrile selenides **178** are generated as very labile transients, which decompose to nitriles and selenium, by photolysis of 1,2,5- and 1,2,4-selenadiazoles **179** and **180**, respectively (equation 42)[244]. Photolysis at low temperatures (20 K, 85 K) allows the



(42)

characterization of compounds **178a–c** by IR (2,200 cm^{-1} absorption in solid nitrogen for **178c**) and UV spectroscopy (255. 340 and 362 nm in PVC film for **178c**). While compounds **179a,b** and **180** undergo photolysis at room temperature exclusively via the singlet state, **179c** photolyses both via triplet (20%) and singlet (80%)[244]. Benzonitrile selenide is thermally less stable than sulphide, so that trapping experiments have been uniformly unsuccessful.

XI. ACKNOWLEDGEMENTS

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CHAPTER 19

Conformation of cyano and isocyano compounds

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I. INTRODUCTION

The cyano group possesses distinctive conformational properties. The short C—CN bond length (ca. 1.47 Å) has the effect of placing the cyanide carbon near in space to *gauche* vicinal groups on a substituted ethanic skeleton. Despite the rather close contacts dictated by the short bond length, cyanide does not have the properties of a space-demanding group. The cylindrical symmetry of cyanide or isocyanide does not impose a time-dependent space requirement on the system. In contrast, groups such as phenyl or carbomethoxy alternatively exist as space-demanding or relatively small in effective size as rotation occurs[1].The entropy properties of cyanide vs. groups such as phenyl would be a desirable study vis-a-vis the conformational properties of these groups.

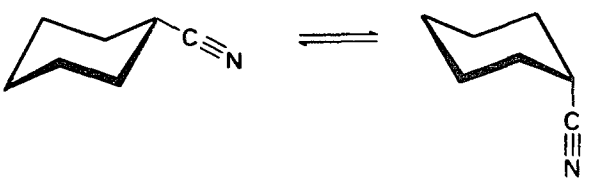
Another factor that affects the conformational preferences of cyanide compared to groups such as methyl, etc. is the lack of hydrogen at cyanide carbon. At one time,

Allinger emphasized the dominating influence of hydrogen–hydrogen interactions in conformational equilibria (principally, the hydrogens directly attached to the ethanic skeleton)[2]. However, other work has suggested that these interactions are not extraordinarily significant[3,4]. Nonetheless, it is noteworthy that groups such as methyl or trifluoromethyl have much more pronounced conformational preferences than other groups of similar size, e.g. bromine or sulphur[5]. The former possess hard, nonpolarizable atoms near the point of attachment to the ethanic skeleton, and generally appear to be much more space-demanding. As will be seen, the nonhydrogenic cyanide group repeatedly tolerates sterically congested conformations.

The following chapter is organized in terms of an overview of the general topic, followed by a more detailed consideration of the conformational preferences of cyanide or isocyanide in simple molecules, special cases and in more complex systems. The casual reader may wish to omit the second or third parts.

II. OVERVIEW

Most chemists look at the energy differences between axial and equatorial conformers in a substituted cyclohexane as a useful measure of the conformational preferences of a given group. The cyanide group has a small preference for the equatorial position as in **1a** (ΔE ca. 0.15 kcal mol^{-1})[6–8]. The magnitude of the preference is rather similar to ethynyl, another sp group of cylindrical symmetry, lacking hydrogen near the point of attachment to the ring (ΔE ca. 0.18 kcal mol^{-1})[9].

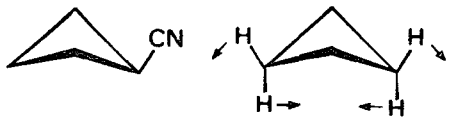


(1a) (1b)

Calorimetric studies on *endo*- and *exo*-bicyclo[2.2.1]heptane-2-carbonitrile (**2** and **3**) have disclosed a moderately greater stability for the *exo* isomer ($\Delta H^0 = 0.96 \pm 0.44$ kcal mol^{-1})[10]. In **1b**, the axial C—CN bond is parallel to C—H_{3ax},H_{5ax} but in **2**, the *endo* C—CN and C—$H_{6\,endo}$ extend toward one another creating a degree of steric interference.

(2) (3)

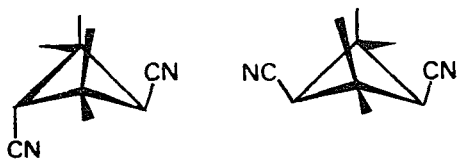
In cyclobutanecarbonitrile (**4**), the cyano group strongly prefers the equatorial position[11]. In cyclobutane, the axial hydrogens actually rotate inward toward one another (cf. **5**), although the H···H interatomic distance remains within the attractive part of the Morse potential[12,13]. In **4**, the larger size of carbon as well as nitrogen of an axial cyanide would quickly lead to a repulsive interaction with the transannular hydrogen if a similar type of rotation occurred. The inward rotation in **5** is desirable in order that bent bonding is minimized for the ring C—C bonds. This type of molecular adjustment



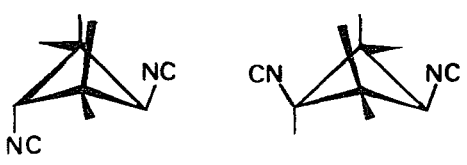
(4) (5)

is probably retained in **4**, and, as a result, the axial cyano group becomes much less favourable than the analogous conformer (**1b**) in a cyclohexane system.

In elegant, although older work, the conformations of 1,3-dicyano- and 1,3-diisocyano-cyclobutanes (**6–9**) were studied[14]. The *cis* isomers were found to be more highly puckered, e.g. 42–51° in **7**. As in many 1,3-disubstituted cyclobutanes, the *trans* isomers were closer to planarity, in order to avoid transannular interference by the axial CN. The angle of puckering is ca. 18° in **6**. These data are somewhat similar to the 1,3-dichlorocyclobutanes, in which the *cis* isomer was found to be more stable by a factor of 1.4[15].



(6) (7)



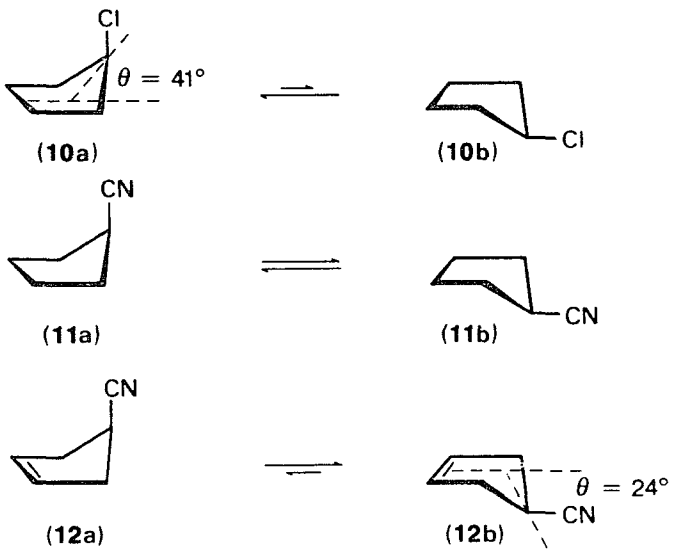
(8) (9)

As indicated above, the cyanide group is often compared to the halogens in conformational properties, e.g. both groups have small preference for the equatorial position in cyclohexane systems. However, in acyclic systems, differences are apparent (*vide infra*). These differences may be related to the fact that halogens such as chlorine have nonbonded electrons, whereas the cyanide group possesses only bonded electrons (i.e. in the π bonds) located in a position that would impinge upon a vicinal group. The C—Cl bond is somewhat longer than the bond to cyanide (1.78 Å vs. 1.47 Å). The cyanide possesses a larger dipole moment (group moment ca. 1.5 D for C—Cl vs. ca. 4 D for CN)[16].

In a microwave investigation of chlorocyclopentane (**10**), and the analogous cyclopentanecarbonitrile (**11**), Harmony and coworkers[17] interpreted the data in terms of a preferred conformation **10a** in which the chlorine occupied a pseudo-axial conformation at the apex of the cyclopentane envelope. The pseudo-equatorial position (cf. **10b**) is less stable by over 800 cal mol^{-1}. In the cyanide, the axial and equatorial forms are about equal in stability. The angle of pucker is about the same in **10** and **11**. These data are in agreement with the findings of Dutch scientists, who have investigated cyclopentanes in considerable detail[18]. Substituents are frequently found at the tip of the envelope.

It is difficult to explain the preference for the equatorial position in the unsaturated nitrile **12** (the axial form is less stable by ca. 400 cal mol^{-1}). The angle of pucker in both **12a** and **12b** is small. It is possible that the preference for the axial chloro-derivative **10a** is due to an attractive interaction of chlorine with hydrogens at C(3) and C(4). These hydrogens are splayed outward in cyclopentanes compared to the axial

hydrogens at C(3) and C(5) in cyclohexane. The greater separation may have changed the interaction from slightly repulsive in chlorocyclohexane to attractive in chlorocyclopentane (cf. the Lennard–Jones potential). The interaction is not so favourable for the cyanide, **11**, in view of the shorter C—CN bond. The unsaturated cyanide **12** lacks hydrogens at C(3) and C(4) capable of interaction and the equatorial form becomes slightly more favourable. For the axial chloride, as in **10a**, hyperconjugation with the *trans* vicinal hydrogens is possible. The situation with regard to hyperconjugation for the cyanide **11a** is unclear. It is noteworthy that many cyanides and vicinal hydrogens do exist in a *trans* relationship in the preferred conformation of a number of compounds to be reviewed in this chapter. However, even at best, the existence of such phenomena of hyperconjugation is likely to be the source of some controversy in years to come[19].



In heterocycles such as **13** and **14**, Eliel and coworkers have determined conformational preferences via the facile acid-catalysed equilibration of the two isomers[20]. The pattern of results is substantially different than the effect of the same groups X on cyclohexane conformations. In polar solvents, X = F and X = CN prefer the axial position. In nonpolar solvents, X = CN prefers the equatorial position in order to reduce dipolar repulsions between CN and the two ether dipoles.

In view of the variability of the data found for the dioxanes, **13** and **14**, as well as in many other molecules, it would be advantageous to review the factors that affect molecular conformation. These are divided into 'Molecular factors' and 'Group factors'.

With regard to group factors, the interaction of vicinal substituents on an ethanic skeleton is considered as basically similar to the interaction of the same groups on two separate molecules that happen to approach one another. On the other hand, molecu-

lar factors involve interactions that occur through the molecular orbitals of the ethanic skeleton. Even distant groups may interact.

The following list of factors is a composite of the effects covered by various speakers at the 'Symposium on Nonbonded Interactions', at the 172nd National Meeting of the American Chemical Society, San Fransisco, CA, September 1976.

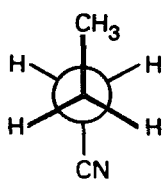
Molecular factors:
(1) Quantum-mechanical effects, e.g. hyperconjugation.

Group factors:
(1) Steric interactions, and related interactions such as van der Waals' forces, dispersion effects, etc.
(2) Hydrogen bonding.
(3) Electrostatic effects.
(4) Dipolar interactions, etc.
(5) Donor–acceptor interactions (primarily charge-transfer interactions).
(6) Solvent effects.

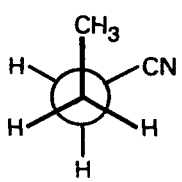
The above factors are not mutually exclusive. Obviously, a hydrogen bond may also be considered as a donor–acceptor interaction. These categories are intended merely as convenient headings under which the sources of conformational variation may be discussed.

III. SIMPLE MOLECULES

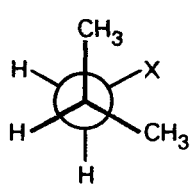
In the gas phase, butanenitrile (**15**) prefers the *gauche* conformation[21]. In the case of 3-methylbutanenitrile (**16**), similar populations of the *gg* and *tg* conformers were evident. The conformational designations *gg* and *tg* (i.e. *gauche–gauche* and *trans–gauche*) refer to the orientation of X with respect to the methyl groups. Ordinarily, the *gg* form would be expected to be sterically hindered and thus unlikely (cf. Section VI). The analogous molecule, 1-chloro-2-methylpropane (**17**), prefers the expected *tg* form. However, it is noteworthy that cyanide is *trans* to hydrogen in both **15b** and in **16a**, which appeared to be substantially populated in this study.



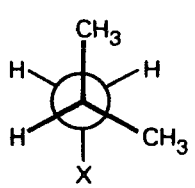
(**15a**)
~30%



(**15b**)
~70%



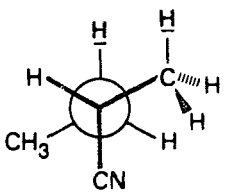
(**16a**) X = CN
(**17a**) X = Cl
} *gg*



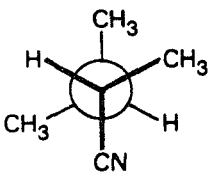
(**16b**) X = CN
(**17b**) X = Cl
} *tg*

In solution, infrared data on 2-methylbutanenitrile (**18**) showed a dominance of conformer S_{HH}[22]. This type of conformational notation indicates that two vicinal hydrogens (underlined in structure **18**) are *trans* to the (secondary) functional group in question[23,24]. The coupled motion of groups *trans* to cyanide gives rise to different bending modes depending upon the type of group. Thus, different infrared absorptions arise. The assignment of bands is not always straightforward, however, and some assignments were made on the basis that the most intense peak probably arose from the most stable conformer, which was then assumed to be the conformer that had the minimum steric interactions.

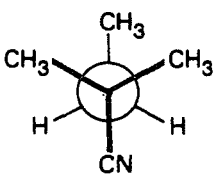
In the more highly substituted molecule, 2,3-dimethylbutanenitrile (**19**), several infrared absorptions were observed, suggestive of the existence of several conformers. The most intense band was assigned to the conformer presumed to be the most stable, S_{CH}. In 2,2-dimethylbutanenitrile (**20**), the T_{CHH} conformer was believed to be dominant. Other molecules of general structure R^1R^2CHCN were also investigated. These compounds, especially **20**, where one methyl seems highly hindered, would bear reinvestigation by other techniques in order to verify these assignments.



(**18**) (S_{HH})

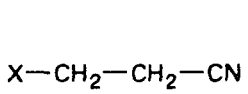


(**19**) (S_{CH})

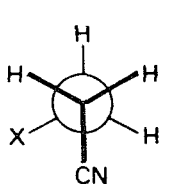


(**20**) (T_{CHH})

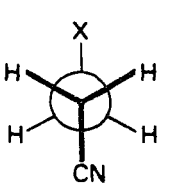
Substituted cyanoethanes, e.g. **21**, have been extensively investigated. Infrared studies of the neat liquids showed that *gauche* (**21a**) as well as *trans* (**21b**) conformers were populated[25,26]. The weight of the *gauche* conformer increased in the order: X = F, Cl, Br, I, with energy differences between the *trans* and the more stable *gauche* forms of 0, 0.44, 0.54 and 0.87 kcal mol^{-1}, respectively. The polarity of the phase (gaseous, liquid or solid) in which the measurements are performed is critical. The gas phase is essentially nonpolar, whereas the solid phase may be considered rather highly polar in the case of most cyanides. The liquid phase is variable depending upon the solvent. Polar solvents usually enhance the weight of the more polar conformer, i.e. **21a**, in which the dipole vectors are partially additive[27]. Solute–solvent interactions of an electrostatic nature stabilize **21a**, and the polar solvent may also insulate the solute dipoles from one another to a certain extent. In the gas phase, it was predicted that the *trans* form, **21b**, would assume greater importance, as in the case of 1-fluoro-2-haloethanes (**22**)[28]. However, recent data has shown that 1,2-difluoroethane occupies the *gauche* form in both the liquid and gaseous phases[29]. In the solid phase **21** (X = Cl, Br) prefers the *gauche* conformer, compared to a mixture of both conformers in the liquid state[30].



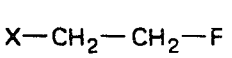
(**21**)



(**21a**)



(**21b**)

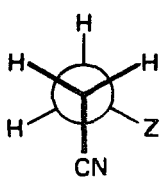


(**22**)

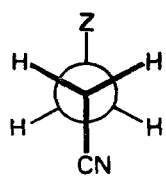
In the case of the hydroxy derivative (**21**, X = OH), the *gauche* and the *trans* conformers are about equally populated in the gaseous state, although the *gauche* form is slightly preferred[31]. In contrast, 2-chloroethanol exhibits a stronger preference for the *gauche* form, compared to the cyano alcohol **21**, X = OH ($\delta\Delta G$ ca. 0.7 kcal mol^{-1}). The hydrogen bond between the hydroxyl and the π bond of the cyanide function is weak (estimated to be 1kcal mol^{-1} in energy). Thus hydrogen bonding, in itself, does not provide much stabilization for the *gauche* form. However, hydrogen bonding is also weak in 2-chloroethanol[23]. In contrast, intermolecular hydrogen bonding between hydroxyl and the cyanide lone pair is comparatively strong (3–6 kcal mol^{-1})[32,33].

Polymorphism of the crystalline state is of great importance. In one polymorphic form of **21**, X = OH, a mixture of *gauche* and *trans* conformers was found, whereas in a second polymorph, only the *gauche* form was evident[31]. The different packing arrangements of the molecules is significant with regard to the conformation adopted[34,35]. In the solid state, intermolecular hydrogen bonding should become much more prevalent, at the expense of intramolecular hydrogen bonding[36]. Since intermolecular hydrogen bonding does not require the existence of the *gauche* OH and CN groups, it is somewhat surprising that this form is so prominent. Since unoccupied space in the crystal would amount to a perfect vacuum, it can easily be seen that a variety of intermolecular forces, including van der Waals' forces and dipolar attraction, are accentuated[37,38]. In view of the significance of these interactions, one should regard conformational weights determined in the solid state with considerable caution.

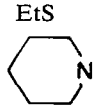
In contrast to the 3-halopropanenitriles (**21**, X = halogen), Rouvier found that 3-piperidino-, 3-ethylthio- and 3-ethoxy-propanenitriles (**23**) preferred the *trans* conformer in solution[39]. The mole fraction of the *trans* conformer (n_T) ranged from 0.6 to 0.8 for these groups[39–41]. The weight of the *trans* conformer is larger for more highly electron-donating substituents.



(23a)



(23b)

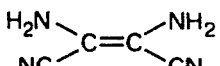
Z	n_T
EtO	0.6
EtS	0.7
	0.8

In butanedinitrile (**23**, Z = CN), the *gauche* conformer is strongly preferred (ca. 75% of the total) in benzene solution[42,43]. The dihedral angle between the cyanides is ca. 90° in the *gauche* form.

The *gauche* conformer is also preponderant in many dihaloethanes, despite steric and dipolar repulsions. Several explanations have been suggested, but this remains one of the most controversial areas of conformational analysis. Wolfe suggested the term 'the *gauche* effect' for these experimental observations, and also suggested the importance of nuclear–electron attractions[44]. Phillips and Wray showed that the effect was

most pronounced for electronegative halogens[45]. Thus dibromides often prefer the *trans* conformer[46]. For 1,2-difluoroethane, Pople and coworkers[47], and other groups[48,49] suggested that the major interaction occurred between fluorine and the vicinal hydrogens. The *gauche* fluorines, *per se*, were considered to interact repulsively. Briefly, the effect may be described as hyperconjugative. The electronegative fluorine removes electrons from the C—F bonding orbital, thus facilitating interaction with the neighbouring CH_2 group. In the case of cyanides, the very large dipole involves the C≡N itself, and the C—CN bond to a lesser extent. Thus, it is problematical whether a similar hyperconjugative effect is to be expected for dicyanides.

In another approach, Bingham considers the X—C—C—X molecular fragment in terms of a set of interacting orbitals, similar to the X—C=C—X system, in which the interaction via the p orbitals is perhaps more familiar to the reader[50]. For a large number of 1,2-dihaloethanes, the *cis* isomer is the more stable[51]. Bingham compares 1,2-dihaloethanes to butadiene dianion, an isoelectronic system in which the *cis* isomer is also the more stable[52]. The electronic interaction is considered to be conjugatively destabilising in the *trans* isomer, but less so than in the *cis* isomer. It is noteworthy that diaminomaleonitrile (DAMN) (**24**) is more stable as the *cis* isomer[52]. In the *cis* form electron-donating groups are *trans* to electron-withdrawing groups. In butanedinitrile itself, the *trans* form is the more stable.

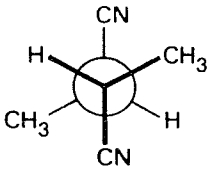


(24)

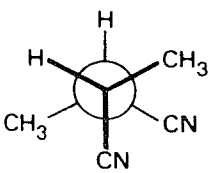
Epiotis suggests that the halogens of *gauche* 1,2-dihaloethanes interact via lone pairs in essentially a stabilizing manner[53]. In the *gauche* conformer, lone pairs at each halogen are unavoidably directed toward, and impinge upon one another. This interaction leads to a splitting of the lone-pair energy levels such that one lone pair then exists in a lower energy state and the other in a higher energy state. Usually the increase in energy of the latter lone pair is more significant, leading to a net destabilization of the system. However, Epiotis believes that the higher energy electrons are stabilized by interacting with the unfilled (C—C)* orbital, which has appropriate symmetry for the interaction. This secondary interaction reduces the energy of the strongly antibonding electrons, and permits an overall stabilization of the *gauche* halogen orientation. In **23** (Z = CN), the CN π electrons could also undergo a similar type of energy level splitting, if the cyanides are *gauche*. However, only the electron-deficient cyanide carbons are really close in space. If the dihedral angle between cyanides is indeed 85–90°, even these carbons may not interact appreciably.

Thus, a variety of interpretations have been advanced: (1) *gauche* fluorines interact repulsively (but the *gauche* orientation is stabilized by interaction of each fluorine with vicinal hydrogens), (2) *gauche* halogens are more or less neutral in stability; the conformer with *trans* halogens is in fact destabilized and (3) *gauche* fluorines interact in an attractive manner, although interaction with the (C—C)* must be invoked. However, Abraham[54] believes that the interaction of halogens does not require special explanations. The conformational preferences of several fluoroalkanes are correctly predicted by a conventional molecular mechanics treatment.

In other work, Craig and coworkers[55] have calculated the conformational preferences for the *meso* and *dl* isomers of 2,3-dimethylbutanedinitrile (**25**, **26**)[55]. The *ab initio* technique used essentially involved the union of separated halves of the molecule. The pairwise additive nature of the interaction of the ethanic substituents was noted. Thus, group effects, and not effects transmitted through the orbitals of the ethanic skeleton appear to be dominant. As in Abraham's work, possibly the molecules from which the pairwise additive effects were originally evaluated (e.g. butanedinitrile



(25)

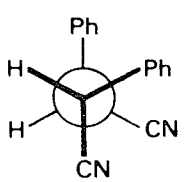


(26)

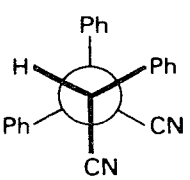
and butanenitrile) have molecular orbital effects 'built in'. This possibility does not seem strong, in view of the different nature of the two types of calculations.

Several types of quantum-mechanical calculations have been reported for butanedinitrile (**23**, Z = CN). Extended Hückel calculations favour the *trans* conformer, **23b**; CNDO-2 calculations predict the existence of the *'cis* form', which seems unlikely; the STO-3G approach again favours the *trans* form by a small amount[56]. As indicated earlier, experimental techniques show that the *gauche* form is dominant[57]. However, calculations show that the barrier to rotation involving cyanide passing hydrogen is 3.2 kcal mol^{-1}; the barrier when two cyanides pass one another is 6.8 kcal mol^{-1}. These values seem quite reasonable. Quantum-mechanical calculations of conformer energies commonly involve the differences between huge energy terms, and in view of the approximations made on most types of calculations, it is not altogether surprising that the calculations reproduce the small energy difference between **23a** and **23b** (Z = CN), i.e. 250 cal mol^{-1}, with difficulty, if at all. For similar reasons, the difficulty in dissecting the energy terms into distinct categories that could be considered the 'cause' of a certain conformational preference has been repeatedly noted in the literature.

In the highly substituted molecules, *meso*- and *dl*-2,3-diphenylbutanedinitrile (**27** and **28**), conformational weights were determined in a variety of solvents by dipole moment techniques[58–60]. The *meso* isomer showed a surprisingly high weight of conformer(s) having *gauche* cyanides, e.g. conformer **27a** (33–42%). The analogous dichloride, *meso*-1,2-dichloro-1,2-diphenylethane, strongly prefers the *trans* conformation, like most *erythro* or *meso* diastereomers having phenyl, carbonyl, sulphur, phosphorus or other nonhydrogenic substituents (*vide infra*)[61]. The preference for **27a** in the case of the dinitrile occurs despite a higher degree of dipolar repulsion than for the dichloride. In the *dl* isomer, conformers with *gauche* cyanides, e.g. **28a**, were present at 23–29% of the total weight. The *dl* isomer in most diastereomeric pairs is frequently conformationally mixed, due to a balance between opposing forces. The *meso* isomer usually provides a clearer picture of the response of the molecule to the presence of nonbonded repulsions or attractions. For the *meso* isomer, the importance of **27a** is indeed unusual, which suggests the existence of attractive interactions.



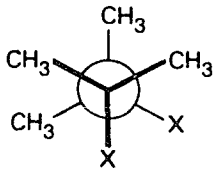
(27a)



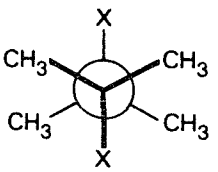
(28a)

In 2,2,3,3-tetramethylbutanedinitrile, the conformer with *gauche* cyanides (**29a**) is present at 24–37% of the total depending upon solvent and temperature. This finding should be viewed in light of the observation that conformer **30a** of 2,3-dimethylbutane is present at ca. 50%[4,62]. In the latter, bond angle changes have occurred between

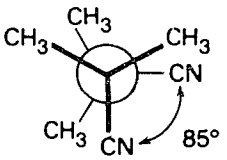
geminal methyl groups, increasing the 'normal' 120° dihedral angle. As a result, conformer **30a** and **30b** have about the same stability, even though **30a** has three sequential *gauche* interactions between methyl groups, whereas **30b** has only two *gauche* interactions. In the latter case, the *gauche* interactions are more severe, since the vicinal dihedral angles are diminished between *gauche* methyls due to the expanded geminal angles. In the case of the dinitrile **29** Chiu and coworkers[58] suggested that the dihedral angle between *gauche* cyanides (cf. **29a'**) was ca. 85°. If so, three rather severe *gauche* interactions would be present.



(**29a**), X = CN
(**30a**), X = H



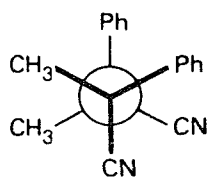
(**29b**), X = CN
(**30b**), X = H



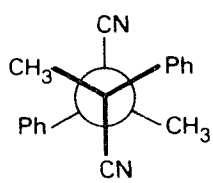
(**29a'**)

In *meso*- and *dl*-2,3-dimethyl-2,3-diphenylbutanedinitrile (**31** and **32**), about equal resultant dipole moments were in evidence (ca. 3.3 D)[58]. In **31**, the weight of the *gauche* conformer, **31a**, is ca. 33–42%. In contrast, the *gauche* conformer of tetraphenylbutanedinitrile (**33**) is nonexistent. It is difficult to pin-point the reasons for these conformational preferences in view of the fact that a number of different types of interaction exist, and the molecule strikes a balance between all repulsive and all attractive forces involving these different interactions.

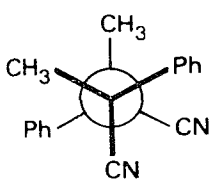
The preference for the *trans* conformer in **33** should be considered in view of the fact that tetraphenylethane strongly prefers the *trans* conformation, in contrast to tetraalkylethanes[63,64]. In early work, an attractive interaction between *gauche* phenyl and cyanide groups was postulated. A charge-transfer interaction between cyanide and phenyl is a second possibility. However, the interaction, at best, is rather weak[65]. A cyanide–phenyl attractive interaction would be expected to lead to an even greater preference for the *trans* conformers in the phenyl-substituted dinitriles, **27** and **31**, than actually present (ca. 60% each). In **33**, the *trans* conformer may be preferred because of a favourable arrangement of the phenyls (cf. tetraphenylethane). In addition, an attractive phenyl–cyanide interaction may stabilize **33a**. Other types of attractive



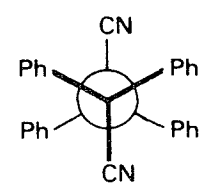
(**31a**)



(**31b**)



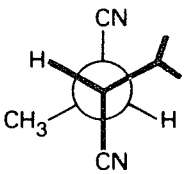
(**32a**)



(**33a**)

interaction have also been postulated, e.g. Ph···alkyl[66] and CN···CN[67]. Thus, a detailed understanding of these conformational preferences awaits proof of exact spatial relationships.

In secondary dinitriles lacking phenyl groups directly attached to the ethanic skeleton (**34** and **35**), the *erythro* isomers show a strong preference for the conformer having *trans* cyanides (ca. 90%). The *threo* isomers are conformationally mixed, as usual[60,61]. The situation is quite different in analogous molecules having COOH present in place of CN, but substituted with a phenyl group on the ethanic skeleton, e.g. **36** and **37**. In both *erythro* and *threo* diastereomers, the conformer with *trans* vicinal protons is favoured (consisting ≥80%). As explained earlier, this type of behaviour occurs principally when nonhydrogenic substituents exist on the ethanic skeleton (e.g. halogens, sulphur, phosphorus, carbonyl, etc.). This behaviour is especially prevalent when one or more of the previously named groups is present along with phenyl in the same molecule. In fact, 2,3-diphenylbutanedinitrile (**27**, **28**) and similar nitriles are the chief exceptions. Various ideas have been suggested to account for the presence of *trans* vicinal hydrogens in molecules such as **36** and **37**[68,69]. Of these, the most promising idea at present seems to be related to the distinctive shape of phenyl, or, possibly, carbonyl. X-ray data show that a phenyl substituent on an ethanic skeleton is oriented so that one *ortho* carbon–hydrogen bond extends parallel to the smallest possible vicinal substituent, i.e. hydrogen. The other *ortho* hydrogen is roughly parallel in orientation to the other hydrogen of the ethanic skeleton (cf. structure **37'**). If alkyl substituents are present, this effect appears to be overridden. The hydrogenic alkyl groups prefer a *trans* orientation to one another irrespective of what conformation other groups are forced to assume, cf. **34**. The failure of cyanides to follow this trend may be associated with the small effective size of cyanide and perhaps a phenyl–cyanide attractive interaction. This question will be explored later.



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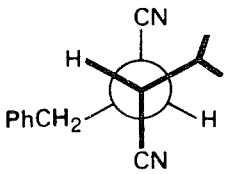

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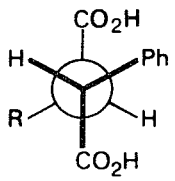

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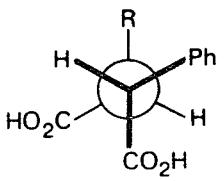

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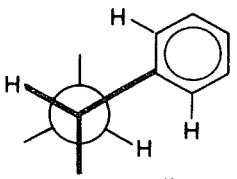
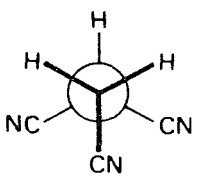


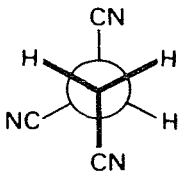
(37')

In the tricyano compound **38** infrared data indicate that only a single conformer exists in the crystal, but in solution, conformers **38a** and **38b** have approximately equal weights[70]. The high weight of **38a** is remarkable in view of the dipolar repulsion that must exist. However, in 1,1,2,2-tetracyanoethane (**39**) and in 1,2-dichloro-1,1,2,2-tetracyanoethane (**40**), the *trans* conformer strongly predominates in solution.

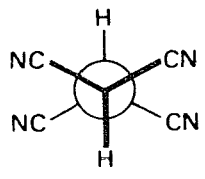
Bodot and coworkers[71] investigated the possibilities for an attractive interaction between vicinal cyanides in molecules such as **41**. The possibility of an attractive interaction was earlier suggested by Peterson, who found that the equilibration of the *meso* and *dl* isomers of 2,3-dimethyl-2,3-diphenylbutanedinitrile (**31**, **32**) gave predominately the *dl* form (*meso*:*dl* ratio, 0.8:1).[67] The steric interactions likely to be



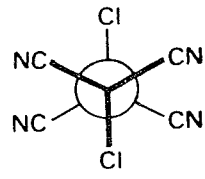
(38a)



(38b)

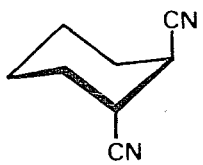


(39)



(40)

present were discussed in terms of *trans* Ph conformers, e.g. **32a**, which were reasonable guesses, but not completely in accord with later findings. The greater stability of the *dl* form, despite what seemed to be less steric hindrance in the *meso* form, was explained in terms of an attractive CN—CN interaction. In *trans*-1,2-cyclohexanedicarbonitrile (**41**), it was concluded that the CN—CN attraction was weak, which is in accord with the 85–90° dihedral angle believed to be present in other vicinal dicyanides. The work on **41** did cogently illustrate the extreme effect of solvent. Conformer **41a** is dominant (weight 55%) in nonpolar solvents such as CS_2, as the strong repulsion between CN dipoles is thus minimized. In polar solvents such as DMSO, **41b** (78%) becomes dominant.



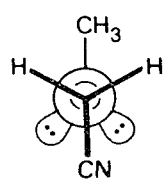
(41a)

(41b)

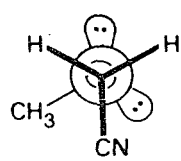
In methoxyethanenitrile (**42**) as in the case of dimethoxymethane, the *gauche* conformer (reviewed through the C—O bond), **42b**, is preferred over **42a**[72,73]. A hyperconjugative interaction of cyanide with the oxygen lone pair may be involved[48]. This interaction should be of greater significance than the cyanide–*trans*-hydrogen hyperconjugative interaction discussed earlier, if indeed the latter exists at all. Obviously, the cyanide, **42**, has no possibilities for 'rabbit ear' types of lone pair interactions[74]. Like many molecules having lone pairs present at the major atoms, instead of hydrogen, the barrier to rotation (ca. 2 kcal mol^{-1}) is not large[73].

CH_3OCH_2CN

(42)



(42a)



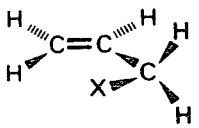
(42b)

The final simple molecules that will be considered are the unsaturated nitriles. Of these molecules, 3-butenenitrile (**43**, X = CN) has been exceptionally thoroughly studied. The conformers of this allylic system are termed *cis*, *gauche* and *trans* (**43a–c**, respectively). The literature is in agreement that the *trans* form has a small, and possibly zero, weight. Recent *ab initio* calculations indicate an order of stability: *cis* > *gauche* > *trans* by 0.5 and ca. 0.8 kcal mol^{-1} respectively[75]. Microwave studies indicate an even larger preference by 1.3 kcal mol^{-1} for the *cis* form over the *gauche* form. The *trans* form is not observed[76].

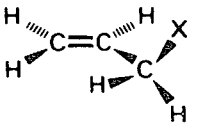
In the solid phase, a preponderance of the *cis* conformer has been observed by

infrared/Raman techniques[77]. Similar results are found in solution[75]. In analogous molecules, the 3-halopropenes, the NMR data have been interpreted in terms of increasing weights of the *cis* form, as the electronegativity of X increases[78].

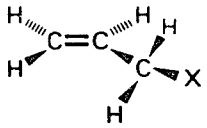
An explanation based on orbital symmetry has been advanced to explain this observation[79]. Briefly, it has been shown that the component of CH_2X that mimics a p orbital in symmetry properties interacts with a p orbital at C(1) in a destabilizing manner in the *trans* form (e.g. **44a**). In the *cis* conformer, **44b**, these orbitals are distant. In the *cis* form, the orbitals of X interact with the π bond in a complex manner[80].



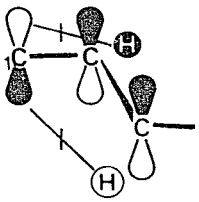
(43a)



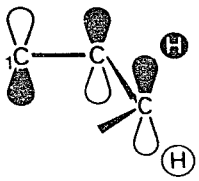
(43b)



(43c)

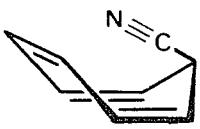


(44a)



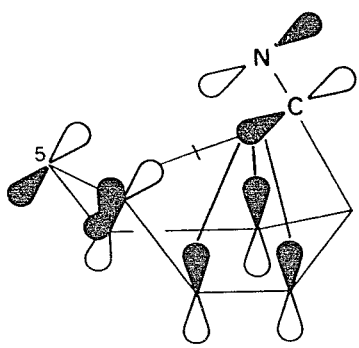
(44b)

In 2,4,6-cycloheptatrienecarbonitrile (**45**), the low-temperature NMR spectrum indicates a strong dominance of one conformer, whose structure has been assigned as **45a**[81]. The disfavoured conformer **45b** is somewhat analogous to the disfavoured *trans* allylic conformer, **43c**, in orientation of groups. For the *gauche* conformer, orbital symmetry effects may impart an added stabilization. The problem is somewhat similar in orbital interactions to the cycloheptatrienyl carbonium ion[82]. One possibility for the orbital interaction is shown in **46**. Models suggest that nitrogen is too distant to play



(45a)

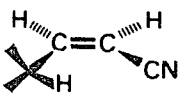
(45b)



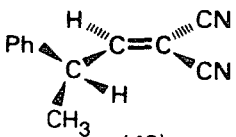
(46)

much of a role, although formally, it could interact with the orbitals at C(4) and C(5) in a stabilizing manner, if it were nearer in space.

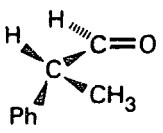
Vinyl cyanides, of course, have only a single orientation of cyanide. However, it is of interest to see the effect of cyanide on conformational changes elsewhere in the molecule. In **47**, Lacondie and coworkers have found that the isopropyl hydrogen is eclipsed with C=C, and lies close in space to CN[83]. A high degree of conformational purity is believed to be present. In our laboratory, studies of carbonyl derivatives $R^1R^2C = C(CN)_2$, e.g. **48**, have indicated quite different conformational properties than the parent aldehydes (**49**)[84]. The hydrogen of **48** is eclipsed with C=C, whereas in the case of the aldehyde **49**, other groups, e.g. methyl, are eclipsed with carbonyl [85]. High conformational purity (> 90%) pertains in **48**, but not in **49**, in the usual types of solution conducive to NMR study. The data may be explained simply on the basis of a preference of the molecules **47** and **48** for the least strained environment.



(47)

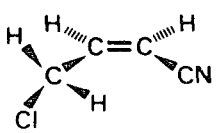


(48)

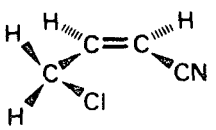


(49)

In (*Z*)-4-chloro-2-butenenitrile (**50**), temperature effects on vicinal NMR coupling constants have been analysed in terms of the existence of two conformers[86]. The more stable conformer is preferred by ca. 1.1 kcal mol^{-1}. Conformational diagrams are not presented. However, the nature of the NMR coupling constants is consistent with a preferred conformation having chlorine *gauche* to C=C, i.e. **50a**, with ca. 60% weight. The weight of the minor conformer, **50b**, is sizable considering that chlorine and cyanide undergo both steric and dipolar repulsions.

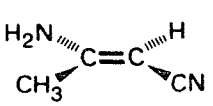


(50a)

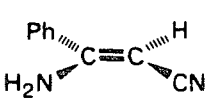


(50b)

In 3-amino-2-butenenitrile (**51**), the *E* isomer is more stable, but in 3-amino-3-phenyl-2-propenenitrile (**52**), the *Z* isomer is preferred[87]. While it may be argued that these interconversions represent configurational changes, not conformational, the $E \rightleftharpoons Z$ equilibration of these enamines is very facile, and the distinction between conformation and configuration becomes unclear[88]. It is clear that hydrogen bonding in **51** is not sufficiently strong to stabilize the *Z* isomer. Amino groups are not strong donors, and the cyanide π bonds are weak acceptors[89]. The preference for the *E* isomer in **51** results from the longest path for resonance between the amino and the cyanide functions. It is unlikely that **51** is preferred for steric reasons, as the methyl–cyanide steric interaction is probably worse than the amino–cyanide steric interaction in the *Z* isomer. In **52**, the tendency of the phenyl group to be coplanar with the remainder of the π system is probably a factor. To be coplanar, phenyl requires the smallest group possible (hydrogen) in the *cis* position.

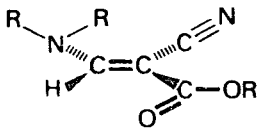


(51)

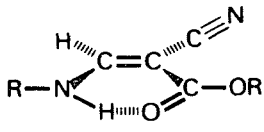


(52)

In the *N,N*-dialkylenamine **53**, the *E* form **53a** is favoured, whereas in the *N*-alkyl compound, the *Z* form (**53b**) is substantially populated[90]. In the latter case hydrogen bonding is a factor. The N—H evidently prefers to hydrogen bond to the oxygen lone pair, rather than to cyanide.

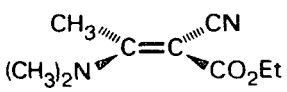


(**53a**)

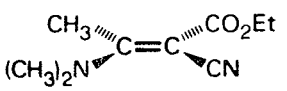


(**53b**)

In related molecules, Dahlqvist[88] has determined the energetics of intramolecular rotation. In **54**, analysis of the NMR signal coalescence phenomena has indicated a lower barrier for C=C isomerization than for C—NMe_2 rotation: for C=C isomerization, $\Delta H^{\neq}$ ca. 14 kcal mol^{-1} and $\Delta S^{\neq}$ ca. − 3 e.u. For C—NMe_2 rotation, $\Delta H^{\neq}$ ca. 15 kcal mol^{-1}, but $\Delta S^{\neq}$ 8 to 14 e.u. Entropies of this magnitude are not common in conformational equilibria[91]. Thus, possibly systematic errors are involved. Such errors are difficult to avoid in complex analyses of NMR line-shapes of this type[92]. The *E/Z* isomerization **54a** ⇌ **54b** is facile due to resonance, which imparts a higher degree of C—NMe_2 double-bond character and reduces the C=C double-bond character. At equilibrium, slightly more of the *E* isomer **54a** is present (K_{eq} = 1.3), reflecting the sterically preferred opposition of NMe_2 with cyanide. In **53**, Dahlqvist[88] found that the barrier to C—NMe_2 rotation was ca. 3–4 kcal mol^{-1} higher. In **54**, the additional methyl group imposes a steric strain that is relieved upon approach to the transition state[93]. In highly polar solvents, e.g. DMSO, the barriers to conformational interconversion are lowered due to facile accommodation of charge separation.

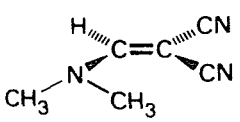


(**54a**)

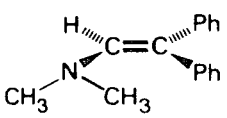


(**54b**)

Mannschrekt[94] has shown that the barrier to rotation of the C—NMe_2 group in **55** is comparatively high ($\Delta G^{\neq}$ ca. 18 kcal mol^{-1}). This barrier is rather similar to that found for **53**. In **56**, however, the barrier is much smaller ($\Delta G^{\neq}$ ca. 12 kcal mol^{-1}). In **55**, the higher degree of resonance interaction between the electron-donating amino function and the electron-withdrawing cyanides enhances C—NMe_2 double-bond character.



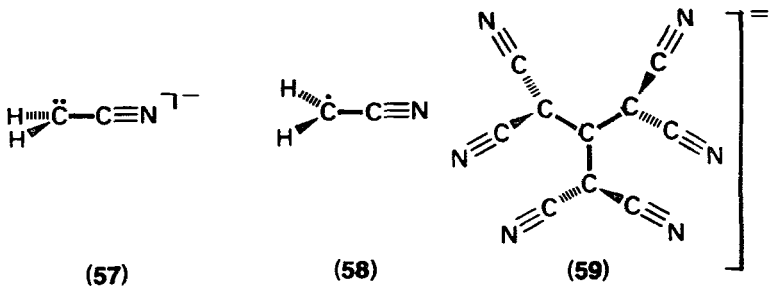
(**55**)



(**56**)

IV. SPECIAL CASES

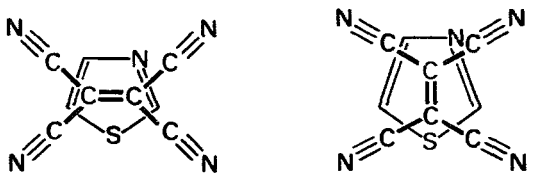
According to calculation, the carbanion derived from ethanenitrile (i.e. **57**) is not planar, but rather it is pyramidal in shape, although the pyramid is flattened[95]. As in nitronate anions or anilines, electron delocalization does not necessarily impart planarity. On the other hand, the free radical **58** is believed to be planar, similar to dicyanomethyl and tricyanomethyl radicals[96].



(57) (58) (59)

The dianion derived from 2,4-dicyano-3-(dicyanomethyl)-2-pentenedinitrile (**59**) was found to be planar in crystallographic studies of the calcium salt.[97]. The parent carbon acid is as acidic as sulphuric acid, and like sulphuric, it is dibasic. Although the central carbon is planar, the dicyanomethide groups are rotated from the molecular plane ca. 24° in propeller fashion.

The orientation of charge-transfer complexes involving tetracyanoethene (cf. **60**) has been studied by theoretical calculations[98]. At the energy minimum for separation of the molecular plane of the donor and the acceptor ca. 3.4 Å, the '0° form' (**60a**) was predicted to be the more stable, but for slightly greater intermolecular separations, the '90° form' (**60b**) should be preferred.

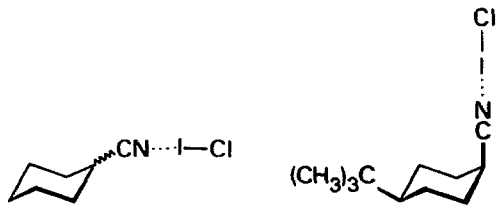


(**60a**) (0° form) (**60b**) (90° form)

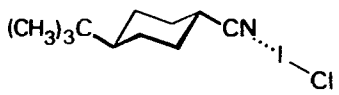
Matsubara and coworkers[99] have investigated the conformational preferences of dicyanides as complexes with metal salts. In the solid state, the complex of butanedinitrile with silver ion exists in an extended zig-zag arrangement of molecules in which the *gauche* conformer is present. Uncomplexed butanedinitrile (**23**, Z = CN) prefers the *gauche* conformer in solution[42]. On the other hand, pentanedinitrile complexed with copper (II) occupies the *gauche*/*gauche* orientation of each terminal cyanide with vicinal carbons, although the free dinitrile is conformationally mixed.

A study that hastened the demise of the Winstein–Holness method of establishing conformation weights in cyclohexane derivatives[100] concerned the complexing ability of cyclohexanecarbonitrile (**1**) with iodine monochloride, compared to 'standard' molecules, *cis*- and *trans*-4-*t*-butylcyclohexanecarbonitrile (**61** and **62**)[101]. In carbon tetrachloride, **1** gave a *larger* equilibrium constant for complexation with ICl (K_{eq} = 19.9) than either standard (**61**, K_{eq} = 15.4; **62**, K_{eq} = 18.5). Thus one could not merely interpolate between the values for **61** and **62** to find the weight of the axial conformer in the ICl complex of **1**. The *t*-butyl group was believed to have caused a deformation of the molecule such that H_{3ax} and H_{5ax} were tilted toward C(1), and thus affected the degree of complexation. If a simple conformational equilibrium such as indicated above fails, the application of the Winstein–Holness treatment to chemical reactions is indeed suspect.

One last type of molecule, which involves interactions between rather unusual types of groups, is cyanomethyl diethylphosphine oxide **63**[102]. Dipole moment studies show that the compound prefers the *trans* conformer **63** (74% of the total). Analogous molecules show similar conformational preferences. The disfavoured *gauche* con-

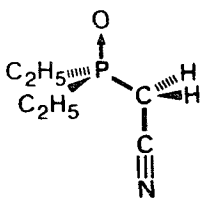


(1) (ICl complex) (61) (ICl complex)



(62) (ICl complex)

former is undoubtedly affected by dipolar repulsion between the phosphine oxide, which has a large group moment (ca. 2.9 D), and the cyanide (group moment, ca. 4 D).



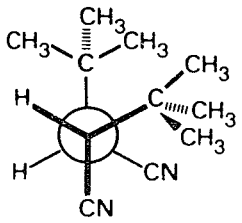
(63)

V. COMPLEX MOLECULES

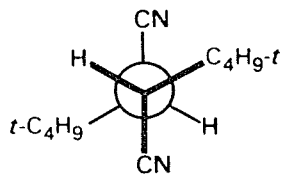
The last part of this chapter treats relatively complex molecules, in which the choice of conformation involves the interplay among a number of factors. This apparent disadvantage can sometimes be turned into an advantage. If some effect is well understood qualitatively and semiquantitatively, this effect and another poorly understood effect may be pitted against one another. By observation of the resultant conformational preference of the molecule, it may be possible to assess the characteristics of the less well understood factor.

The first group of molecules appear rather simple, but involve complex effects that are not firmly understood. The conformational preferences of cyclic and acyclic *t*-butyl compounds will be considered. Bodot and coworkers[103] have extensively investigated the puzzling effects of the *t*-butyl group. This group always seems to have extreme effects on conformation, that are not always predictable from simple steric considerations. For example, in our laboratory, dipole moment studies have shown that *meso*-2,3-di-*t*-butylbutanedinitrile (**64**), like the corresponding dichloride, exhibits a resultant dipole moment, 2.5 D, well above the 0 D value expected for the 'obviously' sterically favoured *trans* conformer, **64b**[104]. Thus, conformer **64a**, which has *gauche* cyanides, and also *gauche* *t*-butyl groups is substantially populated (ca. 20%). Deformation of the molecule seems likely in order to accommodate *gauche* groups of extreme size.

Bodot's work[103] clearly shows the molecular deformation imposed by the *t*-butyl group. One example involves 2-*t*-butyl-4-oxocyclohexanecarbonitrile (**65**). A nonchair conformation was found to be present by X-ray crystallography (cf. **65a**)[105]. The cyanide is twisted away from the C(1)—C(4) axis due to interference with *t*-butyl (cf. **65a**). However, this movement creates interference between the cyanide and the

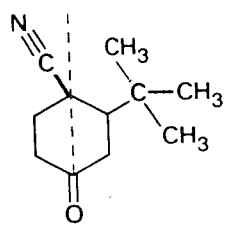


(64a)

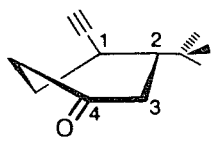


(64b)

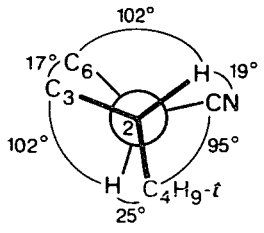
hydrogens at C(6) (cf. **65b**). The nonchair conformation may represent the minimum energy accommodation as the molecule seeks to minimize these secondary interactions; it is also noteworthy that the cyanide assumes a pseudo-axial conformation[106]. It is also noteworthy that the nonhydrogen containing cyanide 'gave ground' rather than the methyls of the *t*-butyl group, or the entire group. Nonchair ring conformations are relatively widespread for cyclohexanones[107]; these conformations lie only a few kcal mol^{-1} in energy above the chair form[108]. This small energy difference is easily overcome by other factors. The lack of hydrogen at carbonyl reduces the incidence of hydrogen–hydrogen eclipsing interactions upon formation of a nonchair conformation, e.g. a twist boat.



(65)

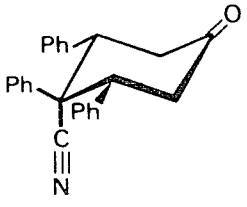


(65a)

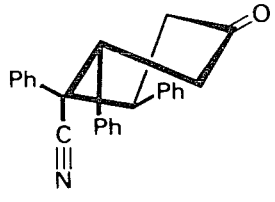


(65b)

Another case in point is the cyanides **66** and **67**[109]. Compound **66** is rather ordinary in that the least sterically demanding group, cyanide, assumes the hindered axial conformation. In **67**, however, rather than placing phenyl axial, a nonchair form is substantially populated. The structure shown is one possibility for this conformer.



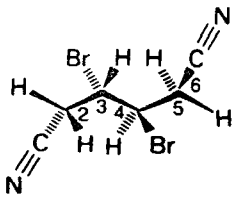
(66)



(67)

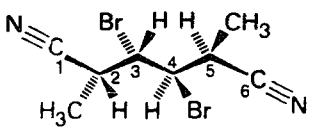
One of the most intensive studies of the conformational characteristics of dicyanides has been carried out by Rabinovich and Shakked[38], as part of their programme to relate solid-state conformation to the stereochemistry of solid-state reactions. For **68**, the cyanides are oriented in an unusual manner. Usually, a zig-zag carbon chain is terminated by a major group, such as methyl. While the two cyanides could terminate the chain in **68**, the cyanides appear to adopt a *gauche* orientation, rather than a *trans* orientation, with respect to the vicinal carbon of the chain. However, Rabinovich and Shakked have shown that intermolecular interactions of an attractive nature (van der

Waals' interactions and donor–acceptor interactions) are very significant. In many instances, a bromine of one molecule is oriented in a colinear manner with a cyanide of a neighbouring molecule. Bromine and nitrogen exist within the combined van der Waals' radii (observed separation ca. 3.2 Å; combined radii, ca. 3.45 Å). In other cases, an interaction of a cyanide nitrogen with a cyanide carbon of another molecule is of importance.

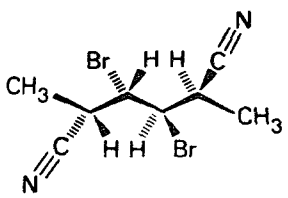


(68)

Like **68**, **69** and **70** prefer the conformation about C(3) and C(4) in which bromine atoms are *trans* and the chain carbon atoms, C(2) and C(5) are *trans*. Similar conformations are found for a large number of *erythro* and *meso* dibromides[46]. In **70**, two different crystal modifications, **70** and **70'**, have been observed. The difference in solid-state conformation is difficult to portray by means of extended structures, but it is clearer in the Newman projections given later in the chapter. Dihedral angles involving hydrogens are quite different in **70** and **70'**. The reader is encouraged to consult the original paper for the precise geometric relationships.



(69)

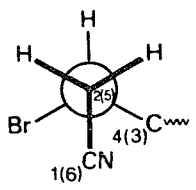


(70,70')

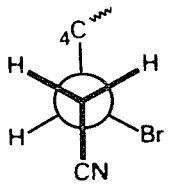
Unlike **68**, **69** and **70** terminate their respective chains with a major group, methyl or cyanide, not hydrogen. Concerning long-range interactions, **68–70** follow the usual finding in conformational analysis. This finding is so widespread that it might be termed a principle. A large group at a given carbon, e.g. the C(2) CH_3 in **69** opposed to a small group (hydrogen) at C(4). A large group (bromine) at C(4) is opposed to a small group (hydrogen) at C(2). Thus, 1,3-interactions are minimized in **68–70**, as in most molecules. Certain nitriles, however, do appear to be exceptions[109,110].

The experimental findings for **68–70** have been augmented by force field calculations, which emphasize torsional and nonbonded interaction terms. The conformers calculated to be the most stable for **68** include the observed conformer **68a**, plus another conformer, **68b**, which is not observed despite roughly equal energy. In **68a**, the intermolecular interactions may be sufficient to dictate the preference for this conformer, but gross changes in orientation of groups do not occur. For **70**, the conformers calculated to be the most stable are shown in Newman projection form (**70a–c**). The experimentally observed conformer (**70a**) again is very similar to the conformer calculated to be the most stable. In **70a**, the C(3)—Br is *trans* to C(2)—H and the C(2)—CN is *trans* to C(3)—H. While this orientation could result from hyperconjugation, it is doubtful that the calculation parameters used in the calculation implicitly included such interactions.

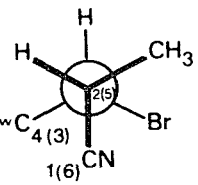
With regard to conformers **70a–c**, it is surprising that **70b** is destabilized by only 4 kcal mol^{-1} relative to **70a**, in view of its obvious torsional problems. The barriers to rotation range from ca. 6 kcal mol^{-1} (**70a** → **70b**) to over 20 kcal mol^{-1} for subsequent rotations, which seems all too high. Perhaps the calculations did not permit relaxation, i.e. the changes in all molecular parameters, as rotation occurs. Specifically, bond angles change significantly as the eclipsed state is approached[91a,b].



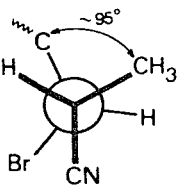
(**68a**)



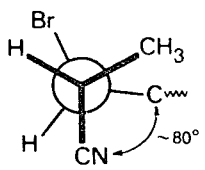
(**68b**)



(**70a**)

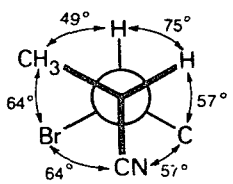


(**70b**)

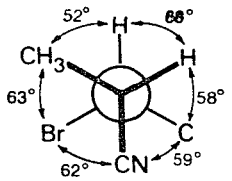


(**70c**)

The Newman projections shown below illustrate the dihedral angle variations observed in the two crystal modifications, **70** and **70′**. It is difficult to perceive reasons for these rather large changes. It is interesting to note, however, that the conformations at carbons bearing bromine (not illustrated) is relatively constant throughout the series of compounds.



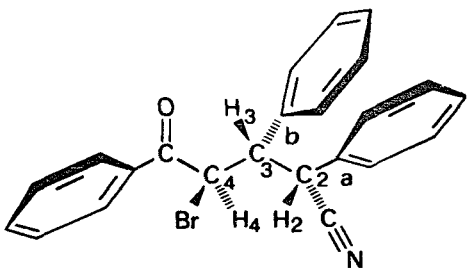
(**70**)



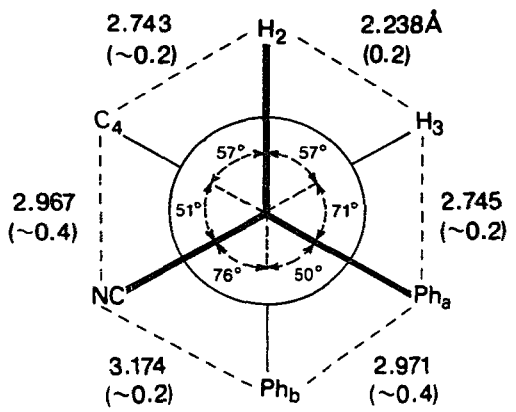
(**70′**)

Another case involving a relatively complex molecule again concerns the competition between cyanide and other types of groups for the most comfortable orientation in space. In 4-bromo-5-oxo-2,3,5-triphenylpentanenitrile (**71**), the conformation as observed by X-ray crystallography is very similar to that observed in solution by NMR[110b]. As usual, the nonhydrogenic substituents at C(3)—C(4) (i.e. Ph_b, Br and COPh) adopt the conformation having *trans* vicinal hydrogens. The substituents at C(2)—C(3) include the cyanide group, and although these substituents are equally nonhydrogenic, a conformation with *gauche* vicinal hydrogens is tolerated. The C(2)—C(3) bond length is marginally longer than usual for sp^3–sp^3 bonds, i.e. 1.568(8) Å, but the deviation from the usual value cannot be regarded as statistically significant. It is noteworthy that the *ortho* C—H bonds of Ph_b are roughly parallel to C(3)—H and to C(4)—H. However, Ph_a is tilted so that the *ortho* C—H bond is not parallel to the C(2)—CN bond. Although cyanide and Ph_b are separated by sizable dihedral angles, cyanide lies well within the combined van der Waals' radii with regard

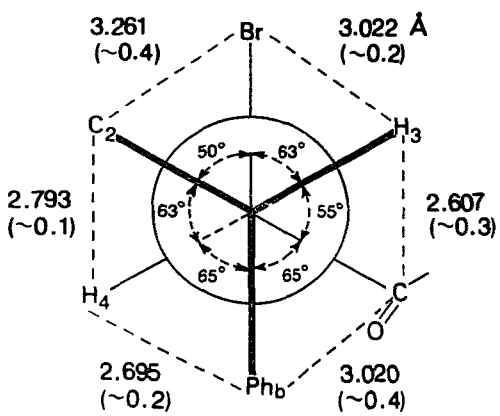
to the *ortho* carbon of Ph_a (ca. 0.5 Å). The two phenyl rings are tilted with respect to one another, but are roughly parallel. These rings also lie well within the combined van der Waals' radii (ca. 0.4 Å, for the *ipso* carbons). The carbonyl n electrons also lie close in space to Ph_b. Thompson[110b] has noted that the separation of each individual pair of vicinal atoms is within the combined van der Waals' radii by a roughly constant distance, indicative of no particularly strong attractive or repulsive interactions. The answer to the question of why this conformation is present probably lies in the interactions present in nonpreferred conformations. The Newman projections (**71a** and **71b**) record exact dihedral angles, separation distances (and factors by which these distances lie within van der Waals' radii).



(71)



(71a)



(71b)

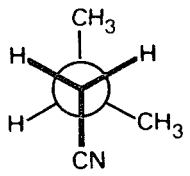
VI. ADDENDA

A final computer-assisted search of the literature was made in an attempt to locate the latest work on the conformation of cyanides. The computer also graciously provided references to previous work, for which a manual literature search had already been completed. It was distressing to note the number of citations the computer located that the previous search missed. Equally distressing was the fact that the computer failed to find some work that the manual literature search uncovered. Thus, apologies are in order to colleagues whose work is inadvertantly slighted in this chapter, as it appears that neither personal nor computer-assisted literature searches are totally reliable.

The remaining sections of this chapter are again organized into discussions of simple molecules, special cases and, finally, complex cyanides. As before, the casual reader may wish to omit the second or third sections.

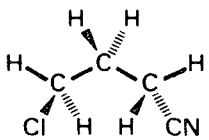
A. Simple Molecules Revisited

Raber and coworkers have investigated the conformational preferences in cyclohexanecarbonitrile (**1**), butanenitrile (**15**), and in 3-methylbutanenitrile (**16**), by lanthanide-induced nmr shifts[111]. This technique has not enjoyed a good reputation, as it has been abundantly proved that the conformation of the lanthanide complex is not necessarily the same as that of the free molecule[112]. However, in the case of nitriles, complexation occurs at the CN lone pair, a site distant from the centres involved in conformational variation. The data obtained are similar to those found by other techniques. Thus, **1** is found to prefer the equatorial conformer (54%). Butanenitrile is preferentially *gauche* (53%), but 3-methylbutanenitrile rather more strongly prefers conformer **16b** (70%). The latter is a stronger preference than indicated by infrared data.



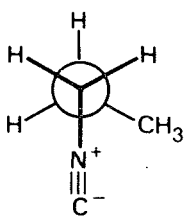
(16b)

Das and coworkers[113] have studied the conformation of 4-chlorobutanenitrile by infrared techniques, and by MO calculations. Surprisingly, it has been found that not only cyanide (cf. **68**) but also chloride is *gauche* to their respective vicinal chain carbon in the preferred conformer **72**.



(72)

The conformation of isocyanides has received little study. However, recent molecular orbital investigation of carbylaminopropane (**73**) corroborated earlier experimental results by Wilson and coworkers which indicated that the preferred conformation was, by a small factor, *gauche*,[114] as shown below. In this regard, the conformational preferences are similar to normal cyanides.



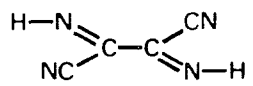
(73)

The popularity of butanedinitrile (**23**, Z = CN) as a substrate for conformational investigations has continued unabated. However, different techniques have now been utilized. Electron diffraction studies have shown that the *trans* conformer is preferred in the gas phase (74%), in contrast to most solutions where the *gauche* conformer is favoured[115]. In the gas phase, the preference for the *trans* conformer is 1.5 kcal mol^{-1}, and is common, the entropy difference (*trans* → *gauche*) is low, 1.4 e.u.

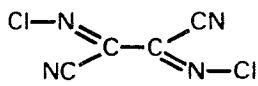
In the solid state, a plastic phase exists in which the molecules enjoy a degree of mobility. Neutron scattering results indicate that the correlation time (roughly equivalent to a half-life of the molecule in a particular orientation), is ca. 10^{-11} s at ca. 300K for the *trans* → *gauche* change in conformation[116]. The correlation time for the reverse change is slightly larger. The entire molecule may also rotate within the 'cage' on roughly the same time-scale. However, it has been stated that molecular rotation occurs preferentially in the extended *trans* conformer.

In solution, Nowak and coworkers have found that the *trans* form of butanedinitrile (**23b**, Z = CN) is more stable in solvents such as benzene, but in solvents having a dielectric constant greater than ca. 5, the *gauche* conformer is the more stable[117]. The details of this sophisticated inquiry into solvent effects are too complex to cover in a brief review. However, quadrupolar interactions of solute with the sphere of solvent molecules oriented around the solute are significant, as are solute–solvent dipolar interactions[27].

Investigations of the conformation of diiminosuccinonitrile (DISN) and its dichloro derivative (**74** and **75**) indicate a strong preference for the *trans* isomer as shown below[118]. The infrared/Raman data have been collected in solvents such as CH_3CN, as well as in the solid phase. No evidence for the existence of the *gauche* conformer has been found. An unusual observation is that the NH···N hydrogen bonding in **74** appears to be stronger in the liquid than in the solid phase. In contrast to diaminomaleonitrile (**24**), the electron-withdrawing groups are *trans*.

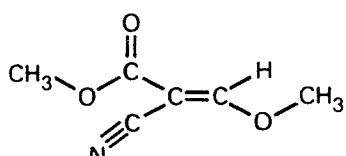


(74)



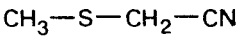
(75)

With regard to other vinyl cyanides, a MO investigation of the detailed orientation of groups in the enol ether **76** indicates a preference for the structure shown[119]. Thus, the methoxy methyl is *trans* to the double bond, rather than *cis*, which is favoured in 1-methoxyethene for orbital symmetry reasons. Perhaps steric interaction between methyl and cyanide destabilize the *cis* conformer. However, the *gauche* conformer should be accessible without undue steric problems. The carbonyl also occupies the *s-cis* conformation with respect to the double bond. In other respects the molecular conformation is similar to the enamines discussed earlier, with methoxyl *cis* to cyanide and *trans* to carbomethoxy. The predicted barrier to isomerization, ca. 29 kcal mol^{-1}, is rather larger than found for the enamines, however.

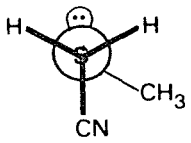


(76)

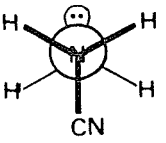
Several studies on the nitrile (**77**) have recently appeared[111c,120]. Like the oxygen analogue (**42**), the *gauche* conformer **78** in which a sulphur lone pair may be considered to be *trans* to cyanide is preferred. From a microwave study in the gas phase, the *trans* form exists at a level of less than 5%. Infrared studies, however, appear to be indicative of a mixture of conformers. For the nitrogen analogue, aminoethanenitrile (**78**), an *ab initio* MO study has likewise indicated a similar conformational preference[121]. A hyperconjugative interaction might be invoked between the presumably somewhat



(77)



(77a)

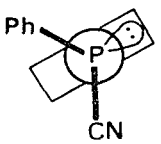


(78)

electronegative cyanide and the lone pair of nitrogen[48]. However, 3-amino-1-propyne (**79**) also occupies the same type of conformation, and thus a hyperconjugative interaction would have to be considered for both molecules or neither.

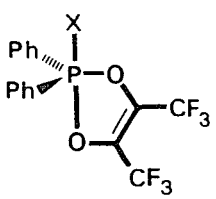
B. Special Cases Revisited

Some additional data have appeared on phosphorus derivatives. In cyanodiphenylphosphine (**80**), it has been found that the *ortho* C—H bond of one phenyl group is eclipsed with the phosphorus lone pair as shown below when viewed through the P—C(1)Ph bond[122].

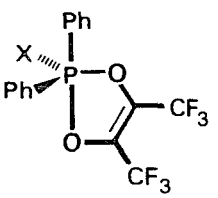


(80)

In the phosphorane **81**, Trippett and coworkers have studied the tendencies for various groups X to occupy the apical position as in **81a** as opposed to the equatorial position as in **81b**[123]. The apicophilicity of a given group is usually regarded as related to the electronegativity of the group in question. For X = CN, the energy required for interconversion (**81a** → **81b**) is ca. 14 kcal mol^{-1}, indicating a *greater* apicophilicity for cyanide than for chloride, for which the value is 12.3 kcal mol^{-1}.

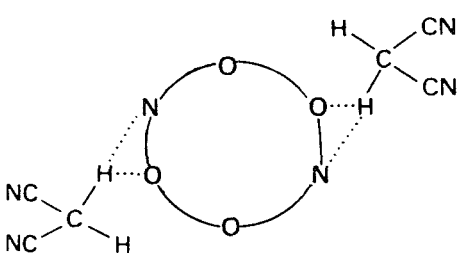


(81a)



(81b)

An interesting study of complexes between crown ethers and neutral molecules has recently been reported[124]. Charge-dipole interactions between ions and the oxygen

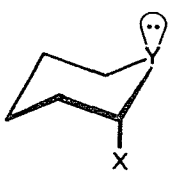


(82)

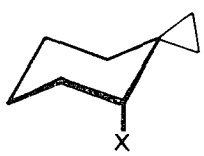
functions of crown ethers lead to strong complexation, and many examples of this phenomenon are well recognized. However, it has been shown that neutral molecules may also complex with crown ethers via dipole–dipole interactions. In a propanedinitrile–crown ether system, a 2:1 complex (**82**) has been observed by X-ray crystallographic means. A bifurcated hydrogen bond has been postulated between one hydrogen of each propanedinitrile and a nitrogen and an oxygen of the crown ether. A propanedinitrile molecule exists on each face of the crown, but no penetration of the cavity is evident.

C. Complex Molecules Revisited

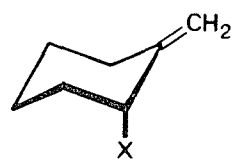
In previous work, Zefirov and coworkers[125] have shown that a strong tendency exists for X to adopt an axial conformation in **83** (the anomeric effect). However, a similar tendency is also observed in the spirocyclopropane (**84**), and in the alkene (**85**). In **85**, the C—X bond parallels the p orbitals of the alkene, and in **84**, the bent bonds of the cyclopropane ring, which approximate p orbitals in character, are likewise oriented in the same direction as the C—X bond. In 2-halocyclohexanones, a similar axial preference has been recognized for some time[126]. Zefirov's study concerns the ketone analogue, **86**. For a variety of X groups, including the halogens, phenyl and carbomethoxy, the axial conformer is strongly preferred. Steric effects effectively prevent X from assuming the equatorial position, and in addition, delocalization effects involving the σ electrons of the C—X bond to the electronegative $C(CN)_2$ function have been considered.



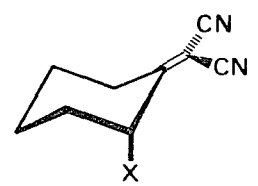
(**83**)



(**84**)

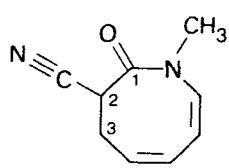


(**85**)



(**86**)

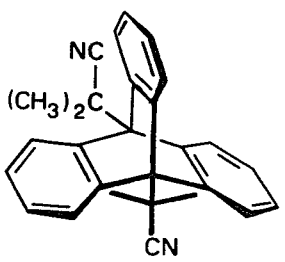
On the other hand, the cyanide in **87** was found to be equatorial in a distorted boat conformation[127,128]. The N—C(1)—C(2)—C(3) dihedral angle is ca. 10°, indicating near-planarity of these atoms. From the stereo drawing of the crystallographic structure, cyanide does not appear to be strictly parallel to carbonyl.



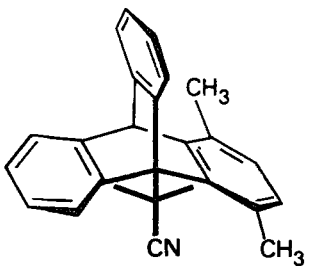
(**87**)

Oki and coworkers have reported some interesting data on the internal rotation in several triptycene derivatives[129]. Compound **88** has been found to have the incredibly high barrier to rotation of the cyanodimethylcarbinyl group of 37 kcal mol^{-1}. As

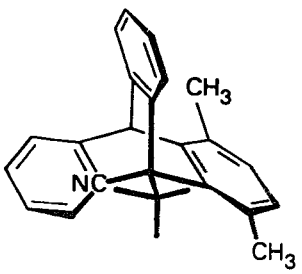
steric hindrance of the system increases, i.e. in **89**, the barrier becomes somewhat smaller, i.e. 36 kcal mol^{-1}. The even more sterically hindered compound in which carbomethoxy replaces cyanide has an even lower barrier of 28 kcal mol^{-1}. This type of observation is not unusual. Incorporation of additional steric hindrance often increases the energy of the ground state more than that of the eclipsed state. The eclipsed 'transition state' for rotation is strongly affected by quantum-mechanical effects associated with the opposition of orbitals. Due to 'relaxation' in which the bond angles of the groups about to become eclipsed widen on approach to the eclipsed state, the additional steric effects may not increase the energy of the 'transition state' that much. In **89**, the *dl* form **89a** is favoured over the *meso* form, **89b**, by factors of 8- to 28-fold, depending upon the substitution pattern in **89** and related compounds.



(88)

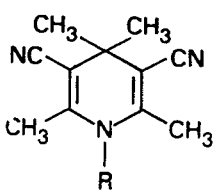


(89a)



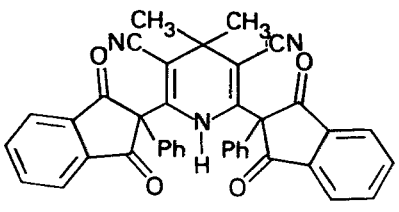
(89b)

In certain dihydropyridines (**90–92**), Sekacis and coworkers have found that the enthalpy change for the boat–planar interconversion is ca. 3.7–6.7 kcal mol^{-1}, depending upon substitution pattern[130]. In the imposing molecule **91**, the enthalpy change is smaller, 3.5 kcal mol^{-1}. In the 4-unsubstituted compound **92**, the transition is too fast to be detected.

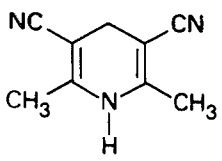


(90)

R = H. C_2H_5. C_5H_{11}



(91)



(92)

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CHAPTER 20

Recent advances in isocyanide chemistry

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I. INTRODUCTION

In recent years the chemistry of isocyanides has been the subject of extensive investigation. As a result, a large number of papers have appeared describing novel syntheses and new interesting chemical reactions of isocyanides. Our knowledge of the synthetic applications of isocyanides has expanded rapidly. Particularly, the α addition of an organometallic reagent to an isocyanide and the reactions of α-metalated isocyanides have received considerable attention. The isolation of naturally occurring isocyanides have initiated interest in their syntheses.

Because of the availability of a monograph[1a] on isocyanides covering the literature prior to 1970, this chapter will focus mainly on the recent developments in the chemistry of isocyanides[1b].

II. TOXICITY OF ISOCYANIDES

Although most volatile isocyanides may be malodorous they do not exhibit appreciable toxicity to mammals. However, 1,4-diisocyanobutane has been shown to be highly toxic and therefore all isocyanides should be handled with due *caution*. Volatile isocyanides show their toxic action by inhalation probably due to their ability, like carbon monoxide, to block haemoprotein and enzyme systems[2]. The toxic action seems to increase if ethanol is present in the body of the experimenter. Van Logren[3] observed that the visible symptoms of intoxication strongly resemble those of dithiocarbamate ethanol intoxication.

III. STRUCTURE AND PHYSICAL PROPERTIES

Isocyanides, which are isoelectronic with carbon monoxide (equations 1a and 1b), have been shown to be linear molecules by both electron diffraction[4] and microwave studies[5]. Like carbon monoxide, isocyanides may be viewed as 'carbenoid' in character.

$$R\ddot{N}{=}C: \longleftrightarrow R\overset{+}{N}{\equiv}\bar{C}: \quad (1a)$$

$$:\ddot{O}{=}C: \longleftrightarrow :\overset{+}{O}{\equiv}\bar{C}: \quad (1b)$$

For characterization purposes the infrared and NMR spectra are particularly useful. Isocyanides absorb in the infrared at ~2150 cm^{-1} whereas the isomeric cyanides absorb at ~2250 cm^{-1}. The ^1H-NMR spectra of isocyanides are unique. Since the nuclear quadrupole coupling in isocyanides is very low, indicating a negligible electric

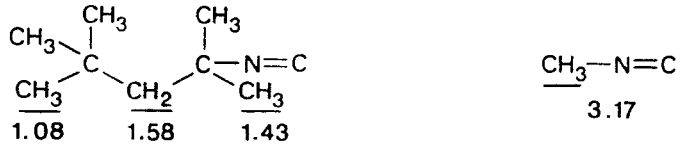


FIGURE 1

field gradient about nitrogen, one usually can observe resonance signals of protons on the carbon atoms α or β relative to the isocyano nitrogen atom[6]. Since ^{14}N has a nuclear spin = 1, one often observes triplet splitting. For example, in the spectrum of 1,1,3,3-tetramethylbutyl isocyanide[7] one observes a singlet at 1.08 ppm corresponding to the δ-hydrogens of the *t*-butyl group (see Figure 1). However, at 1.43 ppm there is a triplet with a coupling constant J = 2 Hz and at 1.58 ppm another triplet with J = 2.3 Hz. Methyl isocyanide[8] shows a ^{14}N–^{1}H triplet absorption for the α-carbon protons at 3.17 ppm and a coupling constant J = 2.4 Hz. This type of coupling with J = 1–3 Hz may be used to characterize the substance as an isocyanide. However, the absence of this coupling does not prove that the molecule is not an isocyanide since aromatic and allenic isocyanides as well as $(CH_3)_3SiCH_2NC$ and $CH_3OCH_2CH_2NC$ do not show this coupling. Stephany and Drenth[9] have extensively studied the effect of solvent and substituents on IR, ^{1}H and ^{13}C chemical shifts and $J(^{14}N–^{13}C)$ coupling constants of a variety of isocyanides. Recently, ^{13}C-NMR spectroscopy has become a particularly useful analytical tool in the investigation of isocyanide–transition-metal complexes[10].

The mass spectra of aliphatic isocyanides are similar to those of corresponding cyanides with predominant β-bond cleavage[11]. However, α-bond cleavage occurs to a greater extent in isocyanides than in cyanides reflecting the weaker R—N bond. Expulsion of HCN is the main mode of fragmentation in aromatic isocyanides[12].

In the molecular orbital model of isocyanides (Figure 2), the nitrogen is bonded to the terminal carbon atom by a σ bond and a π_1 bond in much the same way as with nitriles. However, in contrast to cyanide, the isocyanide nitrogen donates two electrons to form the π_2 bond and a nonbonding pair of electrons resides at the carbon atom in an orbital of sp symmetry. Recently various MO calculations have been reported on a number of isocyanides[13]. They show the isocyano carbon having substantially greater 2s orbital population, but significantly smaller $2p_y$ and $2p_z$ orbital populations. The presence of both nonbonding electrons and electron-deficient π orbitals gives the isocyano carbon a dual nature which is abundantly clear in its chemical properties.

The gross atomic charges obtained from MO calculations indicate that, contrary to the conventional view based on the dipolar canonical structure, the nitrogen is electron-rich relative to both isocyano carbon and the carbon attached to the isocyano group. The gross dipole moment of the isocyano group is directed from the terminal carbon toward the nitrogen ($\overrightarrow{N—C}$) and not in the reverse ($\overleftarrow{N—C}$) direction.

It should be recognized that the dipolar canonical structure, $R—\dot{N}\equiv\bar{C}$, depicts the charge distribution of the π-electron system only and discloses nothing about the

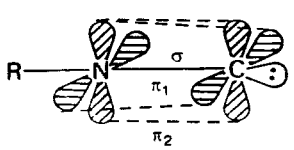


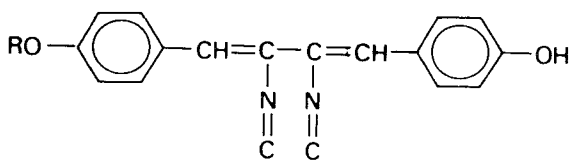
FIGURE 2

charge distribution in the σ-electron system. The calculations show that the dipole caused by the σ charge distribution makes a greater overall contribution than does the π delocalization. This results in a gross dipole moment for the isocyano group which is reversed with respect to the generally accepted direction.

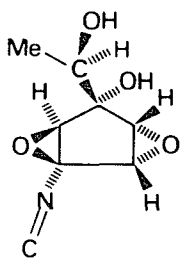
The significance of the nitrogen being electron-rich relative to the α carbon attached to the isocyano group is that it implies that the isocyano group will behave as an electronegative moiety acting largely through an inductive effect similar to oxygen and fluorine. Moreover, if the α carbon contains a negative charge the delocalization of that charge by the isocyano group will be minimal (see Section VIII), but delocalization of a positive charge should be very effective.

IV. NATURALLY OCCURRING ISOCYANIDES

Until recently, antibiotics xanthocillin **1a** and xanthocillin monomethyl ether **1b** were the only two characterized naturally occurring isocyanides[14]. Currently, an increasing number of naturally occurring molecules containing an isocyanide group have been isolated[15]. Trichoviridine **2**, a fungal metabolite isolated from *Trichoderma* sp. was

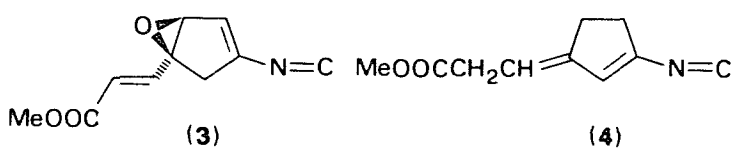


(**1a**) R = H
(**1b**) R = Me



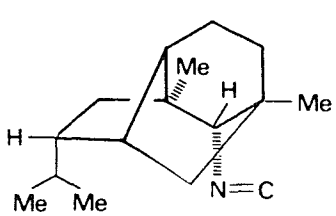
(**2**)

shown to contain a novel isocyano epoxide moiety[16]. Recently, two isocyano acids[17] have been isolated from cultures of the fungus *Trichoderma hamatum* (Bon) as the corresponding methyl esters **3** and **4**. A number of sesquiterpene and diterpene

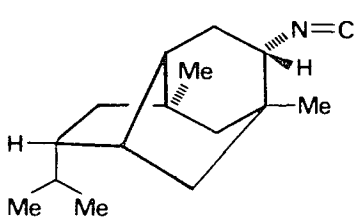


(**3**) (**4**)

isocyanides possessing novel ring-systems have been established as metabolites of marine sponges[15,18]. They constitute an intriguing class of naturally synthesized compounds from both chemical and chemotaxonomic viewpoints. These isocyanides have been reported to show a wide spectrum of antibiotic activity. It is interesting to note that (±)-2- and (±)-9-isocyanopupukenanane (**5** and **6**), a pair of sesquiterpenes

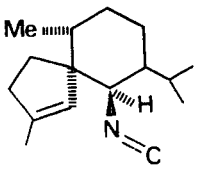


(**5**)



(**6**)

produced by sponge *Hymeniacidon* sp., are used for defense purposes by nudibranch *Phyllidia varicosa*. Total syntheses of both **5** and **6** have been recently published[19]. The (−) isomer of another naturally occurring isocyanide, (+)-axisonitrile-3 (**7**), which was



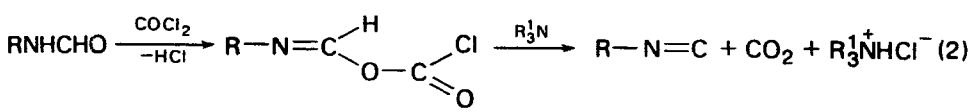
(**7**)

isolated from the marine sponge *Axinella cannabina* has been synthesized by Caine and Deutsch[20]. Isocyanides have also been proposed as precursors for the synthesis of amino acids in the 'Prebiotic soup'[21]. Hydrogen and deuterium isocyanides have been identified in interstellar clouds[22].

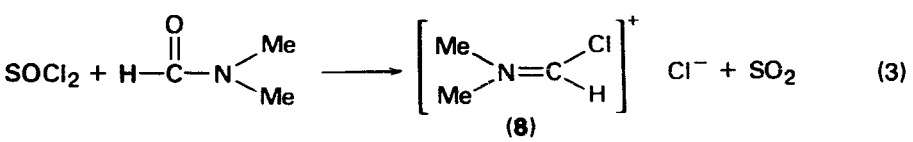
V. SYNTHESIS OF ISOCYANIDES

1. Dehydration of formamides

The ready availability of *N*-monosubstituted formamides makes them an attractive precursor for the formation of isocyanides. Phosgene in the presence of a tertiary amine is the most commonly employed dehydrating reagent[1] (equation 2). However,

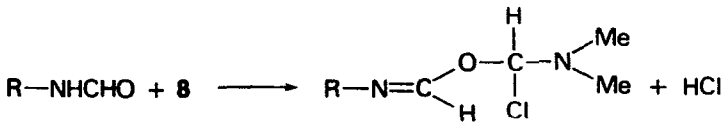


this procedure suffers from the disadvantages inherent in the use of phosgene for large-scale preparations. To circumvent the use of phosgene a variety of new dehydrating reagents have been reported. Walborsky and Niznik selected chlorodimethylformiminium chloride (**8**) (Vilsmeier reagent) as the dehydrating agent for the preparation of isocyanides from formamides[23]. This reagent (**8**) can be readily prepared, *in situ*, from thionyl chloride and *N,N*-dimethylformamide (DMF) (equation 3). The addition of this dehydration reagent, under controlled conditions to the formamide, followed by solid sodium carbonate, leads to excellent yields of

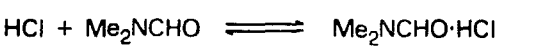


(**8**)

isocyanides (equations 4a–c). This method is general and convenient. Recently Ugi and coworkers[24] modified his original procedure by using diphosgene (trichloromethyl chloroformate) (**9**) in place of phosgene (equation 5). According to Ugi, **9** is easier to handle and gives higher yields than phosgene. Diphosgene is utilized in the preparation of bifunctional isocyanides such as 4-isocyanophenyl chloroformate (**10**) (equation 6), which is used as reagent for the introduction of the isocyano group into polystyrene–divinylbenzene copolymers[25]. Recently a variation of the Vilsmeier reagent, 2-chloro-3-ethylbenzoxazolium tetrafluoroborate (**11**), in the presence of triethylamine has been used to dehydrate formamides (equation 7)[26]. Ziehn and coworkers[27a] have observed that isocyanides are formed very readily by the joint



(4a)



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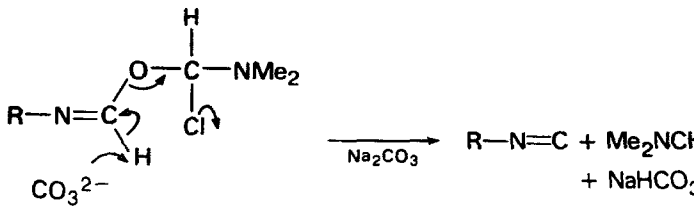
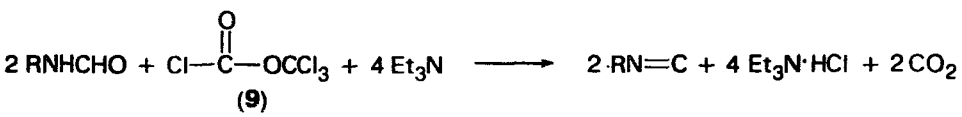
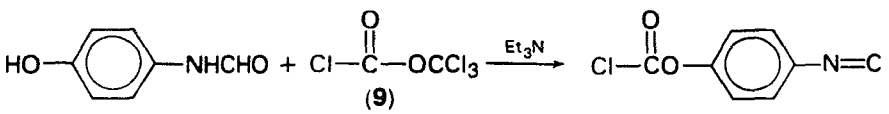


(4c)



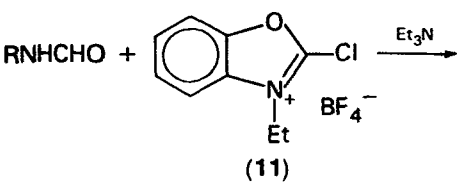
(5)

(9)

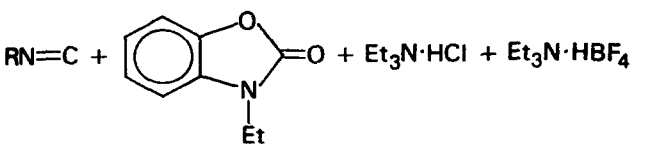


(6)

(9) (10)

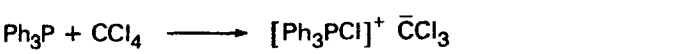


(11)

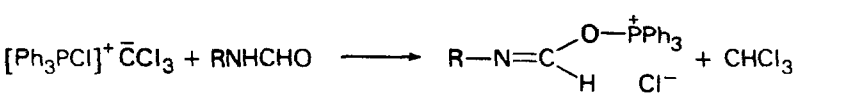


(7)

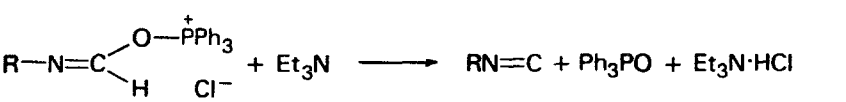
action of triphenylphosphine, CCl_4 and triethylamine on monosubstituted formamides. The elimination of water proceeds stepwise (equations 8a–c). Experiments with formamides deuterated at the nitrogen have shown that the proton of the chloroform comes exclusively from the N—H bond. This reaction has been



(8a)



(8b)



(8c)

successfully applied to the synthesis of *N*-isocyanoiminotriphenylphosphane (equation 9)[27b].

$$HCONHNH_2 + 2\,PPh_3 + 2\,CCl_4 + 2\,NEt_3 \longrightarrow CNNPPh_3 + 2\,CHCl_3 + 2\,Et_3\overset{+}{N}H\ Cl^- + Ph_3PO \qquad (9)$$

2. *Phase-transfer Hofmann carbylamine reaction*

Although the carbylamine reaction involving the dichlorocarbene intermediate is one of the early methods of isocyanide synthesis, it had not been preparatively useful because of lower yields. Recently Ugi, Weber, Gokel and Widera applied phase-transfer catalysis (PTC) to the Hofmann carbylamine reaction and demonstrated that the reaction of primary amines with chloroform or bromoform and 50% sodium hydroxide in the presence of the phase-transfer catalyst, benzyltriethylammonium chloride, produced isocyanides in 40–60% yield (equation 10)[28]. Following a similar

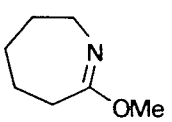
$$CHCl_3 + NaOH \xrightarrow{PTC} [:CCl_2] \begin{cases} \xrightarrow{RNH_2} RN{=}C \\ \xrightarrow{R_2C{=}N{-}NH_2} R_2C{=}N{-}N{=}C \end{cases} \qquad (10)$$

procedure, Jakobsen prepared aliphatic *N*-isocyanoimines from the corresponding hydrazones (equation 10)[29].

Employing a crown ether as the phase-transfer catalyst, Mayer and coworkers synthesized a number of isocyanides by reacting *N*-sulphinylamine with $CHCl_3$ and solid KOH (equation 11)[30].

$$R{-}N{=}S{=}O \xrightarrow[CHCl_3/KOH]{\text{Crown ether}} R{-}N{=}C \qquad (11)$$

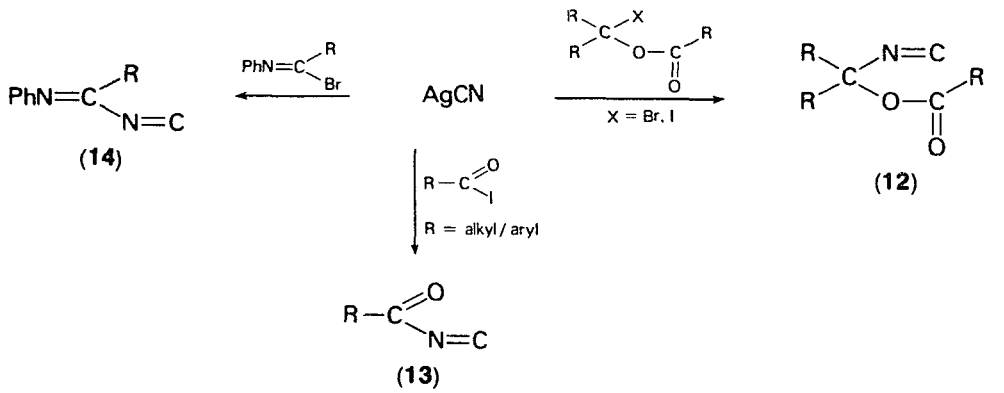
A German patent[31] describes the preparation of ω-isocyanocarboxylic esters by the reaction of the lactim ethers with $CHCl_3$ in the presence of hydroxide and phase transfer catalyst (equation 12).



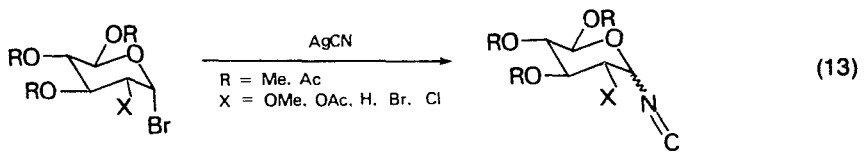
$$\xrightarrow[PTC]{CHCl_3,\ 50\%\ NaOH} MeOOC{-}(CH_2)_5{-}N{=}C \qquad (12)$$

3. *Displacement of halide by cyanide*

In recent years, the revival of another early method of isocyanide synthesis, namely halide displacement by metal cyanide, particularly by silver cyanide, has led to the syntheses of a variety of novel isocyanides, (Scheme 1)[32]. Whereas α-acyloxyisocyanides **12** are stable enough to be isolated and characterized, α-acyl isocyanides **13** and *N*-imidoyl isocyanides **14** are chemically very reactive. Substitution of glycosyl bromides with silver cyanide constitutes a good synthesis of the corresponding glycosyl isocyanides (equation 13)[33]. The reaction is accompanied by anomerization but good yields of mixtures of α- and β-glycosyl isocyanides are obtained.



SCHEME 1



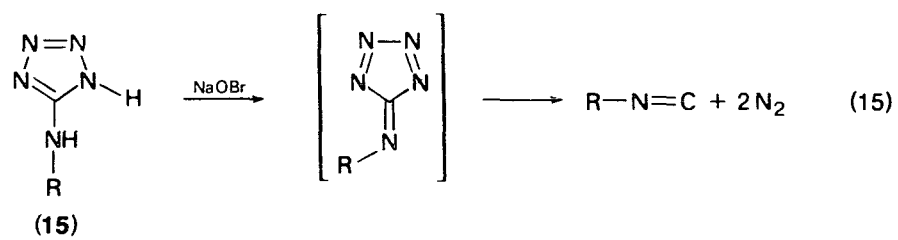
(13)

Songstad and coworkers[34] have shown that by applying onium dicyanoargentates instead of silver cyanide, alkyl isocyanides can be obtained in high yields (equation 14). Under these conditions, acyl halides and aryl halides have been found to be completely unreactive. This synthetic method is useful only for diphenyl and triphenyl carbinyl halides.

$$RX + Me_4N^+\ Ag(CN)_2^- \longrightarrow R{-}N{=}C + Me_4N^+\ AgX_2^- \qquad (14)$$

4. *Miscellaneous methods*

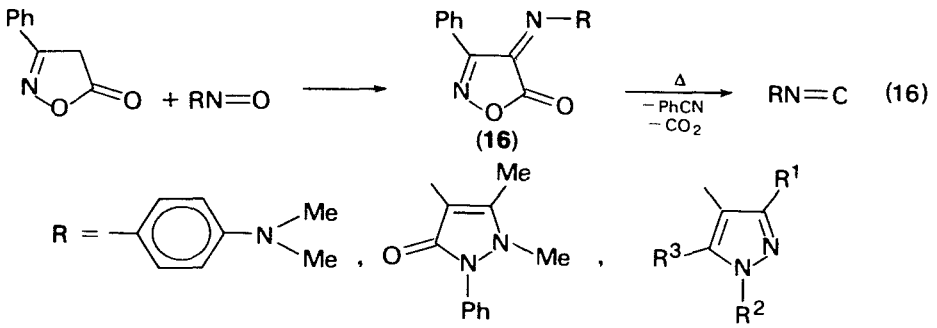
Höfle and Lange[35] have reported a novel 'reagent-free' isocyanide synthesis. The starting materials for their method are the 5-alkyl(aryl)aminotetrazoles **15** which are readily prepared from 5-aminotetrazole or monosubstituted thioureas. Oxidation of **15** leads to liberation of two moles of nitrogen and one mole of isocyanide (equation 15).



(15)

An hitherto unknown class of heteroaryl isocyanides becomes readily accessible from nitroso compounds by using the Wentrup method[36]. The important feature of this procedure is that the thermal decomposition of 4-iminoisoxazolones **16** leads to a pure product and utilizes a very simple experimental procedure (equation 16).

Recently, exploitation of transition metal complexes for the synthesis of novel isocyanides within such metal complexes have been reported. For example, the reactions of isocyanide dichlorides with metal complexes have opened up a general



route to isocyanide complexes (equation 17)[37b] as has the reaction between amines and Fe(II)–dichlorocarbene complex (equation 18)[37a].

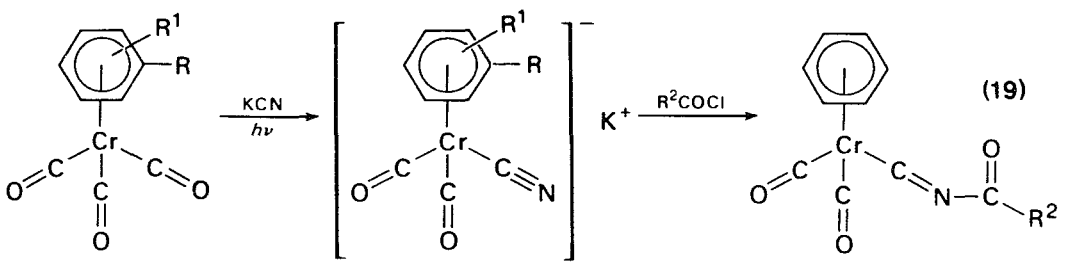
$$Na_2Cr(CO)_5 + R{-}N{=}C\begin{matrix}Cl\\Cl\end{matrix} \longrightarrow Cr(CO)_5C{=}N{-}R \qquad (17)$$

$$R = C_6H_{11}, Ph, COPh, SO_2Ph$$

$$TPPFe^{II}(:CCl_2) + 2\ RNH_2 \longrightarrow TPPFe(RNH_2)(RN{=}C) \qquad (18)$$

$$TPP = \text{tetraphenylporphyrin}$$

Simonneaux and coworkers[38] have prepared a series of various *N*-functionalized isocyanides as chromium and manganese complexes. Their reaction scheme (equation 19) involves electrophilic attack of acyl halides on metal cyanide ions. Fehlhammer and



Degel[39] have prepared α-tetrahydrofuranyl and di- or tri-chloromethyl isocyanide complexes by the thermolysis of arenediazonium pentacarbonylcyano-6*A*-metalates in THF and di- or tri-chloromethane solvent (equation 20).

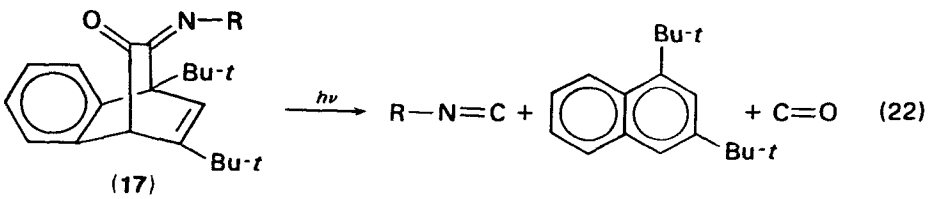
$$[ArN_2^+][M(CO)_5CN] \xrightarrow[\text{or } CHCl_3]{THF\ CH_2Cl_2} M(CO)_5C{=}NR + N_2 + ArH \qquad (20)$$

$$R = \text{(tetrahydrofuranyl)}, CHCl_2, CCl_3$$

$$M = Cr, Mo, W$$

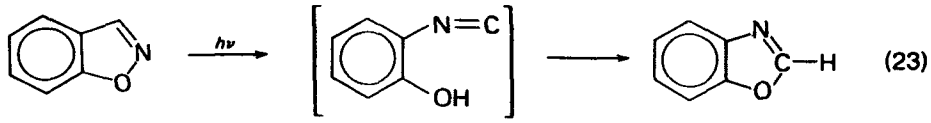
Although photochemical reactions of isocyanides are rare, there are several reports of formation of isocyanides under photolytic conditions. According to Boyer and collaborators[40], photodissociation of formimidoyl cyanide produces the corresponding *N*-alkyl isocyanide (equation 21). Similarly, irradiation of **17** produces isocyanides in

$$R{-}N{=}CH{-}CN \xrightarrow{h\nu} R{-}N{=}C + HCN \qquad (21)$$



(17) (22)

good yields (equation 22)[41]. In the photochemical rearrangement of indoxazene to benzoxazole, isocyanide **18** has been identified as an intermediate (equation 23)[42].



(18) (23)

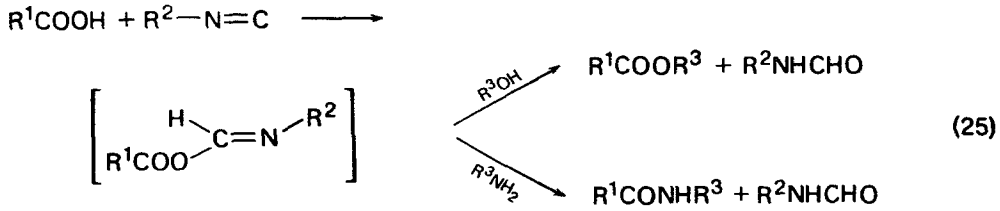
VI. REACTIONS OF ISOCYANIDES

1. General reactions

The reverse reaction of the formation of isocyanides from *N*-monosubstituted formamide has been cleverly used by many workers (equation 24). Isocyanides have

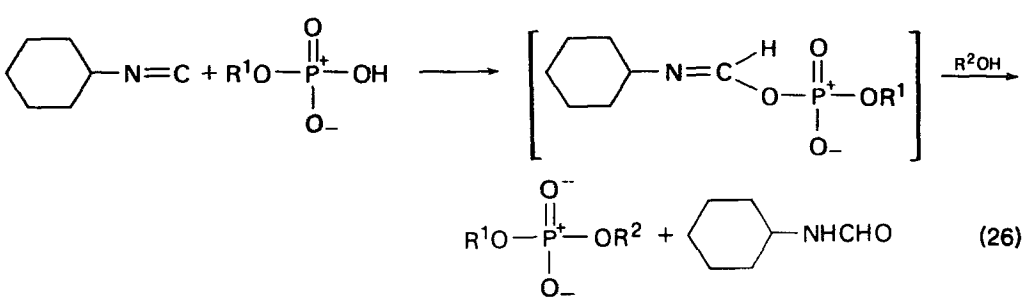
$$\text{RNHCHO} \rightleftharpoons \text{R—N=C} + \text{H}_2\text{O} \qquad (24)$$

been employed as activating reagents for carboxylic acids in the formation of esters and amides (equation 25)[43]. Here, the function of isocyanide is an acceptor of the



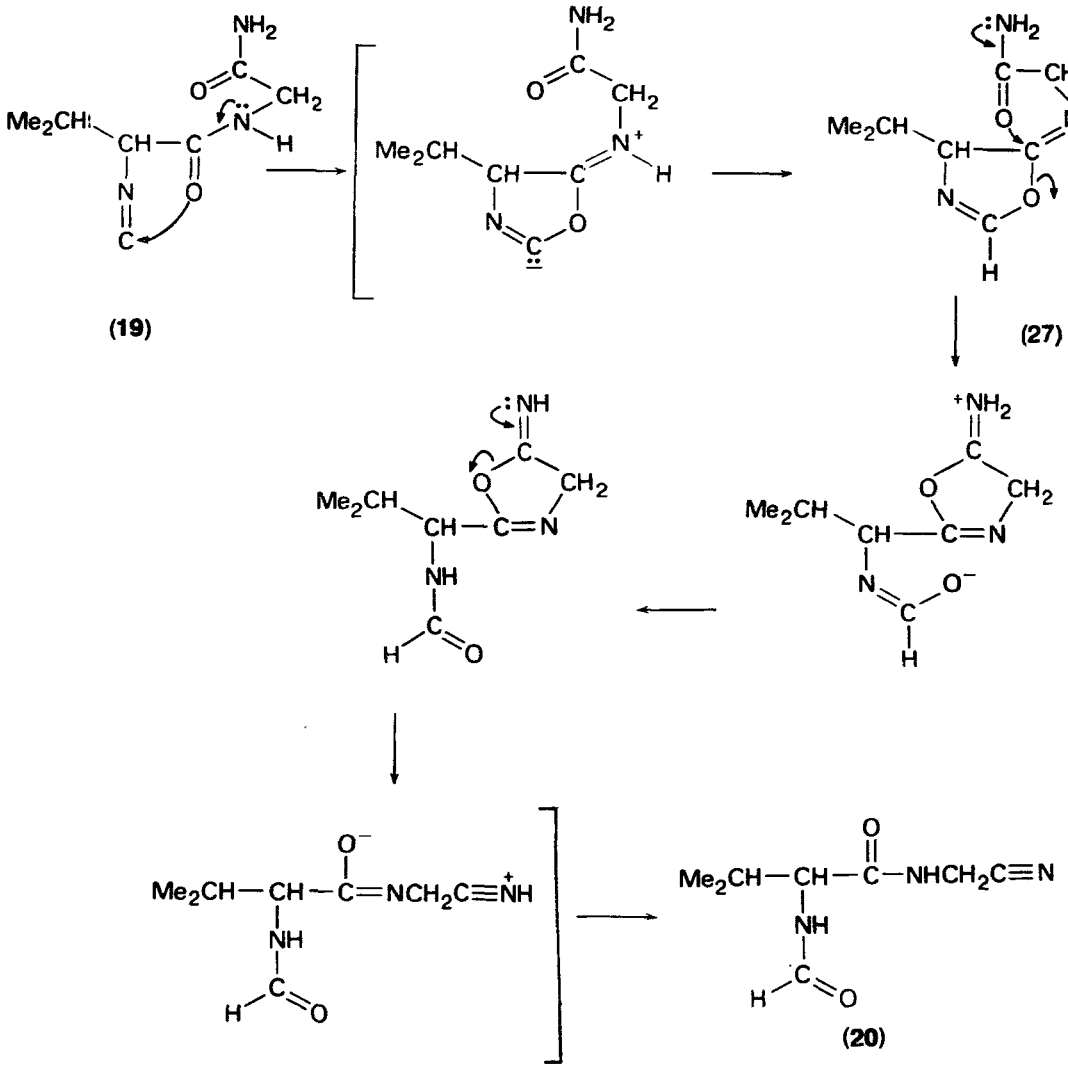
(25)

water molecule produced in the reaction. A recently reported phosphorylation procedure utilizes cyclohexyl isocyanide as an activator of phosphates in a way similar to dicyclohexylcarbodiimide (equation 26)[44]. The dehydrating property of isocyanide



(26)

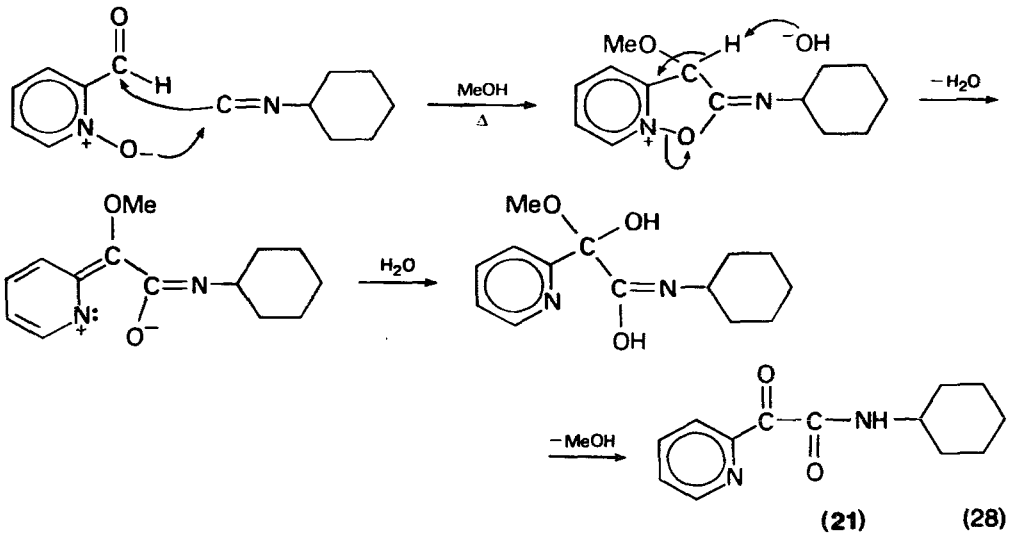
has been used in the rearrangement of isocyanopeptides **19** to give **20** (equation 27)[45]. Mizuno and Kobayashi[46] have reported a novel reaction involving 2-formylpyridine

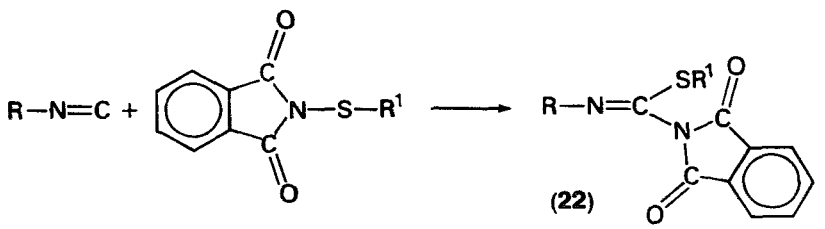


N-oxide and an isocyanide to give **21** which we believe proceeds as depicted in equation (28). It is noteworthy to mention here that the first step in all the above reactions is the α addition of an appropriate reagent to the isocyanide moiety.

The reaction of *N*-monosubstituted phthalimides with isocyanides[47] results in the formation of new α adducts **22** (equation 29). Recently a variety of reactive free radicals have been shown to undergo α addition to the isocyanide carbon to form imidoyl radical **23**. ESR spectroscopy has been used to study the structures and subsequent transformations of **23**[48]. It has been observed that the imidoyl radical may abstract H· to form the product of α addition to the isocyanide (equation 30b) or it may cleave to yield a new radical R· and the cyanide (equation 30c), or if X = O or S, the radical Y· and oxidation products are produced (equation 30d).

Russian workers[49] have reported that perfluoromethacrylic acid derivatives react with cyclohexyl isocyanide to give exclusively 1,4-addition product **24** (equation 31),





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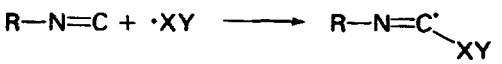
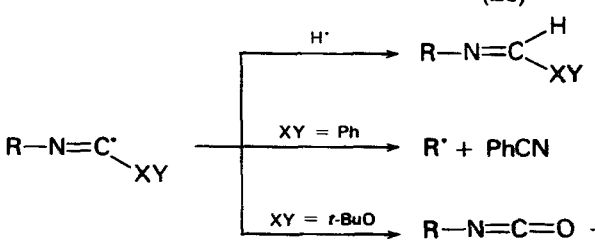


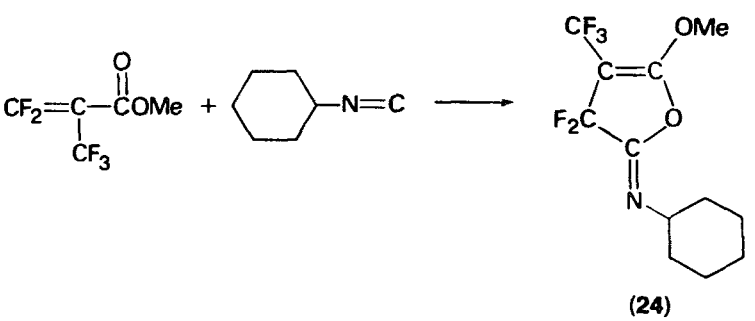
(30a)



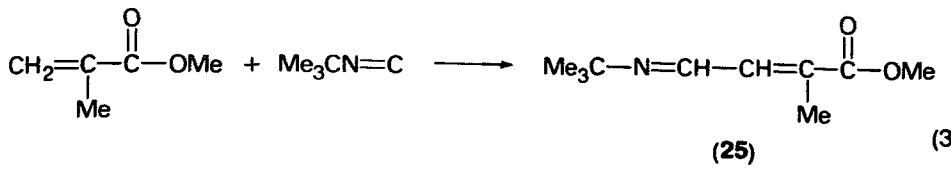
(30b)

(30c)

(30d)



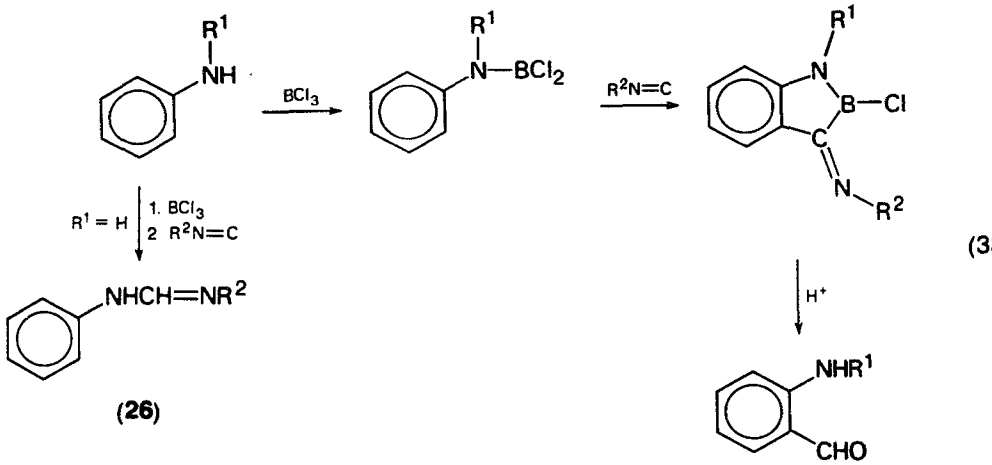
(31)



(25) (32)

whereas the unfluorinated analogue gives the product **25** with *t*-butyl isocyanide (equation 32).

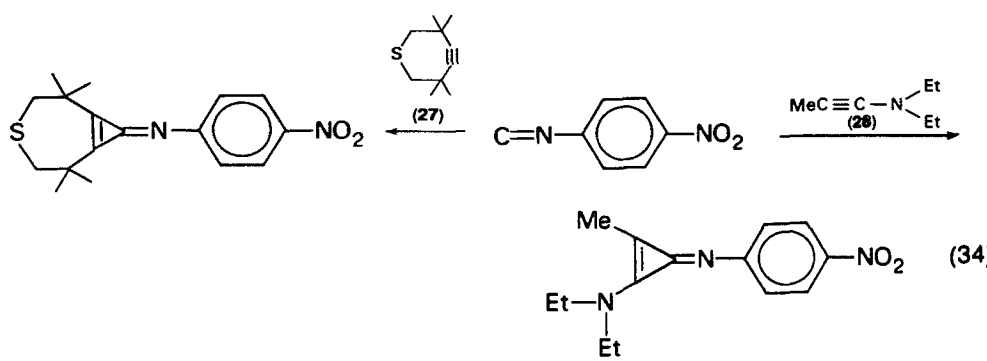
Specific *ortho* formylation of secondary amines has been achieved by the use of isocyanides (equation 33)[50]. When R^1 = H formylation does not take place, but rather the aniline adds to the isocyano carbon giving an α addition product **26**.



(26) (33)

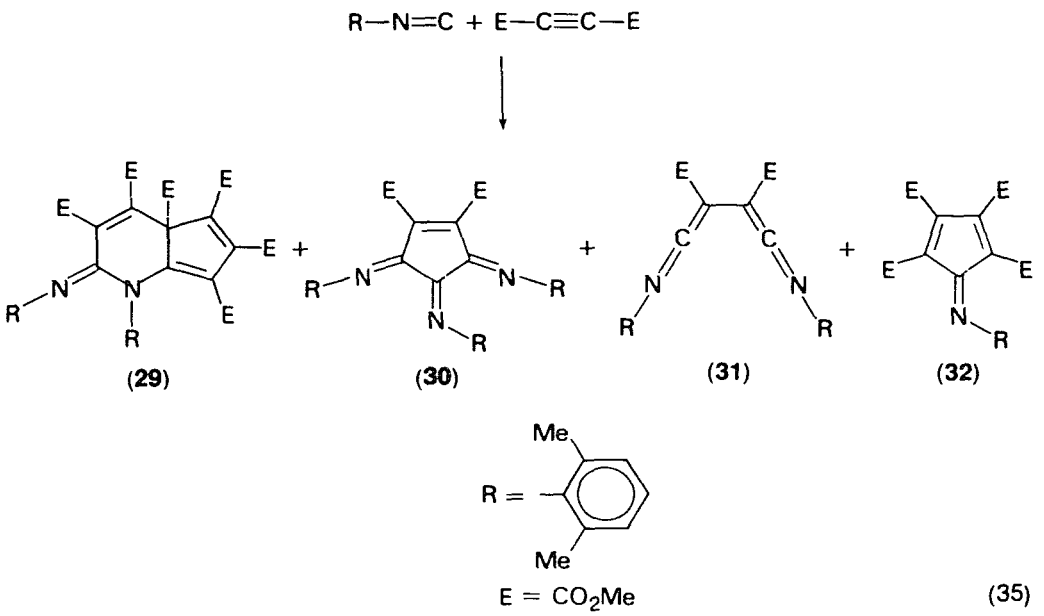
2. Cycloaddition reactions

Isocyanides undergo [1 + 2]cycloaddition reactions with a variety of alkynes. Cyclopropenimines have been postulated as intermediates in these reactions but they have been isolated only from those reactions involving electron-rich alkynes like 3,3,6,6-tetramethyl-1-thio-4-cycloheptyne (**27**) or 1-diethylamino-1-propyne (**28**) (equation 34)[51]. However, in the case of electron-deficient alkynes like dimethyl acetylenedicarboxylate and hexafluorobutyne, the initially formed cyclopropenimine intermediates



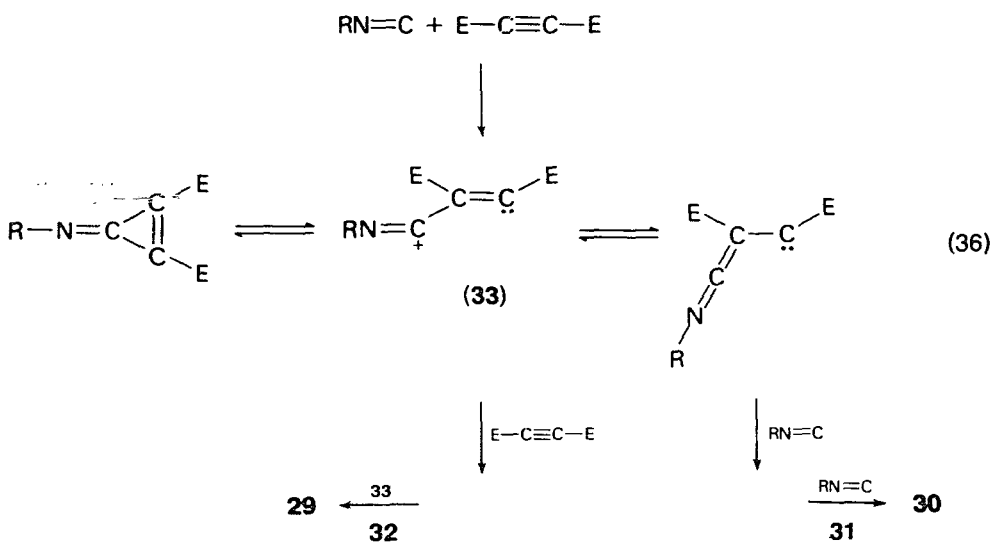
(34)

can undergo further reactions with either isocyanide or alkyne to give secondary products[52]. For example, the cycloaddition reaction of 2,6-dimethylphenyl isocyanide with dimethyl acetylenedicarboxylate produces products **29–32** in various amounts (equation 35). The proposed reaction scheme involves the initial addition of



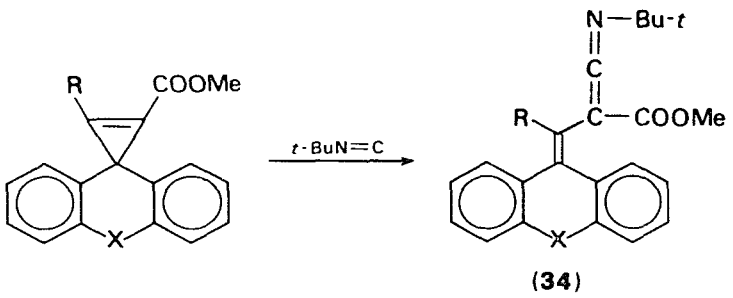
(35)

isocyanide across the triple bond to give **33** which can cyclize in a reversible manner to produce a cyclopropylimine or react further to give secondary products, **29–32** (equation 36). Isocyanides have also been observed to react with cyclopropenes to give



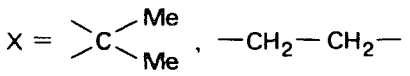
(36)

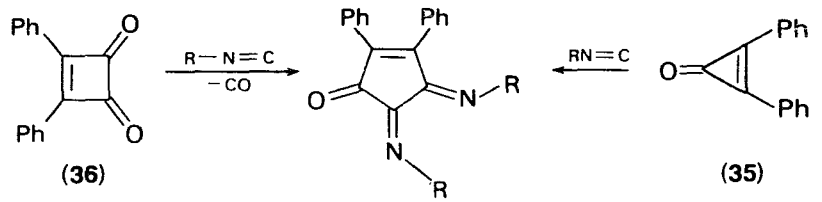
vinylketenimines **34** by nucleophilic ring-cleavage (equation 37)[53]. In contrast, reactions of isocyanides with cyclopropenone **35** or cyclobutenedione **36** produce ring-expanded products (equation 38) in good yields[54]. However, different types of products



(37)

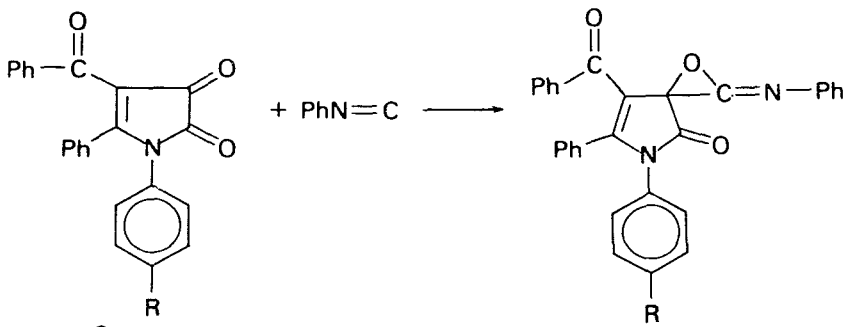
(34)





(36) (35) (38)

are obtained from the reaction of phenyl isocyanide with heterocyclic 2,3-diones (equation 39)[55]. Isocyanides have been observed to undergo 1,3-cycloaddition reactions



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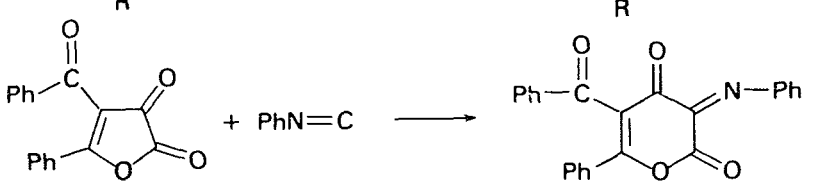
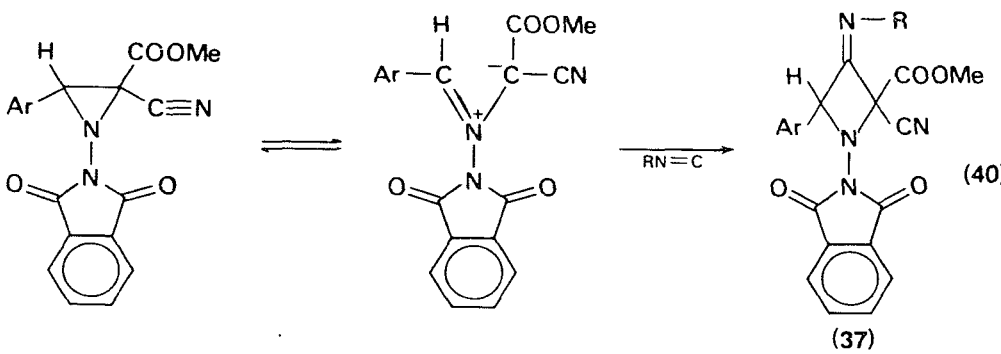




(40)

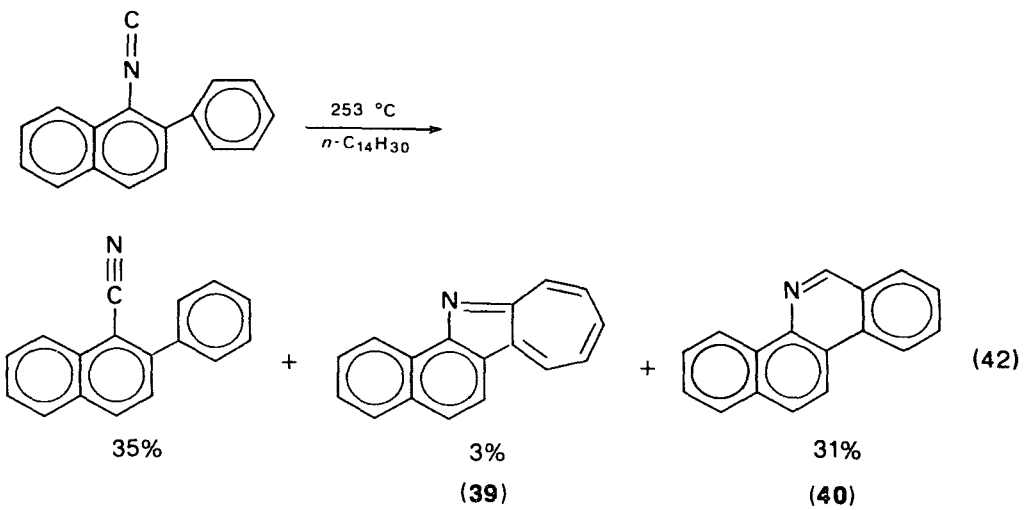
(37)

(38) (41)

with aziridines and amine-*N*-oxides to give **37** (equation 40) and **38** (equation 41) respectively[56]. Although theoretical calculations favour 1,4-cycloaddition of a diene with an isocyanide, so far experimental attempts to observe this type of addition have failed[57].

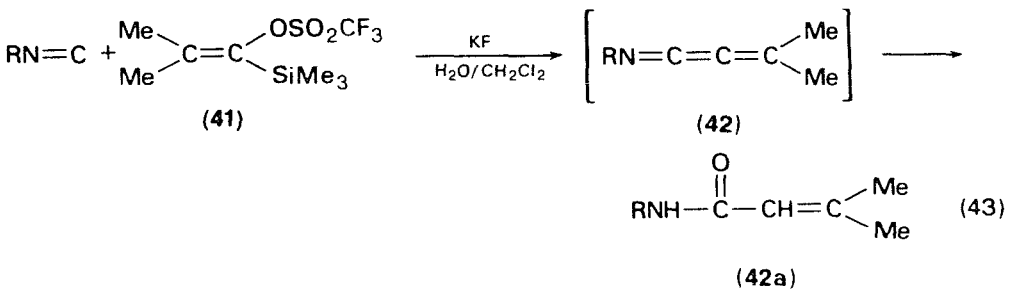
3. *Carbenoid reactions*

Under thermal isomerization conditions, 1-isocyano-2-phenylnaphthalene produces the corresponding cyanide, benzocycloheptindole **39** and benzophenanthridine **40**. The formation of the latter two products represents the first example of thermal insertion of isocyano carbon into C—C and C—H bonds (equation 42)[58]. The reaction



35% (**39**) 3% (**40**) 31% (42)

of isocyanide with **41** under phase-transfer condition produces *N*-substituted acrylamides **42a** providing evidence for the formation of alkadienylideneamine **42** as the intermediate (equation 43)[59]. Japanese workers[60] reported the formation of



(41) (42) (42a) (43)

ketenimines from the photochemical reactions of isocyanides with diazoalkanes (equation 44).

$$RN{=}C + N_2CPh_2 \xrightarrow{h\nu} RN{=}C{=}CPh_2 + N_2 \quad (44)$$

4. Oxidation

Isocyanides are oxidized to isocyanates in acetic acid in the presence of Hg(II), Tl(III) or Pb(IV) acetate through acetoxymetalation[61]. Thallium(III) nitrate trihydrate has been shown to react with isocyanides to give carbamates in high yield (equation 45)[62a]. The redox reaction of isocyanides with amines in the presence of mercury salts gives carbodiimides and ureas (equations 46 and 47)[62b].

$$RN{=}C + Tl(NO_3)_3 \xrightarrow[H_2O]{MeOH} RNHCO_2Me \quad (45)$$

$$RN{=}C + R^1NH_2 \xrightarrow{HgCl_2} R{-}N{=}C{=}N{-}R^1 \quad (46)$$

$$RN{=}C + 3\ R^1NH_2 \xrightarrow[\text{or } HgNO_3]{Hg(OAc)_2} R{-}NH{-}CO{-}NHR^1 \quad (47)$$

VII. REACTIONS OF ISOCYANIDES WITH ORGANOMETALLIC REAGENTS

Organometallic reagents can undergo two types of reactions with isocyanides. If the isocyanide possesses an α hydrogen atom the organometallic reagent will abstract the proton to produce an α-metalated isocyanide **43**. The reactions of **43** have been extensively explored by Schöllkopf and coworkers (equation 48)[63]. When the

$$RCH_2N{=}C + R^1M \longrightarrow R{-}\underset{\displaystyle M}{\underset{|}{C}}HN{=}C + R^1H \quad (48)$$

(43)

isocyanide does not possess α hydrogen atoms, then α addition to the isocyanide occurs to yield a metalloaldimine **44** (equation 49). The chemistry of **44** has been investigated mainly by Walborsky and coworkers[64].

$$RN{=}C + R^1M \longrightarrow R{-}N{=}C\begin{matrix}R^1\\ \diagdown\\ \diagup\\ M\end{matrix} \quad (49)$$

(44)

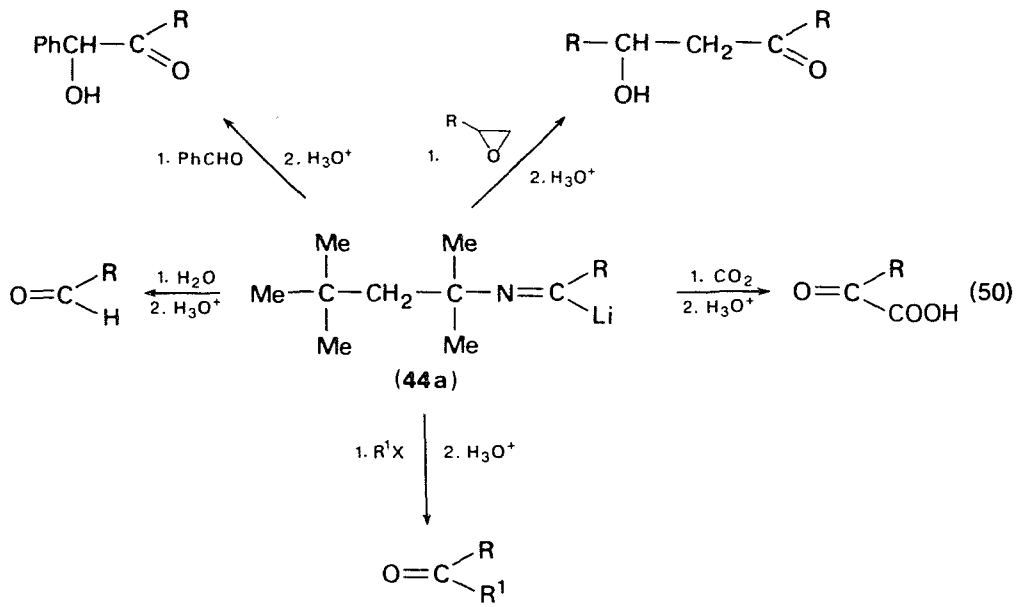
A. α-Addition

1. Preparation and reactions of metalloaldimines[64a]

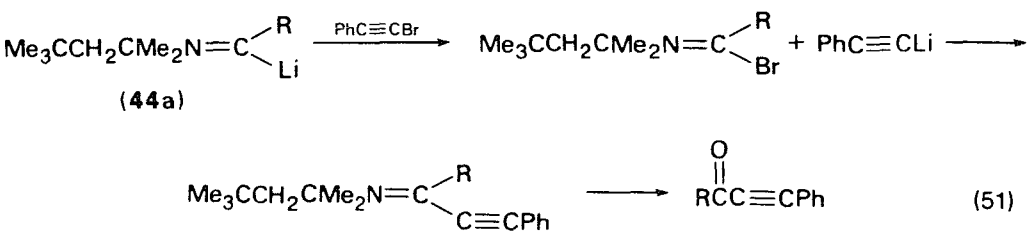
Metalloaldimines (**44**) can be conveniently prepared by either the addition of organolithium or Grignard reagents with the former being the reagent of choice. Although in principle any aryl or *t*-alkyl isocyanide can be used the most convenient one is 1,1,3,3-tetramethylbutyl isocyanide (TMBI) owing to the ease of preparation, low cost and the pleasant observation that it is not offensively malodorous[23]. Thus TMBI reacts with any lithium reagent (R^-Li^+) as long as the conjugate acid of R^- has a $pK_a > 30$. Therefore all primary, secondary and tertiary aliphatic lithium reagents react rapidly to produce excellent yields of the metalloaldimine **44a**[64b]. Aromatic organolithium reagents react to a varying degree but usually not greater than 50%.

Attempts to react anions generated from carbon acids with $pK_a < 30$ resulted in no α addition. Thus allyl- and benzyl-lithium, sodium acetylide and sodium malonate gave no reaction with TMBI. However, intramolecular ring-closure reactions involving α addition of anions of active methylene compounds ($pK_a < 30$) or metal alkoxides can occur.

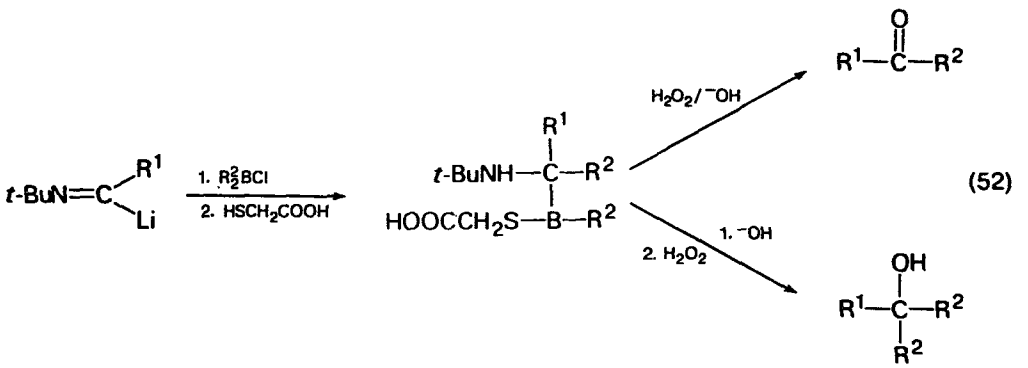
Metalloaldimines may be viewed as masked acyl carbanions. In contrast to the instability of the corresponding acyl carbanion, **44a** is stable in solution. The reaction of **44a** with a variety of reagents followed by hydrolysis of the imine produced introduces the acyl moiety into the product (equation 50). Depending on the reagent used, one is able to prepare a variety of aldehydes (with H_2O), ketones (with RX = MeI, EtI, Me_3SiCl, $PhCH_2Br$, *n*-BuCH=CHI, PhI, α- and β-NpBr, PhC≡CBr), α-hydroxy ketones (with ethylene and propylene oxides) and α-keto acids (with CO_2) (equation 50). The reaction of **44a** with vinyl, acetylenic and aromatic



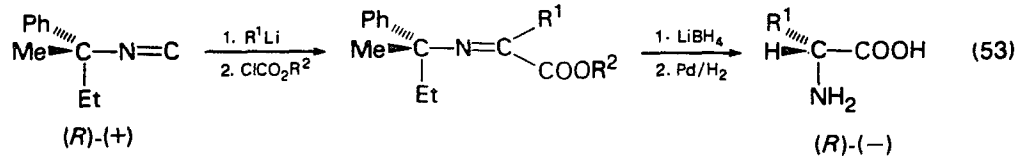
halides involves initially a halogen–metal exchange followed by reaction of the newly formed lithium and imidoyl halide reagents (equation 51)[64c]. Noteworthy is that hydrolysis of **44a** provides a simple and inexpensive synthesis of 1-deutero aldehydes (92% yield, 98% isotopic purity).



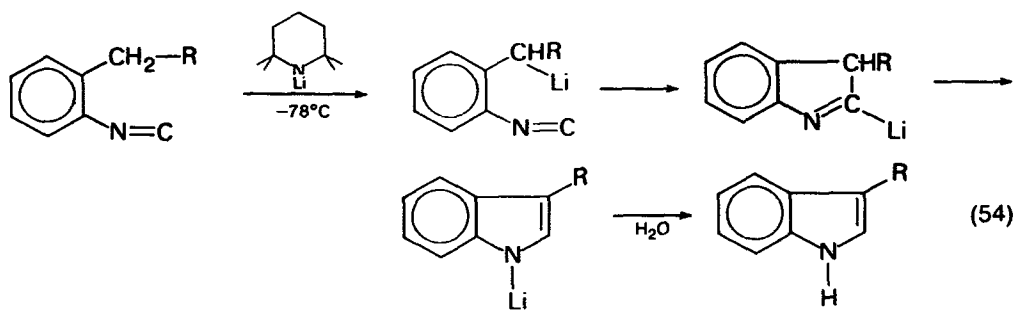
Yamamoto and coworkers[65] have reported that unsymmetrical ketones and trialkyl carbinols can also be obtained by the reaction of lithium aldimines with dialkylchloroboranes (equation 52).

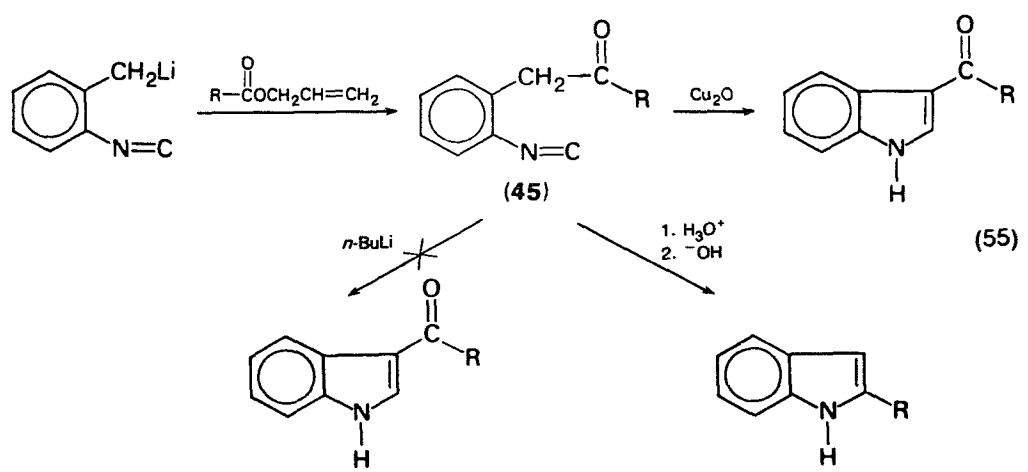


Hirowatari and Walborsky[66] have demonstrated that optically active amino acids can be obtained from an optically active isocyanide via lithium aldimine (equation 53).



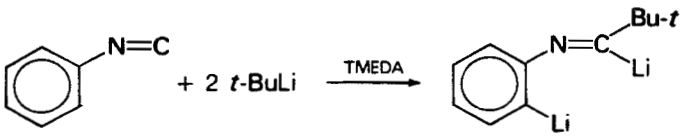
A unique and versatile synthesis of 1- and 3-substituted indoles developed by Ito and coworkers[67] involves the intramolecular α addition of a lithium reagent to an isocyanide (equation 54). Extension of this reaction provides a convenient synthetic





method for the preparation of 3-acylindoles and 2-substituted indoles from **45** (equation 55)[68]. Attempted conversion of **45** to 3-acylindoles by means of butyllithium did not succeed.

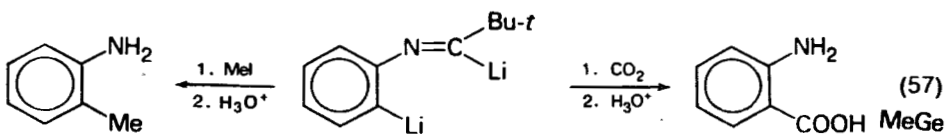
Walborsky and Ronman[69] have observed that the reaction of phenyl isocyanide with *t*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) results in α addition of the isocyano group followed by *ortho* lithiation of the benzene ring (equation 56). The reaction of **46** with MeI and CO_2 produced *o*-toluidine and



(56)

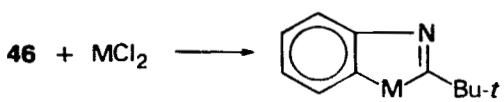
(46)

anthranilic acid respectively. This reaction provides a procedure for selective *ortho* alkylation of simple anilines (equation 57)[69]. Novel heterocyclic products are also obtained by treating **46** with a variety of dihalides MCl_2 (equation 58)[69].



(57)

(46)

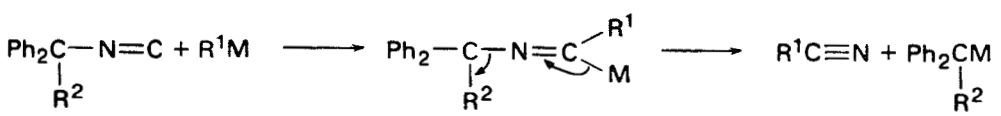


(58)

M = S, PhP, Ph_2Si, Me_2Si, Me_2Ge, Me_2Sn

2. *Dissociation of metalloaldimines*

If R in **44** contains more than one aromatic ring (e.g. **47**, R = CR^2Ph_2), the metalloaldimine is unstable and dissociates (equation 59) to produce a cyanide and a

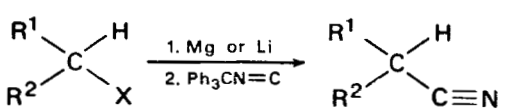


(47)

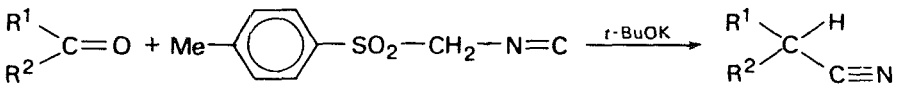
R^2 = Ph, Me

(59)

stabilized carbanion[70]. This isocyanide–metal exchange reaction is best suited for the preparation of secondary and tertiary cyanides from the corresponding halides via Grignard or lithium reagent (equation 60). The significance of this reaction should be recognized from the fact that secondary and tertiary halides ordinarily do not give satisfactory yields of cyanides by the usual S_N2 displacement with cyanide ions. The use of triphenylmethyl isocyanide in the direct conversion of halides to nitriles is



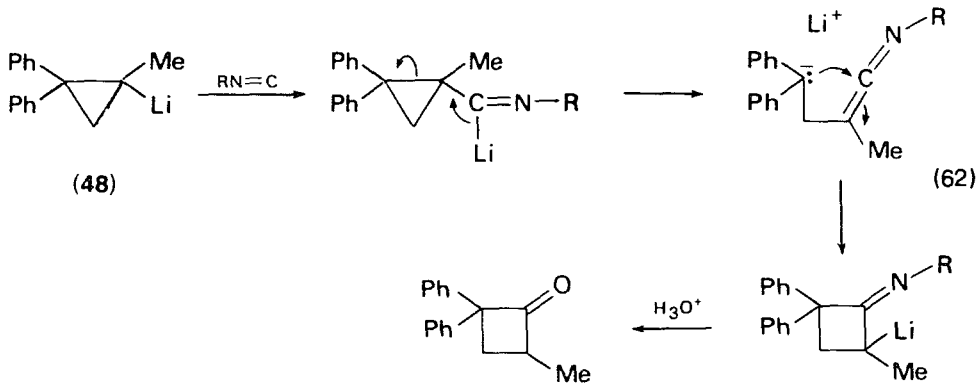
(60)



(61)

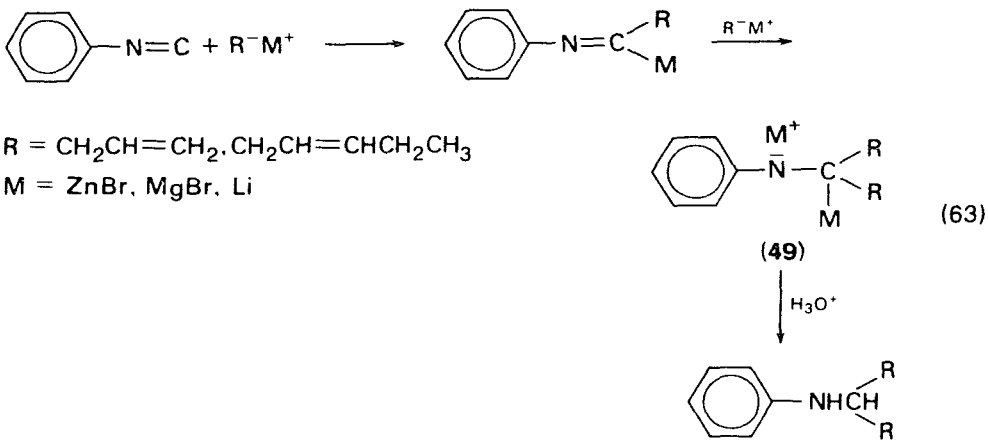
comparable to the use of tosylmethyl isocyanide in the conversion of carbonyl compounds to cyanides (equation 61) (see Section VII.C).

Recently this reaction (equation 60) has been used for the preparation of a number of masked acyl cyanides from lithium dithianes[71]. According to Periasamy and Walborsky[70], both relief of steric strain in **47** (steric effect) and formation of a stabilized carbanion (electronic effect) are the driving forces for the dissociation of metalloaldimines. This is consistent with the observation of Niznik and Walborsky in the reaction of 2,2-diphenyl-1-methylcyclopropyllithium (**48**) with various isocyanides to produce ring-expansion products. Here too, relief of steric strain and the formation of a stabilized carbanion are the driving forces for the three-membered ring-opening (equation 62)[72].



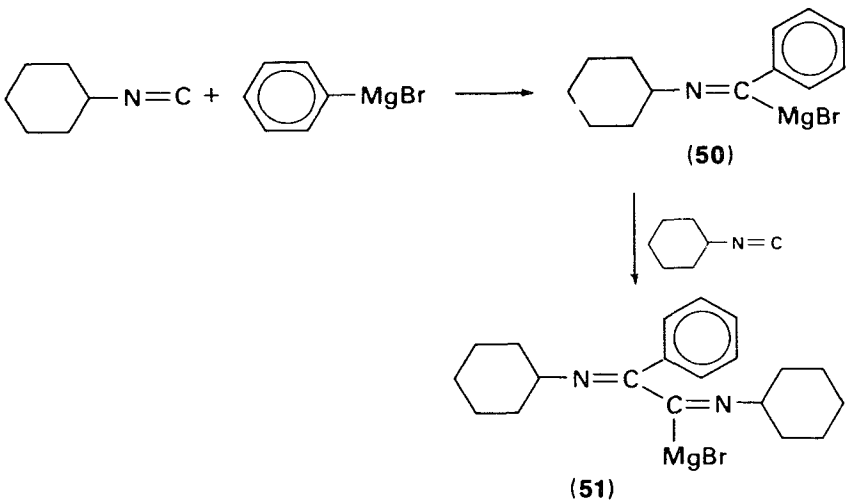
(**48**) (62)

The reactions of metalloaldimines with another molecule of organometallic reagent or isocyanide have been observed. Pornet and Miginiac[73] have reported the preparation of symmetrically branched anilines from the reaction of 2.5–3 equivalents of various organometallic reagents with 1 equivalent of phenyl isocyanide. The feasibility of this reaction is believed to be due to the stabilization of the anion **49** by

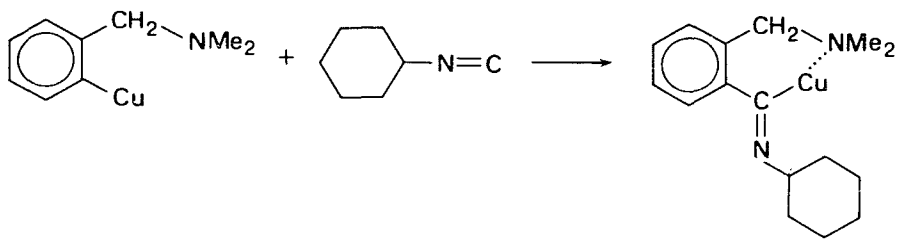


(63)

the benzene ring (equation 63). Ugi and Fetzer[74] noticed that the metalloaldimine **50** reacted with cyclohexylisocyanide to give **51** in 24% yield (equation 64).



Although metalloaldimines are prepared by reacting an isocyanide with either an organolithium or a Grignard reagent, there are several examples of metalloaldimines obtained from the reaction of organocopper and zinc reagents (equation 65)[73,75].

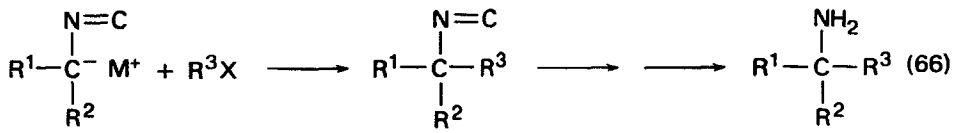


B. α-Metalated Isocyanides

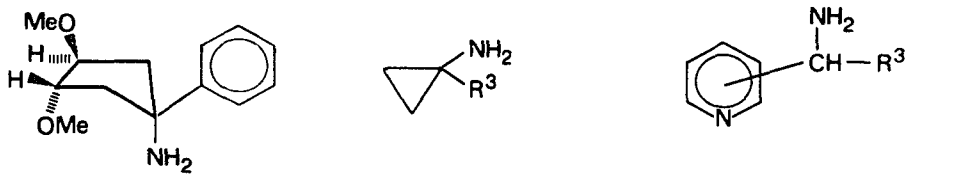
Since their discovery in 1968, α-metalated isocyanides have proved to be versatile in their synthetic applications. Since excellent review articles have been published on this subject, we shall consider only selected recent examples to show the importance of this class of compounds in organic synthesis[63,76].

1. Alkylation

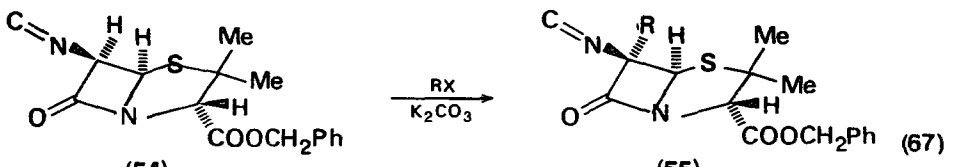
Chain-elongation of primary amines via an α-metalated isocyanide constitutes an important synthetic method for the preparation of amines which cannot be obtained otherwise or only with difficulty (equation 66). For example, tertiary cyclopentyl- and cyclopropyl-amines **52a**, **52b** and 1-pyridylalkylamine **53** are prepared from appropriate α-metalated isocyanides[77]. The reaction sequence followed by Bentley and coworkers[78] in the preparation of 6-substituted penicillins, involves the alkylation of the anion of 6-isocyanopenicillin benzyl ester **54** with RX giving products **55a–c** (equation 67). Under the same conditions benzyl acrylate provides the Michael addition product **55d** and acetone gives **55e**.



(66)



(52a) (52b) (53)



(67)

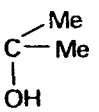
(54) (55)

(a) R = CH_2Ph

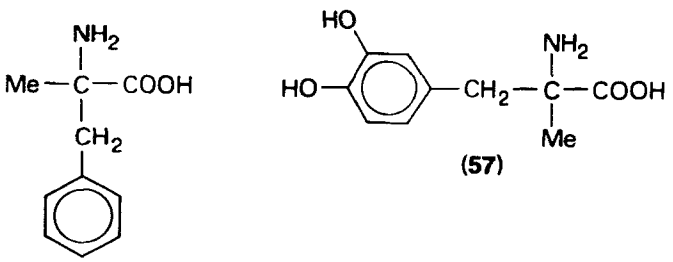
(b) R = CH_2CO_2Me

(c) R = CH_2COPh

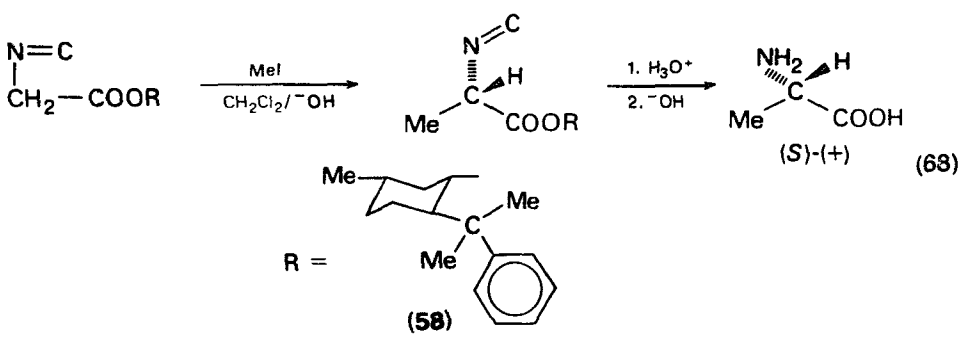
(d) R = $CH_2CH_2CO_2CH_2Ph$

(e) R = 

Alkylation of α-metalated α-isocyanoalkanoic esters followed by hydrolysis leads to the formation of longer-chain or α-branched amino acids. Examples are provided by the synthesis of α-methylphenylalanine (**56**) and α-methyldopa (**57**)[79]. The alkylation



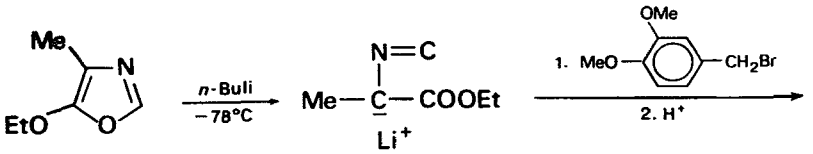
(56) (57)



(68)

(58)

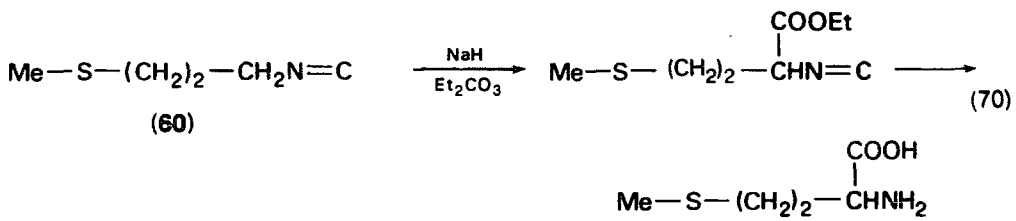
of chiral isocyanoacetic esters with methyl iodide, using the ion-pair extraction method, has been investigated. (*S*)-(+)-Alanine was obtained in 48% optical purity using the chiral Corey ester (**58**) of isocyanoacetic acid (equation 68)[80]. α-Metalated isocyano esters generated by the reaction of 5-alkoxyoxazoles with *n*-butyllithium have been applied to the synthesis of dimethoxy-α-methyldopa **59** (equation 69)[81].



(69)

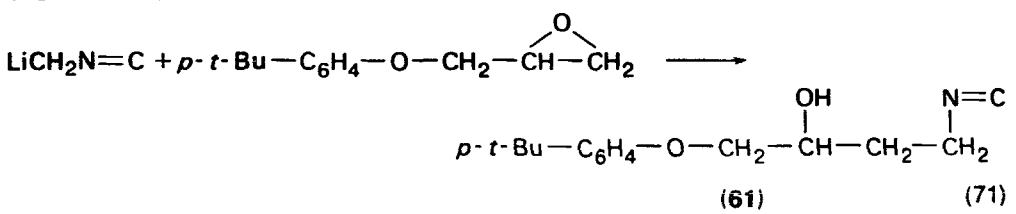
(59)

According to a French patent[82], 3-(methylthio)propyl isocyanide (**60**) when treated with Et_2CO_3 and NaH and the product hydrolysed, produces (±)-methionine (equation 70). Using a similar approach, α-phenylglycine can be synthesized by carboxylation of α-lithiobenzyl isocyanide with CO_2.



(60) (70)

α-Metalated isocyanides can be alkylated by epoxides, episulphides and oxetanes. A useful sedative and hypnotic **61** was prepared by treating methyl isocyanide with *n*-butyllithium in THF, followed by reaction with *p*-butylphenyl-2,3-epoxypropyl ether (equation 71)[83].

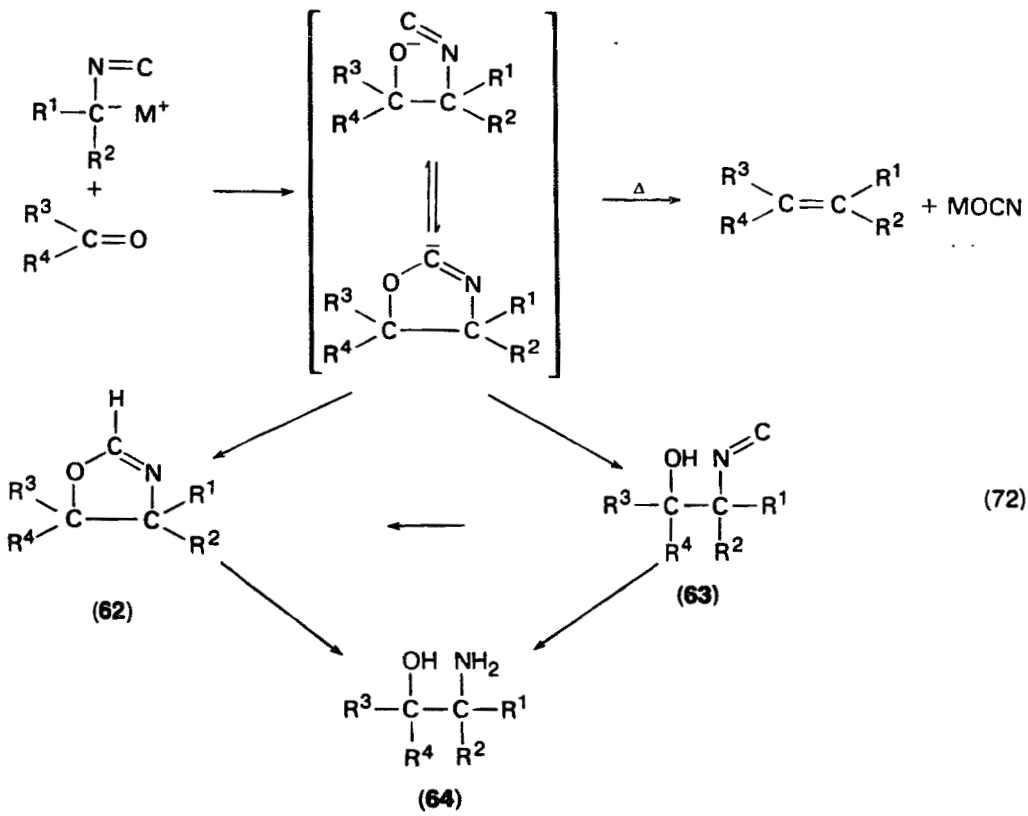


(61) (71)

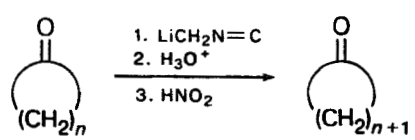
2. *Reactions with carbonyl compounds*

α-Metalated isocyanides readily react with aldehydes and ketones and depending on the work-up procedure can be made to yield either 2-oxazolines (**62**), β-isocyano alcohols (**63**), β-amino alcohols (**64**) or olefins (equation 72)[76c].

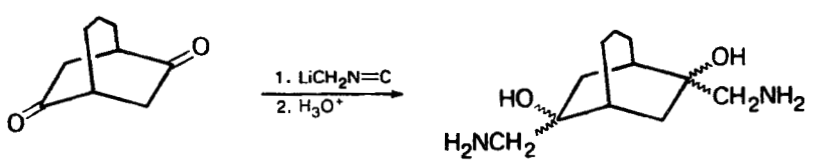
The formation of **64** in combination with the Tiffeneau–Demyanov rearrangement leads to homologation of cyclic ketones (equation 73)[76c]. Bis(aminomethyl) compound **65**, not accessible by conventional methods from its diketone precursor, is obtained in good yield by the addition of isocyanomethyllithium to the diketone[84] (equation 74).



(72)



(73)

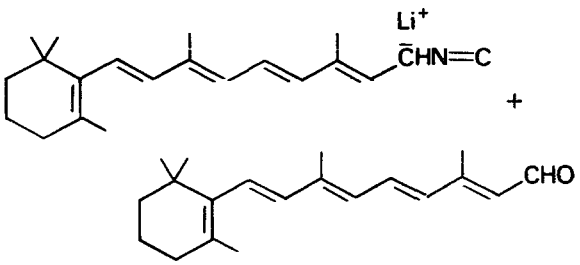


(74)

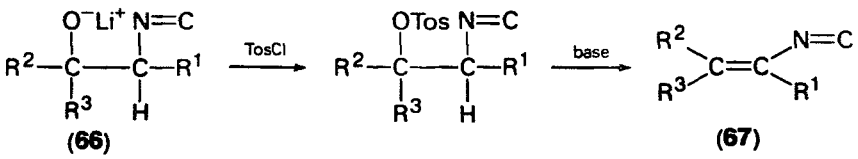
The carbonyl olefination with α-metalated isocyanides is stereospecific as observed in the synthesis of isomer-free (all-*trans*)-β-carotene (equation 75)[85].

Vinyl isocyanides **67**, which are difficultly obtained by conventional routes, are easily prepared by trapping 2-isocyanoalkoxides **66** with *p*-toluenesulphonyl chloride (TosCl) and subsequent base elimination of *p*-toluenesulphonic acid (equation 76).

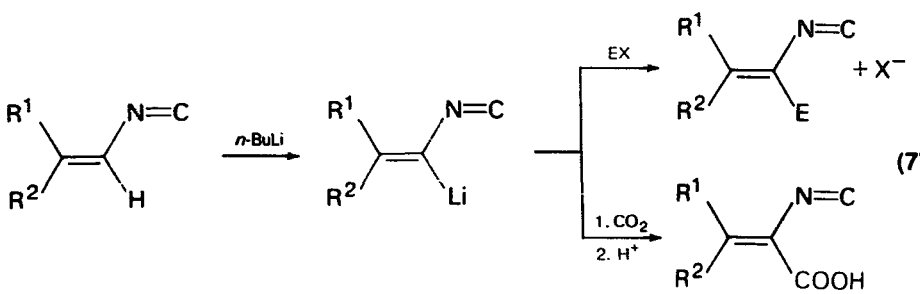
Vinyl isocyanides (**67**, R^1 = H) react with butyllithium to yield the corresponding 1-lithio-1-alkenyl isocyanide and not the α-addition product. Subsequent reaction of the lithium reagent with electrophilic reagents leads to a variety of products (equation 77)[86].



trans-β-Carotene (75)



(66) (67) (76)

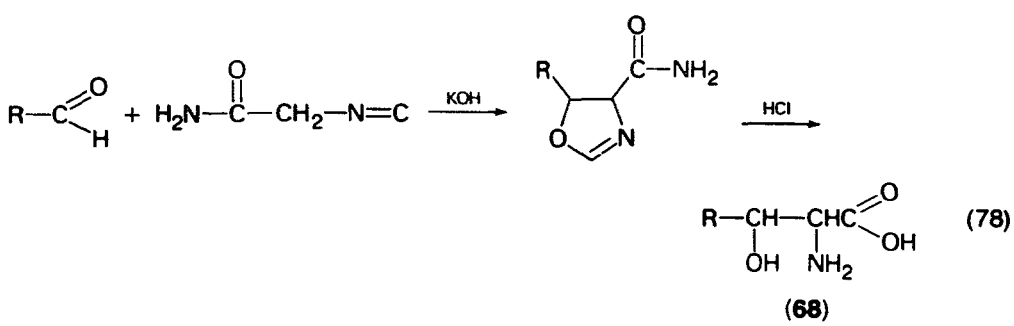


(77)

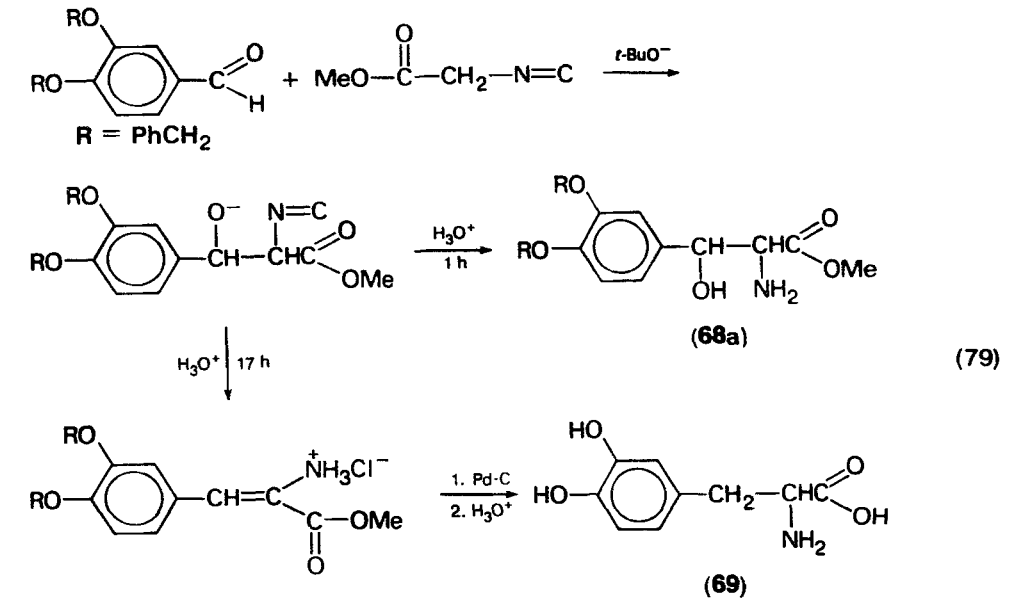
EX = $SiMe_3Cl$, MeI, $ClCO_2Me$, ClCOPh

Syntheses of α-hydroxyamino acids **68** and **68a** and DL-dopa **69** have been accomplished by the reaction of α-isocyanoacetic acid derivatives with aldehydes (equations 78 and 79)[87a–c].

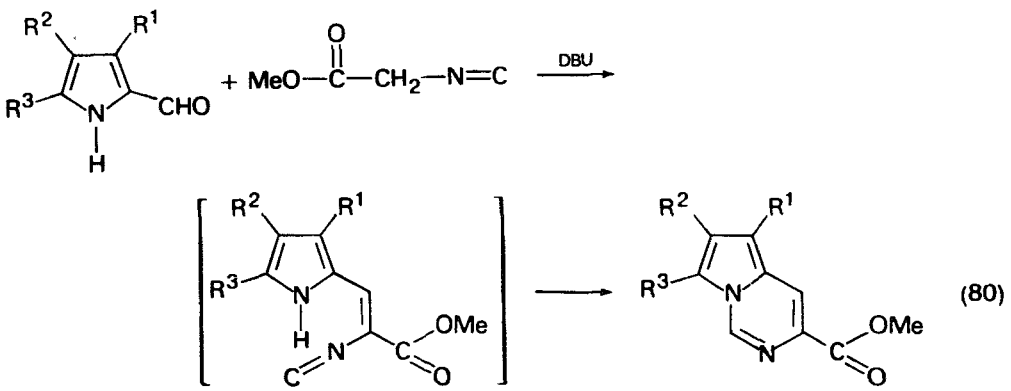
Condensation of methyl isocyanoacetate with substituted pyrrole-2-carboxaldehyde using 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) yields methyl pyrollo-[1,2-*c*]pyrimidine-3-carboxylate in 50–70% yield[87d]. The ring-closure is believed to proceed through a vinyl isocyanide intermediate (equation 80).



(68) (78)

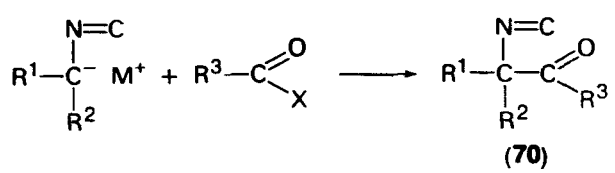


(79)



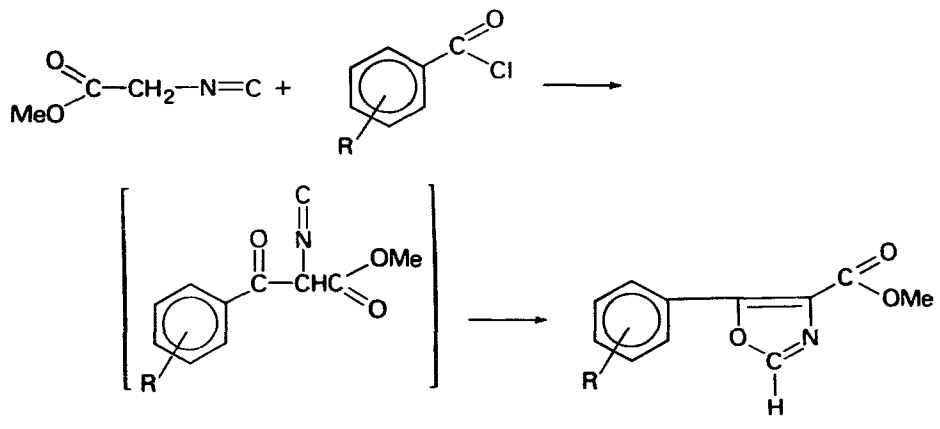
3. *Reactions with acylating compounds*

The α-isocyano ketones **70** obtained by acylation of α-metalated isocyanides undergo various subsequent reactions depending on the nature of the substituents R^1, R^2 and R^3 (equation 81). As an example, the reaction of methyl α-isocyanoacetate



(81)

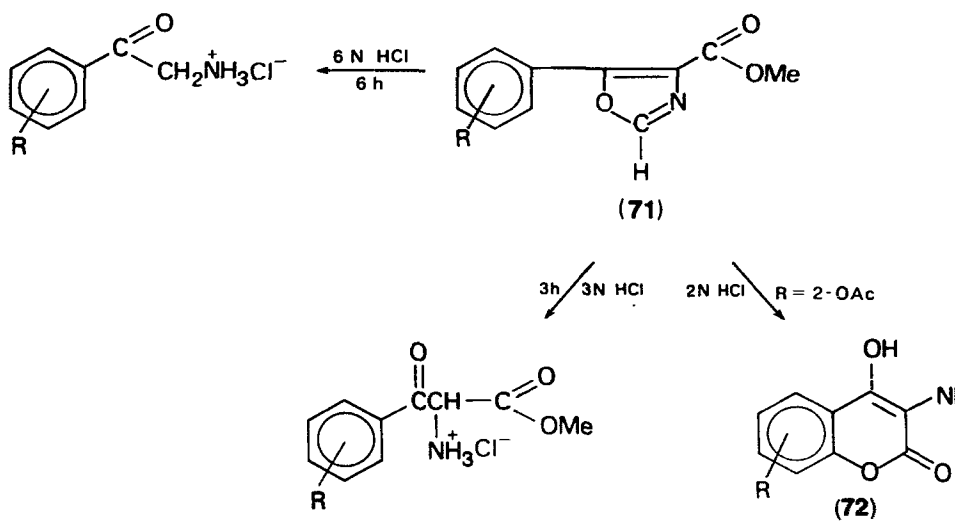
(R^1 = H, R^2 = CO_2Me) with aromatic acid chlorides affords oxazoles **71** in good yields (equation 82).



(82)

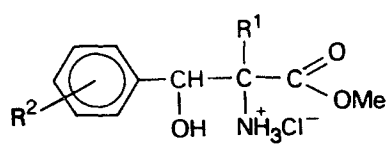
(71)

The oxazole compounds **71** can be readily converted into aroylamino acid derivatives and the corresponding α-amino ketones (equation 83)[88]. When R in **71** is



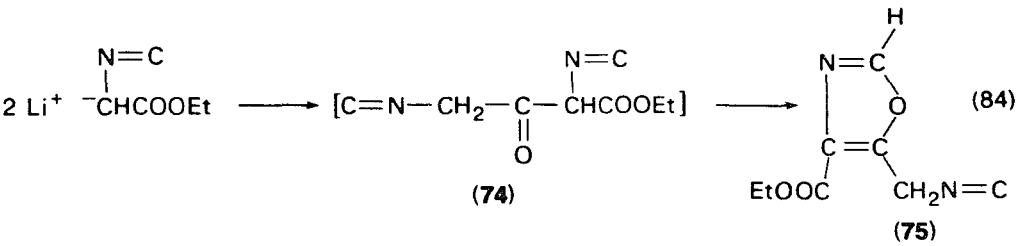
(83)

the 2-acetoxy group, then acid hydrolysis of **71** leads to a convenient synthesis of 3-amino-4-hydroxycoumarin derivatives **72**[89]. Acylation of α-monoalkyl-substituted α-isocyanoalkanoic esters with aroyl chlorides, followed by hydrogenation and acid hydrolysis, yields the hydrochloride salts of α-alkylated β-ring-substituted phenylserine methyl esters **73**[87b].



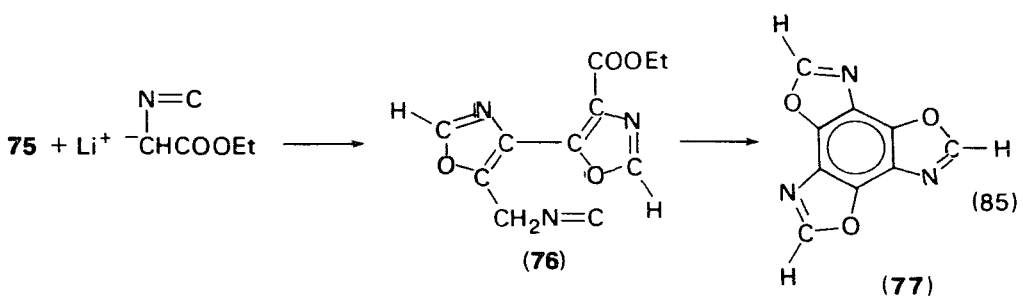
(73)

Oxazoles can also be prepared by acylating α-metalated isocyanides with anhydrides. The decomposition of lithiated ethyl isocyanoacetate yields oxazole **75**, by way of ethyl 2,4-diisocyanoacetoacetate **74** (equation 84). Reaction of **75** with lithiated



(84)

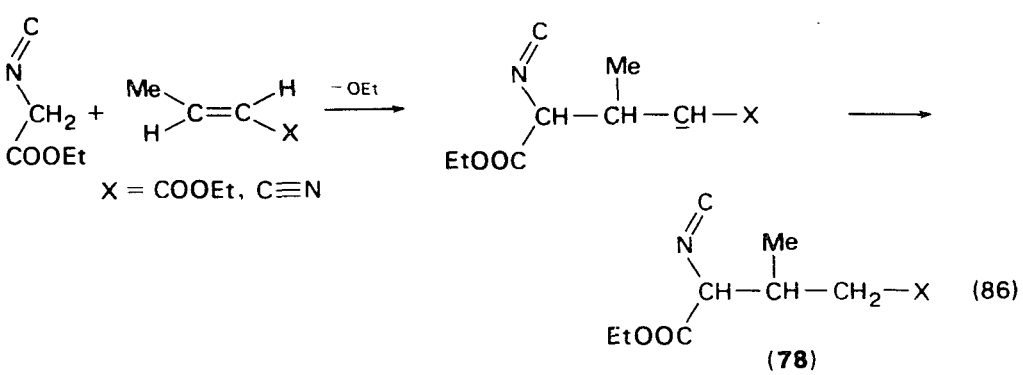
ethyl isocyanoacetate produces **76** which further reacts to give **77** (equation 85)[90] In a similar manner, a variety of heterocyclic compounds have been prepared by reacting α-metalated isocyanides with azomethines, nitriles, imidoyl chlorides, dithioacid esters, thio ketones, carbon disulphide, isothiocyanides, isocyanates, carbodiimides, nitrones, azides and nitrile oxides[76].



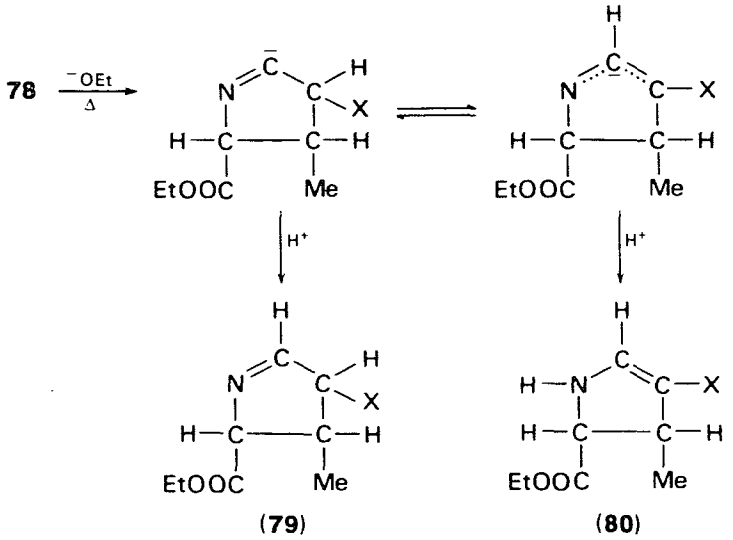
(85)

4. *Addition to activated olefins*

α-Metalated isocyanides undergo Michael addition to a number of activated olefins. Glutamic acid derivatives are obtained when ethyl isocyanoacetate is reacted with acrylic esters and nitriles (equation 86). If the adduct **78** is heated with sodium ethoxide, cyclization to 1- or 2-pyrrolidines takes place (equation 87). Pyrrolidines **79** and **80** are obtained directly if CuO is used as catalyst[123]. If the pyrrolidine ring contains substituents that can be readily eliminated under the reaction conditions, then elimination and aromatization leads to pyrrole derivatives. Thus Matsumoto and

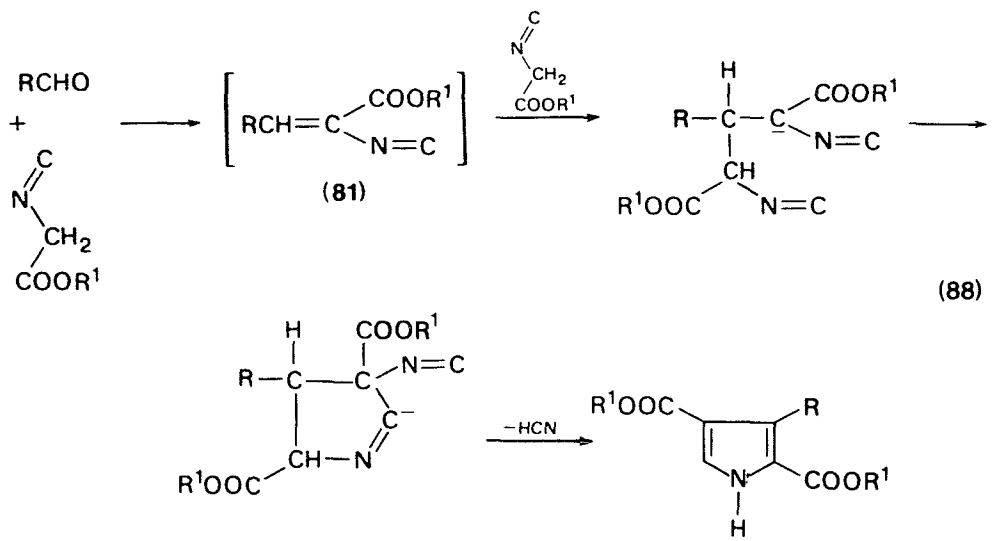


(86)



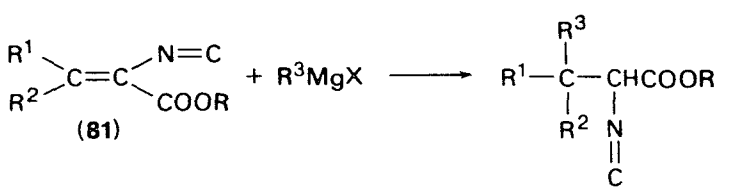
(87)

coworkers[91] have synthesized 3-substituted pyrroles by the reaction of isocyanoacetates with aldehydes in the presence of DBU (equation 88). The above



(88)

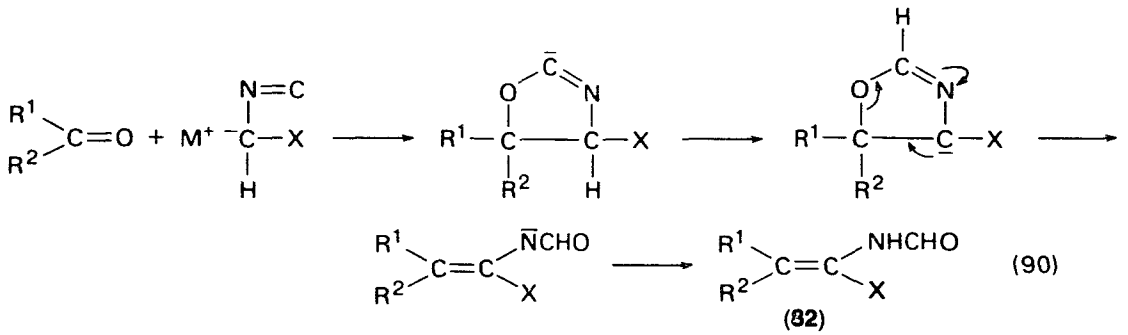
reaction is an example of Michael addition of an isocyano carbanion to 2-isocyanoacrylic ester **81**. Similar additions of Grignard reagents and sodium diethyl malonate to **81** are also known (equation 89)[92].



(89)

5. *Formylaminomethylenation of carbonyl compounds*

The reaction of α-metalated isocyanides possessing a strongly activating group X with carbonyl compounds gives *N*-(1-alkenyl)formamides **82** (equation 90). Since the

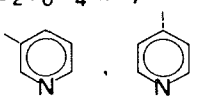


(90)

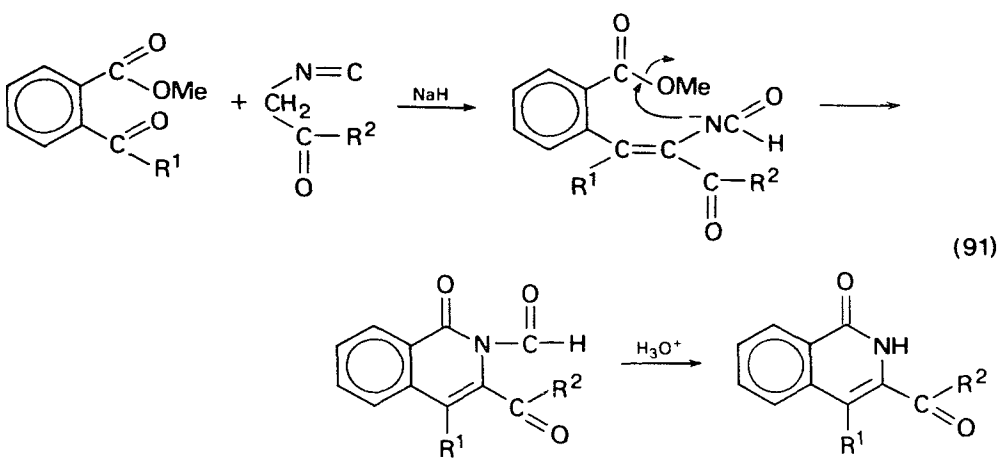
(82)

(a) X = CO_2R

(b) X = $SO_2C_6H_4Me$-*p*

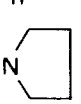
(c) X = 

net result is the replacement of oxo oxygen by a formylamino methylene group, this reaction is called formylaminomethylenation. The *N*-(1-alkenyl)formamides **82** are very useful synthetic reagents. A one-step synthesis of 1-oxo-1,2-dihydroisoquinoline derivatives has been achieved by the reaction of methyl 2-acylbenzoates with methyl isocyanoacetate or isocyanoacetamide using sodium hydride as the base[93]. The reaction involves the *in situ* formation of *N*-(1-alkenyl)formamide anion which cyclizes to yield the 1-oxo-1,2-hydroisoquinoline (equation 91).

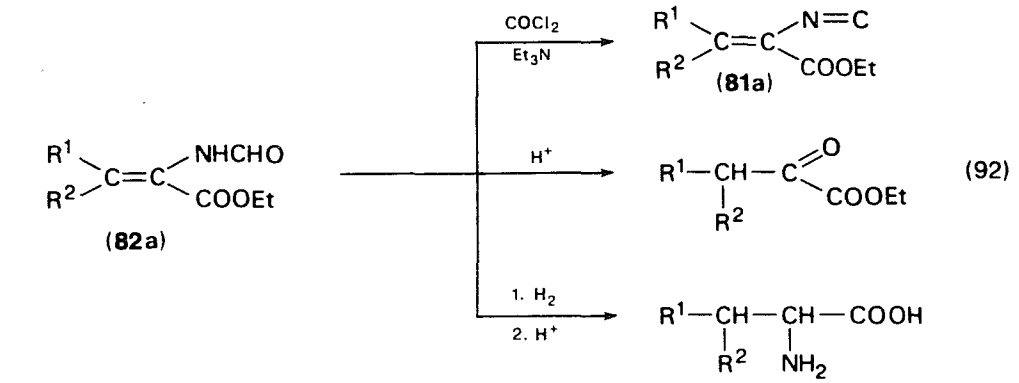


(91)

R^1 = H, Me, Ph

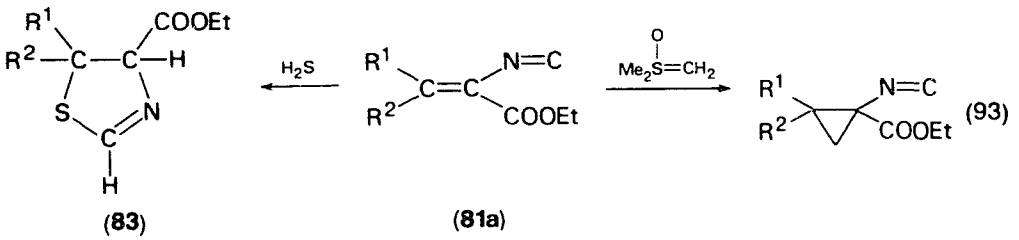
R^2 = OMe, 

When X in **82** is a carboethoxy group, these intermediates are easily transformed to α-keto esters, amino acids and α-isocyanoacrylic esters **81** (equation 92). The



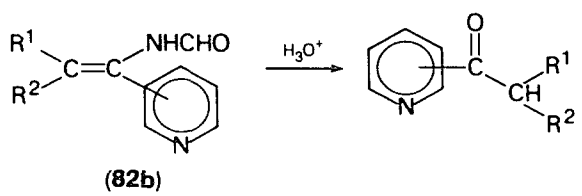
(92)

α-isocyanoacrylic esters have been utilized in the syntheses of 1-isocyano-1-cyclopropanecarboxylic acid esters and 5-substituted 2-thiazoline-4-carboxylic esters **83** which are useful intermediates in the syntheses of penicillins (equation 93). The synthetic application of *N*-(1-toluenesulphonyl-1-alkenyl)formamides in chain-elongation of ketones are described in the next section.

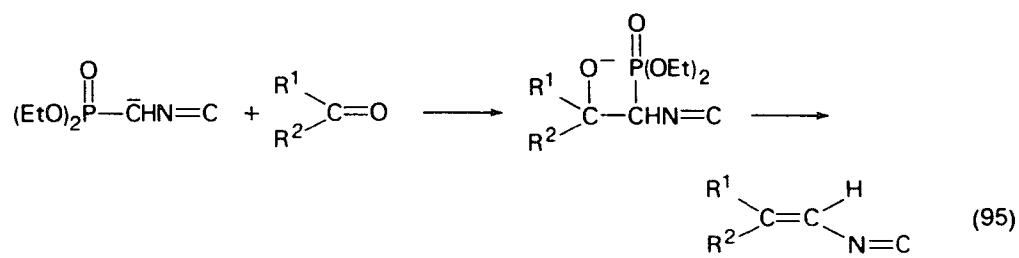


(93)

N-[1-(3- and 4-Pyridyl)-1-alkenyl]formamides **82b** yield upon hydrolysis 3- and 4-acylpyridines which are otherwise accessible only with difficulty (equation 94)[94].

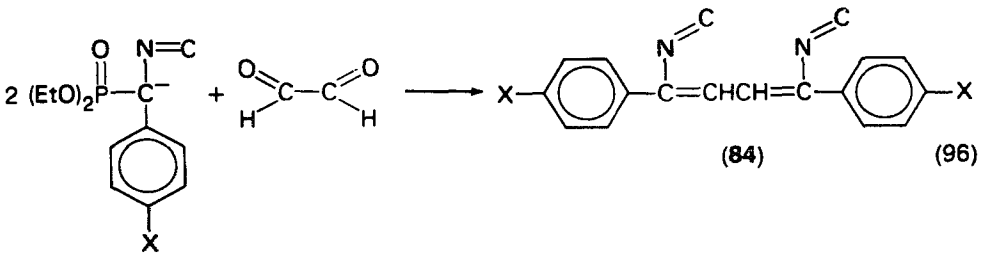


(94)



(95)

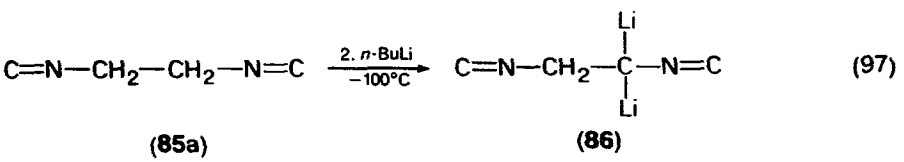
The reaction between diethyl isocyanomethanephosphate and carbonyl compounds does not result in formylaminomethylenation, but instead produces vinyl isocyanides following Wittig olefination (equation 95). This observation has been made use of in the synthesis of an analogue of isoxanthocillin **84a**. The diisocyanide **84b** has been synthesized from α-isocyanophenylmethane phosphate and glyoxal (equation 96).



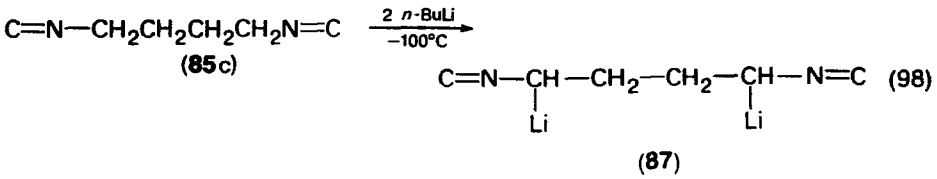
(84) (96)

(a) X = OH
(b) X = H

The α-metalation reactions of α,ω-alkyl diisocyanides C≡N—$(CH_2)_n$—N≡C (n = 2, 3, 4) **85a–c** have recently been studied[95]. An interesting observation is that 1,2-diisocyanoethane **85a** reacted with 2 equivalents of n-BuLi to give 1,1-dilithio-1,2-diisocyanoethane **86** (equation 97), whereas **85c** produced 1,4-dilithio-1,4-diisocyanobutane **87** (equation 98).



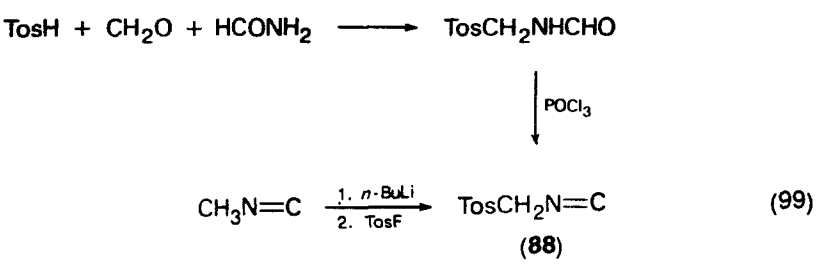
(85a) **(86)** (97)



(85c) **(87)** (98)

C. Tosylmethyl Isocyanide

p-Toluenesulphonylmethyl isocyanide (TosMIC) **88** is an important stable and odourless synthetic organic synthon. The syntheses and reactions have been explored



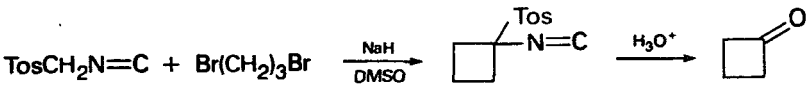
(88) (99)

Tos = p-$MeC_6H_4SO_2$

by Van Leusen's group[96–100]. It can be synthesized by two different procedures. The main route involves a Mannich reaction, followed by dehydration of *N*-tosylmethyl formamide (equation 99). Alternatively, α-lithiomethyl isocyanide can be sulphonylated with tosyl fluoride.

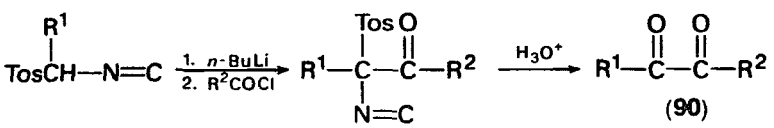
1. Reactions of TosMIC

TosMIC undergoes a wide variety of reactions revealing its diversified synthetic applications in organic chemistry. TosMIC can be selectively alkylated to mono- or di-substituted products[97]. Acid treatment of dialkylated TosMIC provides a new synthesis of ketones as exemplified by the preparation of cyclobutanone **(89)** (equation 100)[98]. Reaction of monosubstituted TosMIC with acid chloride followed



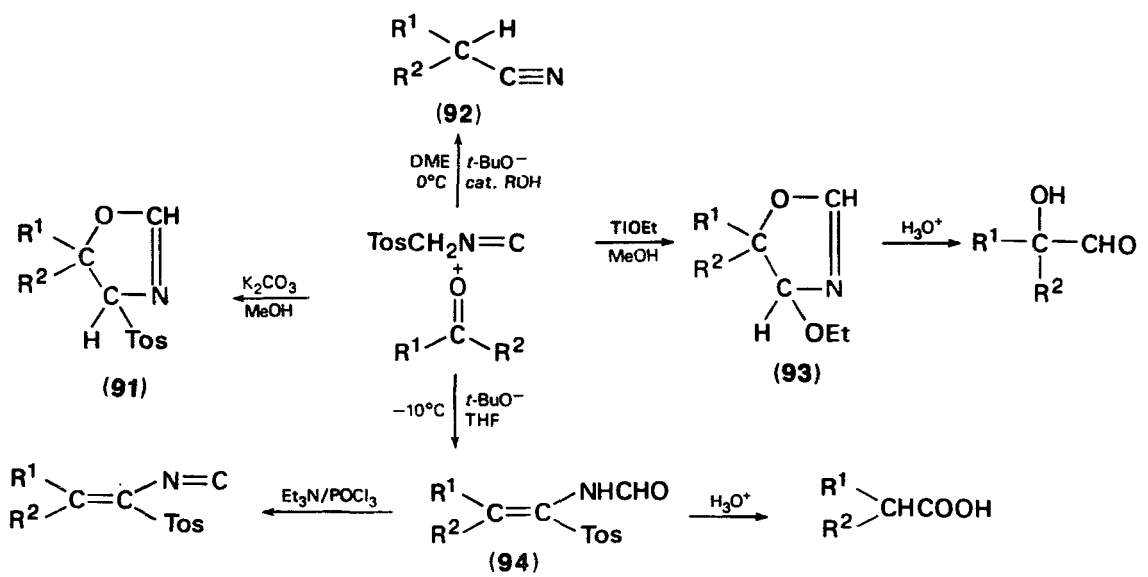
(89) (100)

by acid treatment yields α-diketones **90** (equation 101). It can be seen that, in both reactions, TosMIC acts as a masked formaldehyde reagent[99].



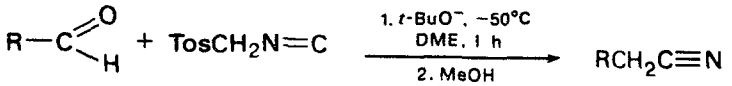
(90) (101)

By a proper choice of conditions, i.e. 1,2-dimethoxyethane(DME)-*t*-butoxide, tetrahydrofuran-*t*-butoxide, methanol–potassium carbonate or ethanol–thallium ethoxide, the reaction of TosMIC with ketones can lead exclusively to **91**, **92**, **93** or **94**. This reaction scheme allows conversion of a carbonyl compound into the next higher cyanide, carboxylic acid or α-hydroxy aldehyde (Scheme 2)[100]. ^{14}C labelling



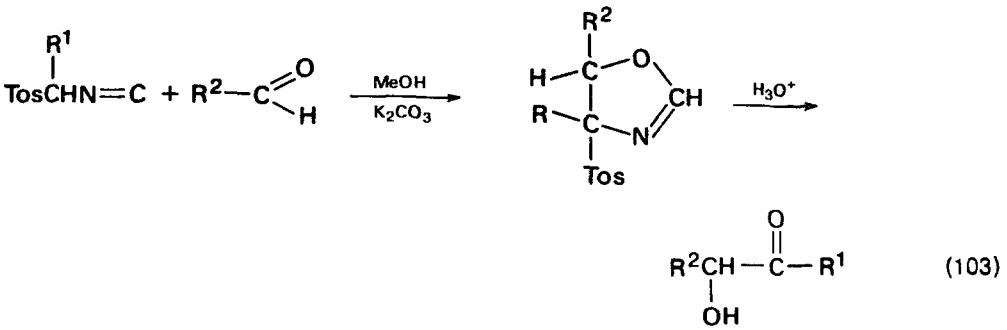
SCHEME 2

experiments have shown that the nitrile carbon in **92** originates from the methylene group of TosMIC. This reductive cyanation method has been widely used in the syntheses of many new nonsteroidal antiinflammatory agents and alkaloids[101]. Extension of this reaction to aldehydes was made possible by a slight modification of the ketone–cyanide conversion procedure (equation 102)[102]. α-Hydroxy ketones are



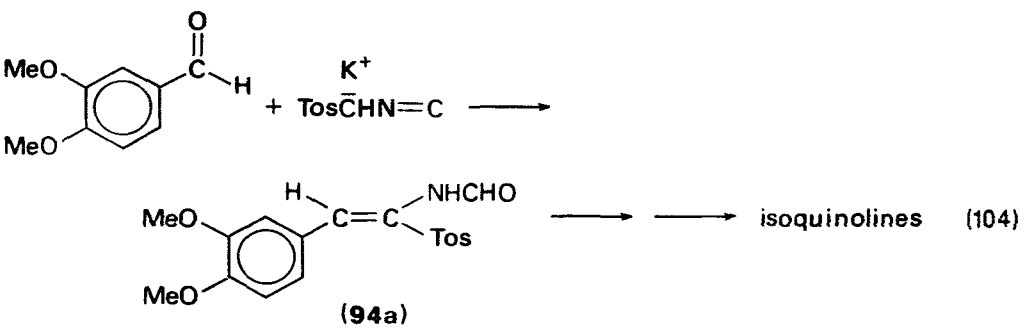
(102)

the products from the reaction of aldehydes with monosubstituted TosMIC and the reaction is called reductive acylation (equation 103)[103]. According to the scheme



(103)

developed by Barton and coworkers[104] the formation of intermediate **94a** is the key step in the synthesis of pharmaceutically useful isoquinoline alkaloids (equation 104).

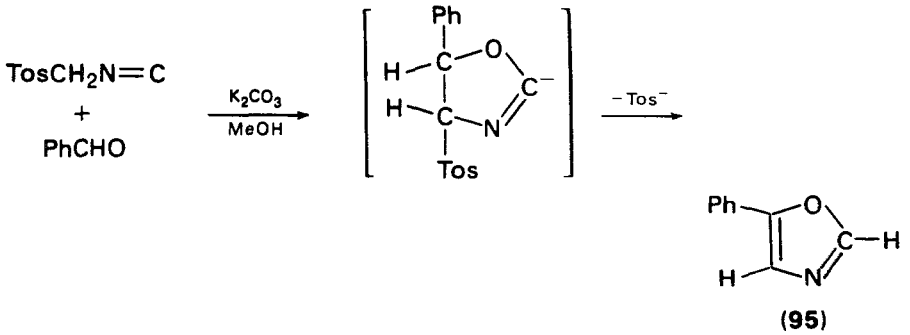


(104)

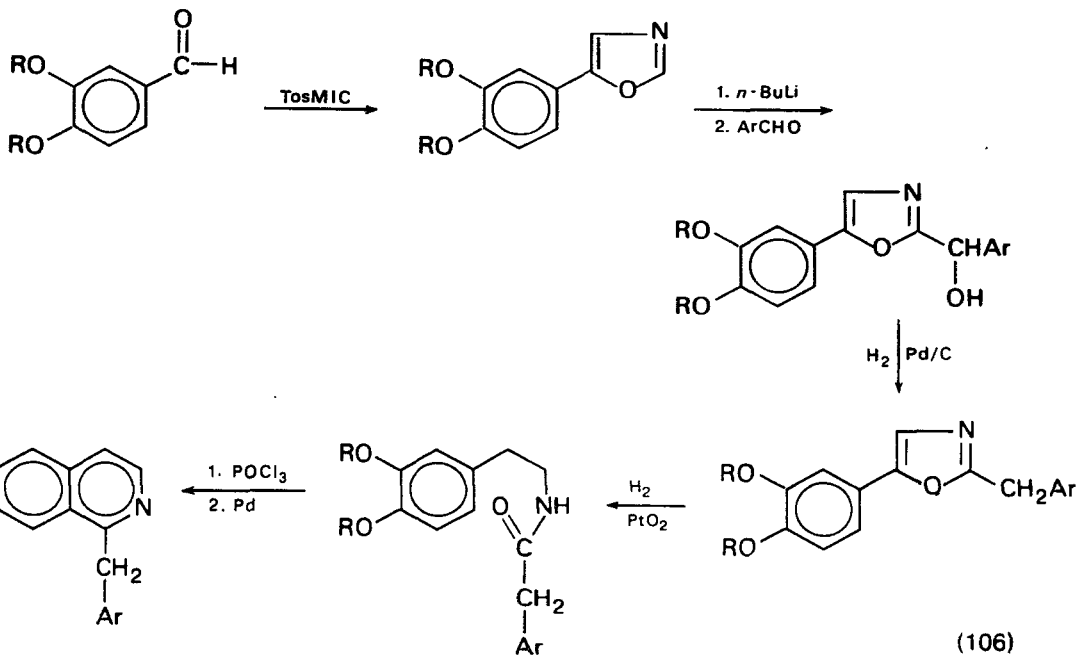
2. *Synthesis of heterocycles*

The reaction of TosMIC with aldehydes provides an extremely simple method for the synthesis of oxazoles **95** (equation 105). The unique feature of this, as well as other related heterocyclic synthetic methods, is that the 2-position of the ring is unsubstituted[100c]. The sulphonyl group of TosMIC plays an important role, in that it activates the adjacent methylene group without participating directly in the reaction. In most cases it is easily removed from the final product. The overall result is the cycloaddition of the CH_2—N=C moiety of TosMIC as a —CH—N=CH unit to the substrate.

A new efficient route to benzylisoquinoline alkaloids is based on the formation of oxazoles from readily available alkoxy-substituted benzaldehydes and TosMIC (equation 106)[105].

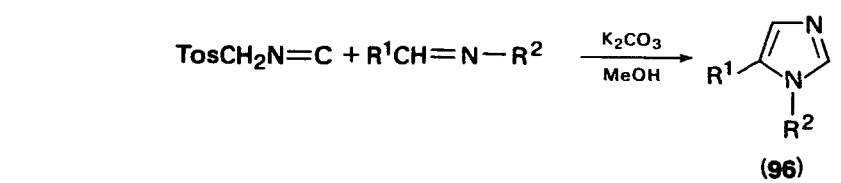


(95) (105)



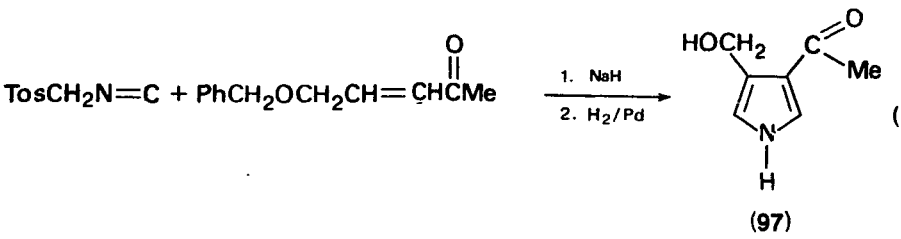
(106)

Base-induced cycloaddition of TosMIC to aldimines gives 1,5-disubstituted imidazoles **96** which are otherwise more difficultly obtained (equation 107)[106].



(96) (107)

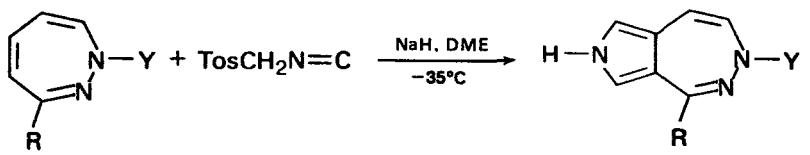
The transfer of the CH—N=C unit of TosMIC to the double bond of Michael acceptors results in the formation of pyrroles as shown in the synthesis of verrucarin (**97**), a secondary metabolite of the soil fungus *Myrothecium verrucaria*, (equation 108)[107a]. A special characteristic of this pyrrole synthesis is that it leaves the positions 1,2 (and 5) of the ring unsubstituted. In addition, 2-unsubstituted 3-acylpyrroles are not readily accessible by conventional methods since Friedel–Crafts acylation occurs



(108)

(97)

preferentially in the 2-position. The Michael acceptors thus far used in the pyrrole synthesis include α,β-unsaturated ketones, esters, nitriles and acetylenic esters[107c]. From the reaction of 1,2-diazepines with TosMIC, pyrrolodiazepines **98** are obtained in good yields (equation 109)[108].



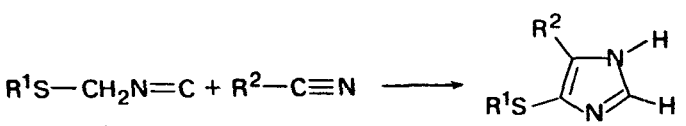
(109)

(98)

R = Me

Y = COOR, COR

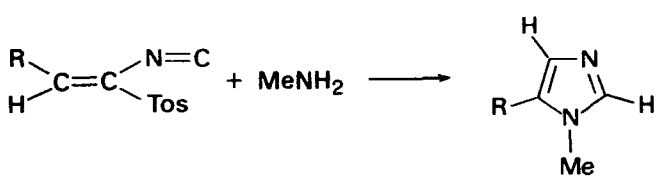
In a similar manner, synthesis of triazoles, pyridimidines and 4-tosyl-substituted imidazoles and oxazoles have been reported[109]. Thiomethyl isocyanides **99** have been prepared and their reactivity is found to be similar to that of TosMIC (equation 110)



(110)

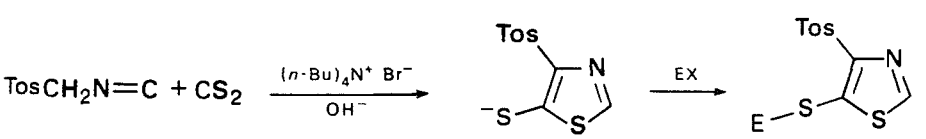
(99) (100)

for the synthesis of thioimidazoles **100**[110]. 1,5-Disubstituted imidazoles **102** are obtained in high yields by the reaction of **101** with primary aliphatic amines including ammonia (equation 111)[100d].



(111)

(101) (102)



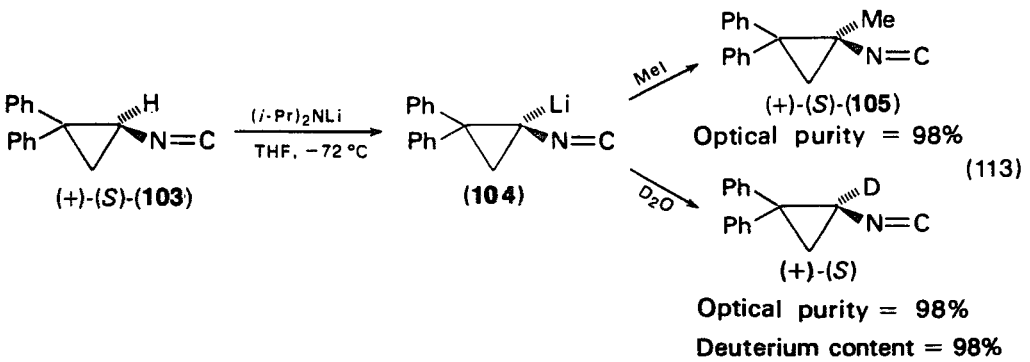
(112)

EX = RX, RCOX

1,3-Thiazoles can be prepared by reaction of TosMIC with carbon disulphide under phase-transfer conditions. Acylation or alkylation of the tetrabutylammonium salt that is formed gives high yields of the desired products (equation 112)[109a].

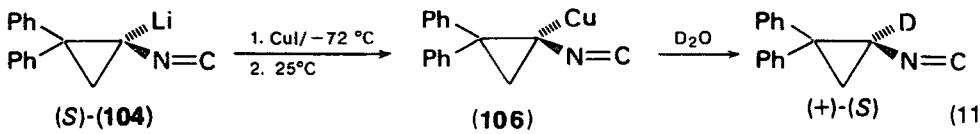
VIII. STEREOCHEMISTRY OF α-METALATED ISOCYANIDES

Although the chemistry of α-metalated isocyanides had been actively explored, the nature of the isocyano group as a substituent in the formation of α-isocyano carbanions had until recently not been established. It was widely assumed that the inductive stabilization by the dipole of the isocyano group was important in the formation of α-metalated isocyanides. To gain more information on this subject, Periasamy and Walborsky[111] studied the α-metalation reactions of optically active isocyanides **103** and 1-phenyl-2-isocyanopropane. They observed that the 1-isocyanocyclopropyllithium **104** obtained by the reaction of **103** with lithium diisopropylamide at −72°C in THF was configurationally stable (equation 113). The stereochemical stability of **104** was



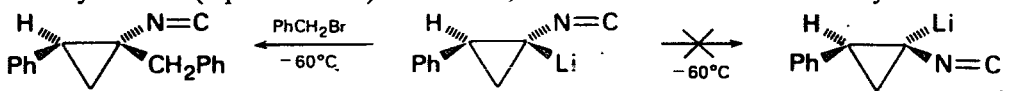
(113)

unaffected by a change in gegenion, by a change in solvent or by the presence of crown ethers, triglyme and hexamethylphosphorus triamide (HMPA). However, as the reaction temperature is raised, there was a gradual loss of optical activity and at −5°C **104** was essentially racemized. In contrast, the 1-isocyanocyclopropylcopper reagent **106** was configurationally stable at ambient temperatures (equation 114)[112].



(114)

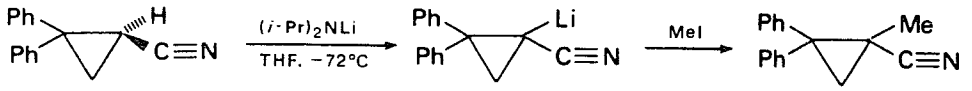
Based on these results, it was concluded that the isocyano group does not act as a delocalizing substituent but behaves as an electron-withdrawing group acting largely through an inductive effect. This conclusion is supported by MO calculations[13] on various isocyanides and by the positive σ^+ value found for the isocyano group[113]. In agreement, Schöllkopf and coworkers[114] have reported that 1-lithio-2-phenylcyclopropyl isocyanide does not undergo *cis–trans* isomerization and is therefore configurationally stable (equation 115). However, it should be noted that acyclic chiral



(115)

isocyanides, (−)-(*R*)-1-phenyl-2-isocyanopropane[111] and (+)-α-phenylethyl isocyanide[115] completely racemize upon treatment with base.

By contrast to the isocyanide **103**, the isomeric chiral 1-methyl-2,2-diphenylcyclopropyl *cyanide* completely racemizes under conditions identical to those in which the *isocyanide* maintains its configuration (equation 116)[116].



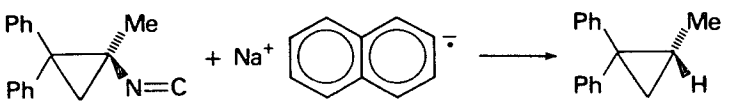
(116)

IX. ISOCYANIDE REDUCTIONS

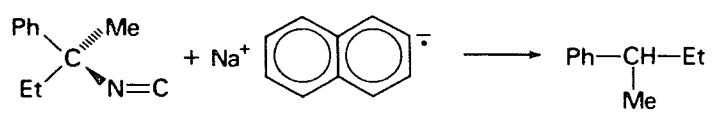
The reductive deamination of an amine to the corresponding hydrocarbon by way of the isocyanide (equation 117) has recently received attention. Niznik and

$$R{-}NH_2 \longrightarrow R{-}N{=}C \longrightarrow R{-}H \qquad (117)$$

Walborsky[117] investigated the mechanism of dissolved metal reduction by employing chiral isocyanides **105** and **107**. Sodium naphthalide reduction of **105** yields the corresponding hydrocarbon with a maximum optical purity of 13% and with overall retention of configuration (equation 118). Under identical conditions **107** produces completely a racemic hydrocarbon (equation 119). Although the stereochemical results are disappointing, the reaction gives quantitative yields of reduction product and therefore provides an attractive means for deamination. The extensive racemization observed is believed to be due to the free-radical nature of the reaction[117].

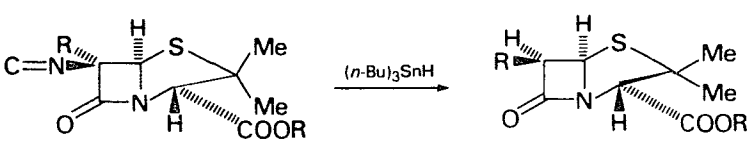


(+)-(*S*)-(**105**) (+)-(*R*) (118)



(−)-(*S*)-(**107**) (±) (119)

Saegusa, Ito and coworkers[118b] have shown that tri-*n*-butyltin hydride is an effective reducing agent for isocyanides. Recently John and coworkers[118a] reported a stereoselective synthesis of 6-alkylpenicillinates (**108**) from 6-α-alkyl-6-β-isocyanopenicillates (equation 120). Barton and coworkers[119] have also used a similar strategy (equation 117) to deaminate amino acid ester, steroidal amines, glucosamine and

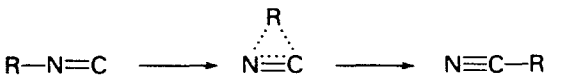


(**55**) (**108**) (120)

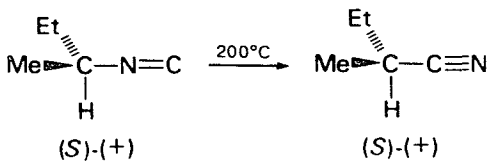
hydrocarbon amines by converting them to isocyanides followed by reduction with tri-*n*-butyltin hydride. The inversion observed in the conversion of **55** to **108** is probably due to the intermediate radical reacting from the least hindered side of the molecule.

X. ISOCYANIDE–CYANIDE REARRANGEMENT

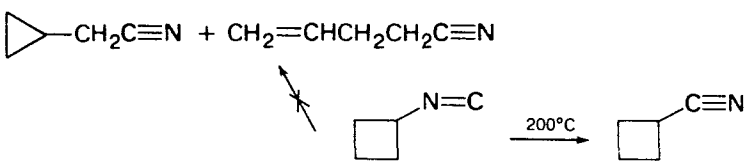
Casanova and coworkers[120e] have shown that the unimolecular first-order thermal isocyanide to cyanide rearrangement proceeds with retention of stereochemical integrity at the migrating secondary carbon atom (equations 121 and 122). The lack of carbon skeleton rearrangement in the isomerization of cyclobutyl isocyanide (equation 123) and the low sensitivity of the reaction rate to variation in *para*-substituents in aryl isocyanides support the suggestion of a synchronous bond-breaking and bond-making of the migrating group and that little charge separation develops in the transition state.



(121)

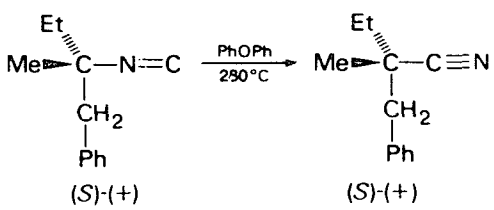


(122)



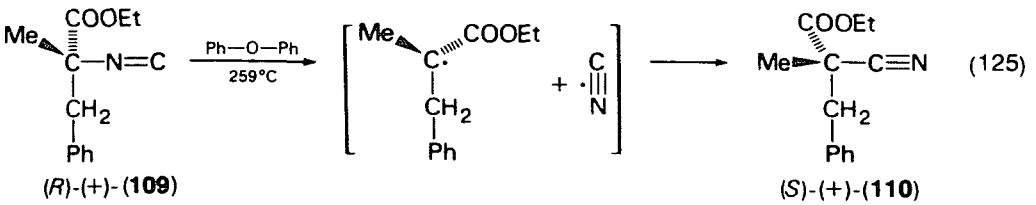
(123)

Yamada and coworkers[120a–d] have extended the isomerization reaction to include isocyanides in which the isocyano moiety is attached to a tertiary carbon atom. The thermal isomerization of (*S*)-(+)-1-phenyl-2-methyl-2-isocyanobutane in refluxing diphenyl ether (280°C) yielded the isomeric cyanide in 86% yield and with 90% retention of configuration (equation 124), a result consistent with the findings of Casanova.

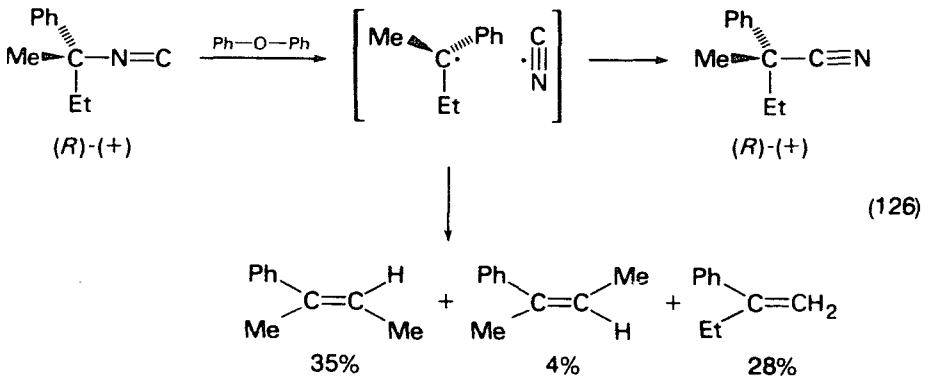


(124)

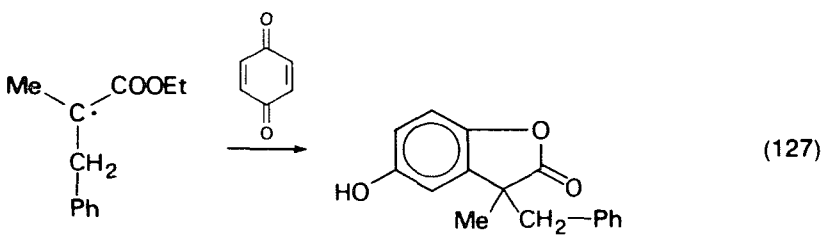
However, when the migrating carbon atom contains delocalizing groups such as carbomethoxy or phenyl then the stereochemical results are markedly different. The rearrangement of ethyl (*R*)-(+)-2-methyl-2-isocyano-3-phenylpropionate (**109**) in diphenyl ether gave a 92% yield of the corresponding cyanide (**110**) but the retention of configuration was only 9% (equation 125). Similarly, (*R*)-(+)-2-phenyl-2-isocyanobutane in refluxing diphenyl ether produced the isomeric cyanide in low yield



(21%) and low retention of configuration (19%). Moreover, three olefins were isolated from the reaction mixture (equation 126).



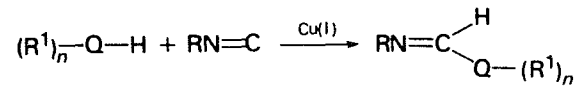
The observed stereochemical results and the product distribution lead to the postulate of radical intermediates for the thermal isomerization reaction. In at least one case (equation 125) the intermediate radical postulated was trapped when quinone was added to the reaction mixture (equation 127).



Aryl isocyanides have been shown to rearrange to cyanides when irradiated at 254 nm in methanol solution[121]. The use of aprotic solvents inhibits the reaction. Infrared laser-induced isomerization of methyl and ethyl isocyanides have been observed[122].

XI. METAL–ISOCYANIDE COMPLEXES

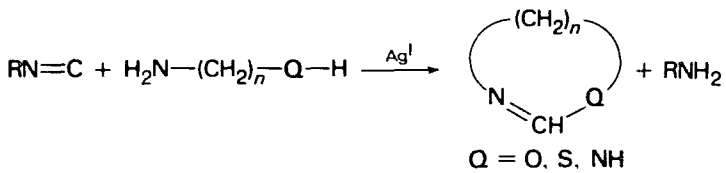
Recently, a number of synthetic applications of metal–isocyanide complexes have been discovered. Saegusa and his coworkers[123a] have reported that Cu(I), Ag(I) and Au(III) salts catalysed the α addition reactions of isocyanides with amines, alcohols, thiols, phosphines and silanes producing formimidoyl derivatives in high yields ('formimidoylation reaction') (equation 128). However the α addition of perfluoroalkyl iodides to isocyanides is said to be catalysed only by copper powder[124]. Extension of the formimidoylation reaction provides a new and versatile method for



(128)

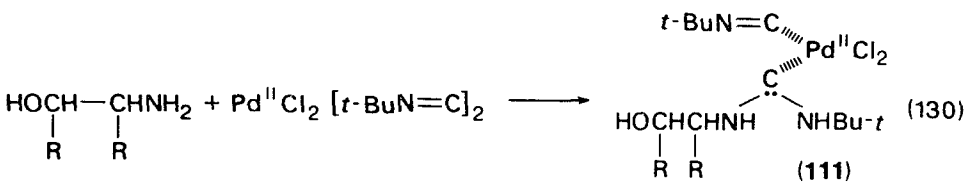
n = 1, Q = O, S; n = 2, Q = N, P; n = 3, Q = Si

heterocycle synthesis which involves Ag(I)-, Cu(I)- and Pd(II)-catalysed cyclization of isocyanides with diamines, amino alcohols and amino thiols. It has been established that both reactions (equations 128 and 129) involve the heteroatom-substituted



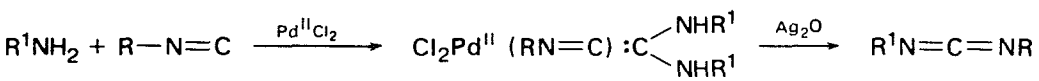
(129)

carbene–metal as the key intermediate. For example, the carbene-coordinated palladium(II) complexes **111** have been isolated from the reaction of β-amino alcohols with a *t*-butyl isocyanide complex of $Pd^{II}Cl_2$ (equation 130). Similar



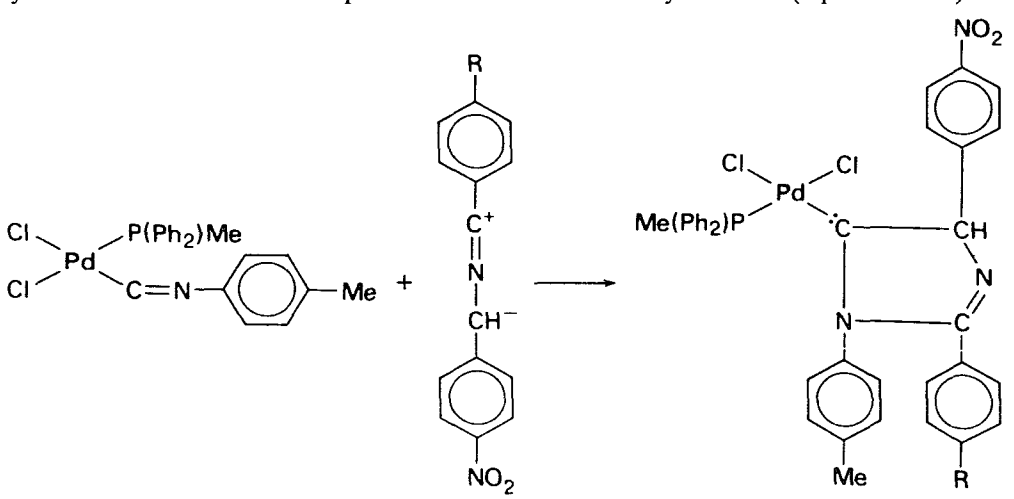
(130)

carbene–palladium complex intermediates obtained from primary amines and isocyanides have been oxidized with Ag_2O to yield symmetrical and unsymmetrical carbodiimides (equation 131)[125]. Another way of preparing novel cyclic



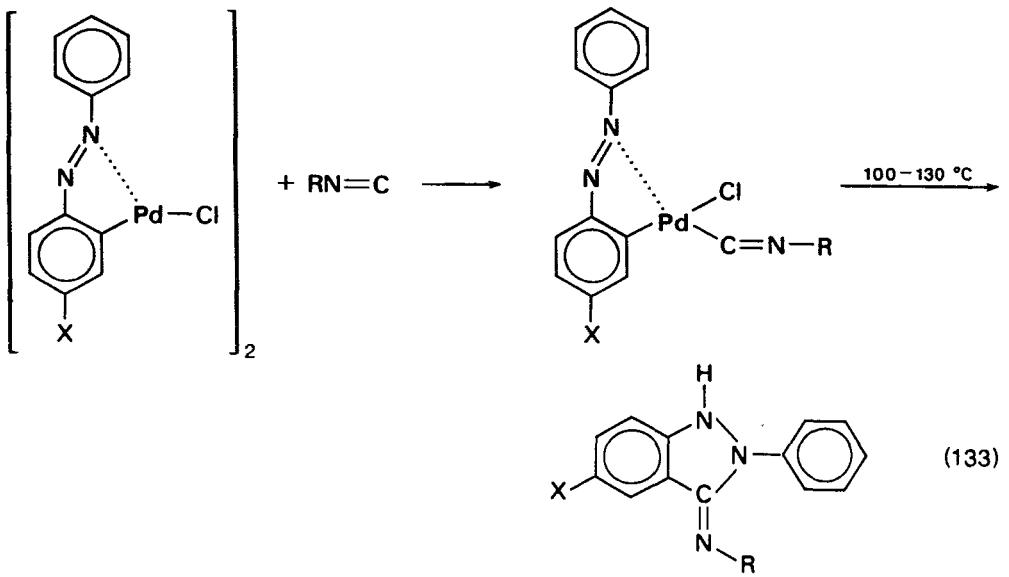
(131)

carbene–palladium(II) complexes is the 1,3-dipolar cycloaddition reaction of nitrile ylides and nitrilimines with palladium-coordinated isocyanides[126] (equation 132).



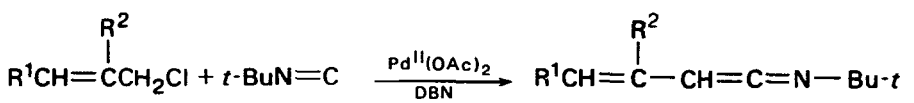
(132)

A convenient synthesis of 3-imino-2-phenylindazolines from the azobenzene complexes of $PdCl_2$ and isocyanides have been reported[127]. The intermediate complex has been isolated and characterized (equation 133).



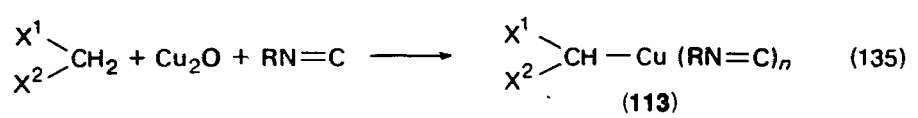
(133)

A new synthesis of vinylketenimines (**112**) involves the reaction of allylic chlorides with an isocyanide in the presence of $Pd^{II}(OAc)_2$ and 1,5-diazabicyclo[3.4.0]nonene-5 (DBN) (equation 134)[123b].



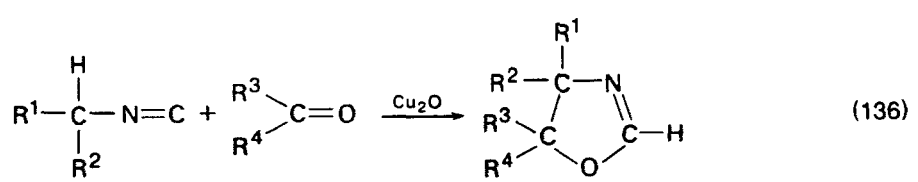
(134)

The reaction of active hydrogen compounds with copper(I) oxide–isocyanide or copper (0)–isocyanide complexes results in the formation of organocopper(I)–isocyanide complexes **113** (equation 135) which have been used in the synthesis of a variety of compounds like 2-oxazolines and 1-pyrrolines (equations 136 and 137).

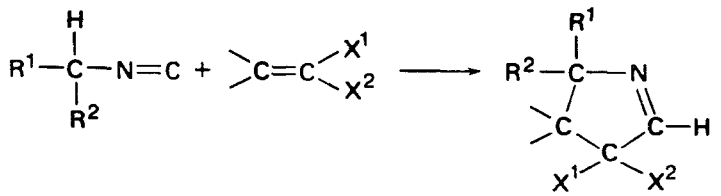


(135)

X^1, X^2 = Halogen, —N=C, —C=N, COOR, COR, Ph



(136)

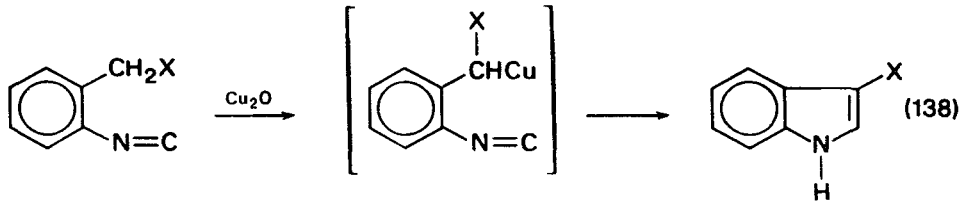


(137)

R^1, R^2 = Ph, COOR

X^1, X^2 = CN, COOR

The Cu_2O-catalysed reactions of **114a** and **114b** represent a new synthetic method for 3-substituted indole derivatives (equation 138)[123c]. The catalytic action of



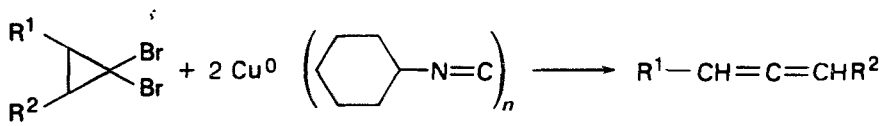
(138)

(114)

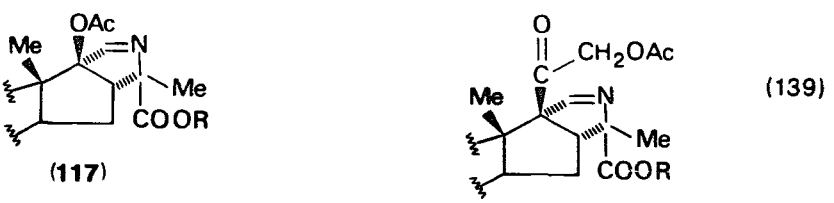
(a) X = CN

(b) X = COOMe

copper(0)–isocyanide complex **115** was utilized in the transformation of *gem*-dibromocyclopropanes into the corresponding allenes **116** (equation 139)[128].



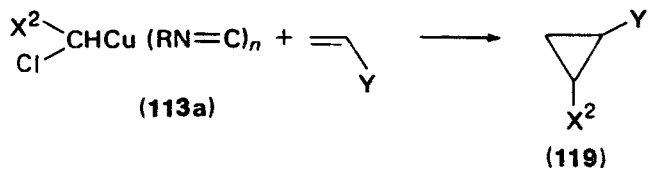
(115) **(116)**



(139)

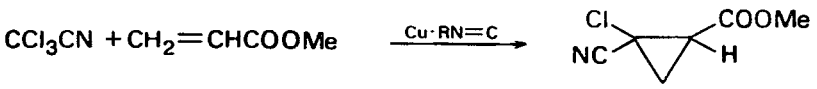
(117) **(118)**

According to a U.S. patent[129], antiinflammatory agents **117** and **118** were prepared by Cu_2O-catalysed cycloaddition of C=N—CH(CH$_3$)—CO$_2$Et to the appropriate pregn-16-ene derivatives. When X^1 is chlorine, the reaction of organocopper(I) complex **113a** with electron-deficient alkenes produces cyclopropane derivatives **119** (equation 140). In a similar manner, copper(0)–isocyanide complexes catalyse the formation of cyclopropane derivatives in the reaction of α,α-dichloro and α,α,α-trichloro compounds with electron-deficient alkenes (equation 141)[123]. Reactions of a substituted 1,3-diiodopropane with α,β-unsaturated esters in the presence of Cu–*t*-butyl isocyanide produce cyclopentanecarboxylate derivatives **120** (equation 142). The catalytic influence of Cu_2O–isocyanide complexes in the

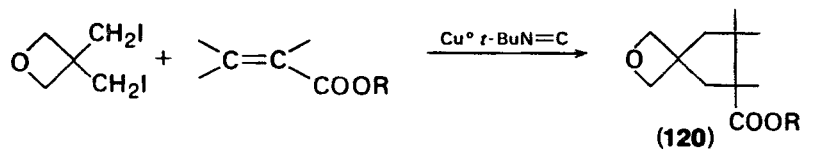


(140)

$X^2 = Y = COOR, CN$

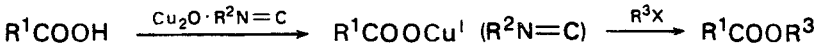


(141)



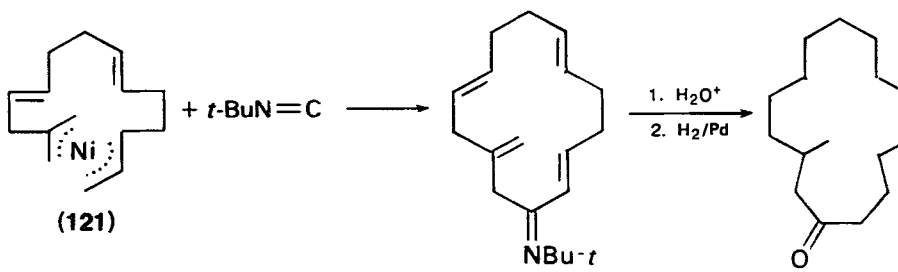
(142)

esterification of carboxylic acids and anhydrides with alkyl halides has been reported (equation 143)[130].



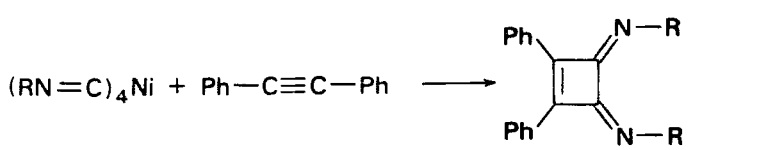
(143)

Bis-π-allyl nickel complexes have been shown to undergo insertion reactions with alkyl isocyanides to produce cyclic imines. Utilizing this reaction, Baker and collaborators[131] synthesized (±)-muscone in good yield from **121** with *t*-butyl isocyanide (equation 144). Novel cycloaddition products are obtained from the



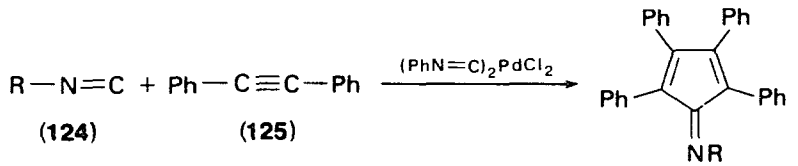
(121) (144)

reaction of isocyanides with diphenylacetylene in the presence of transition-metal complexes. For example, an equimolar mixture of **122** and diphenylacetylene (**125**) reacts to give diiminocyclobutene **123** (equation 145) and the reaction of isocyanide **124** with **125** in the presence of a palladium isocyanide complex gives an iminocyclopentadiene (equation 146)[132]. However, the reaction of 2,6-dimethylphenyl isocyanide with **126** yields[133] 3,4,5-tris(2,6-dimethylphenylimino)diphenylcyclopentene **127** (equation 147). In certain cases the reaction products are isolated as metal complexes. The reaction of diphenylacetylene with



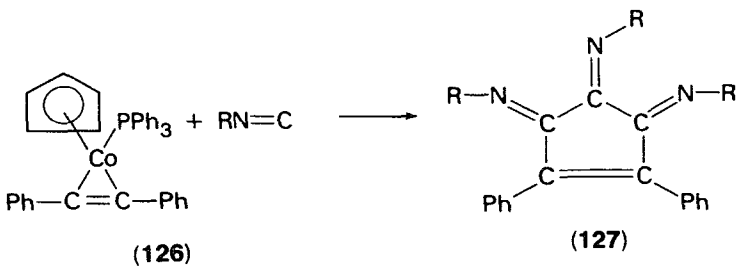
(145)

(122) (125) (123)



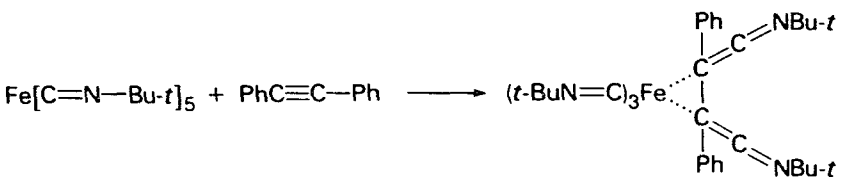
(146)

(124) (125)



(147)

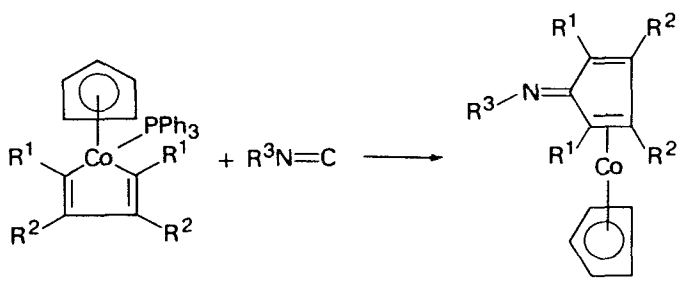
(126) (127)



(148)

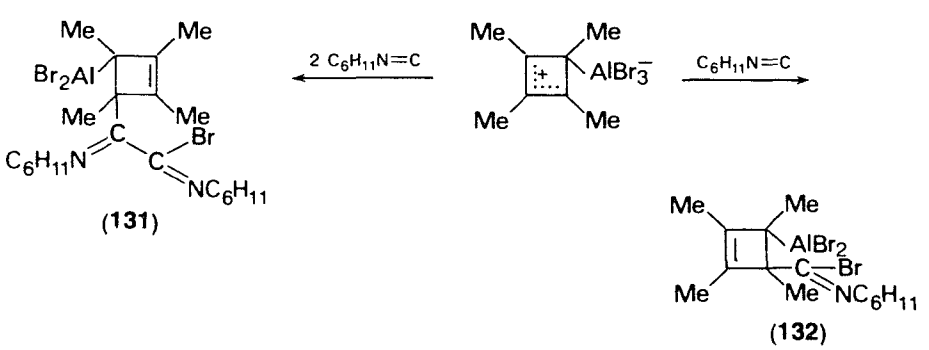
(128)

[Fe(CNB*u*-*t*)$_5$] produces iron complex **128** (equation 148) whose structure has been established by X-ray crystallography[134]. Similarly, the reaction of **129** with isocyanides yields cobalt complexes **130** in good yields (equation 149)[135]. It has been observed



(149)

(129) (130)



(150)

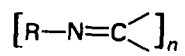
(131) (132)

that the iminocyclopentadiene ligand in these complexes is strongly coordinated to the cobalt in contrast to **127**. The reaction of the $AlBr_3$ σ complex of tetramethyl cyclobutadiene with 1 and 2 moles of cyclohexylisocyanide yields **131** and **132** respectively (equation 150)[136].

In this section emphasis has been focused on the synthetic aspects of isocyanide complexes. However a large number of new transition-metal isocyanide complexes have been prepared and review articles describing the chemistry of those complexes have appeared[137].

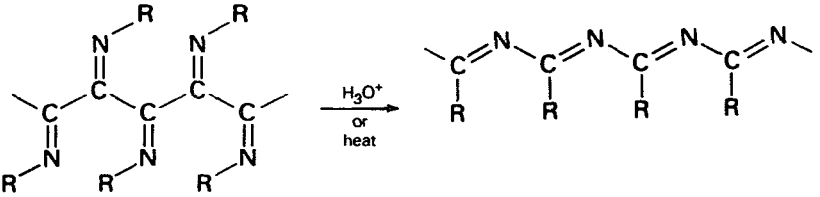
XII. POLYISOCYANIDES

The pioneering work on polyisocyanides was carried out by Millich and an excellent review article summarizing the earlier results has been published[138]. Polymerization of isocyanides can be initiated by the catalytic action of Lewis acids and protonic acids and by the decomposition of metallo–isocyanide complexes. Spontaneous polymerization and polymerization in the presence of ground glass have also been reported. According to Drenth and Nolte nickel(II)-catalysed polymerization is the method of choice[139]. Based on elemental analysis and spectroscopic data, the structure of polyisocyanides has been shown to be **133**. Therefore according to IUPAC rules, isocyanide polymers are named 'poly(iminomethylenes)'.



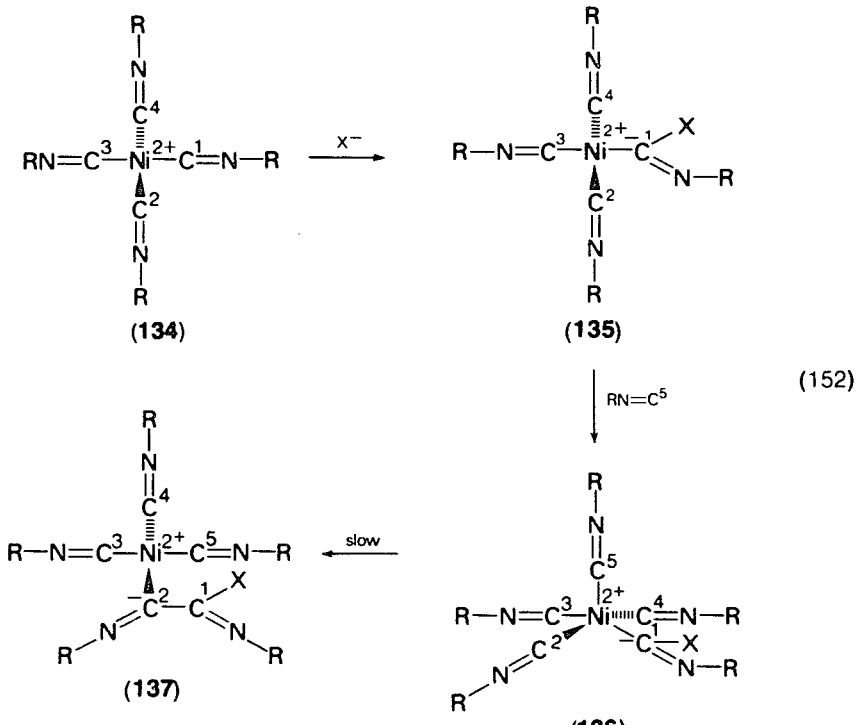
(133)

Upon contact with acid or heat, polyisocyanides are rearranged to polycyanides, poly(azoethenylenes) (equation 151). From viscocity measurements, X-ray scattering and optical rotation data and molecular models, Millich first proposed that polyisocyanides have rigid rod helical structures. In support of this Drenth and his workers were able to resolve poly(*t*-butyl isocyanide) by column chromatography, using poly(+)-*s*-butyl isocyanide and poly(−)-*s*-butyl isocyanide as the supporting medium, into fractions with (+) and (−) signs of optical activity[140].

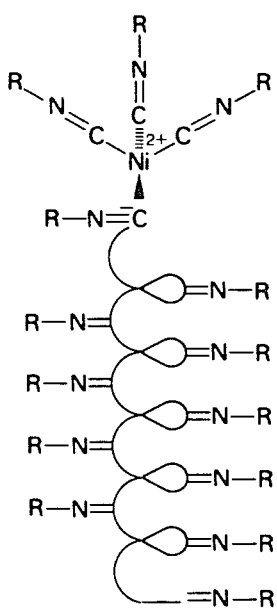


(151)

The mechanism proposed by Drenth and coworkers for the homogeneous polymerization of isocyanides by nickel(II) involves a merry-go-round sequence of ligand insertions at the reaction site (equation 152)[141]. The initiation step involves an attack on one of the four isocyanide ligands by a nucleophile, e.g. a chloride ion or an alcohol solvent, giving **135** in which the plane of the ligand $C^1(X)=N-R$ is approximately perpendicular to the plane of other carbons and nickel. Now in **135**, carbon atom C^1, due to its increased nucleophilicity, is capable of attacking a neighbouring isocyanide carbon. Such an attack is favoured when a new ligand $C^5=N-R$ from solution coordinates with **135** to form **136**. In **136** C^1 can attack either C^2 or C^4. When the isocyanide is achiral the attacks on C^2 and C^4 are of equal possibility although in **137** the attack has occurred on C^2. Continuing the sequence of attack C^1 on C^2, C^3 on C^4 etc. in a merry-go-round manner, the polymer helix **138**



(134) (135) (136) (137) (152)



(138)

grows downwards from the nickel plane. The probable polymerization termination could be either blocking of the circular sequence around nickel or attack on the tail-carbon of the chain by a proton. Based on steric effects and the ligand properties of R^1, R^2 and R^3 groups, this mechanism will predict the screw sense of the polymers obtained in the nickel(II)-catalysed reaction form a chiral isocyanide $R^1R^2R^3C{-}N{=}C$[142].

The combination of chirality and rigidity gives poly(iminomethylenes) major advantages in their use as solid polymeric support for anchoring homogenous catalysts. Future research work is expected to be focused on the application of polyisocyanides in enantioselective experiments. It is interesting to note that the poly(iminomethylenes) can be viewed as masked poly(carbon monoxide) polymers.

XIII. ACKNOWLEDGEMENT

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XIV. REFERENCES

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CHAPTER **21**

Complexation of aryldiazonium ions by polyethers

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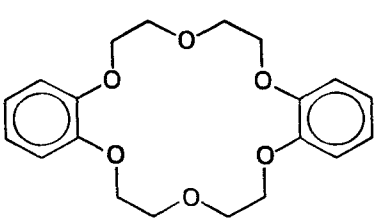
I. INTRODUCTION

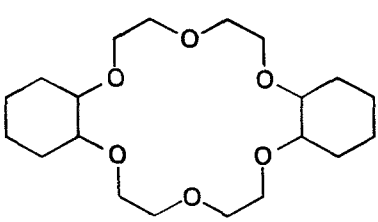
Since their discovery in 1858[1], aryldiazonium salts and their chemistry have been intensively investigated[2–6]. Today arenediazonium salts are well-known and versatile intermediates for the synthetic chemistry which is practised in both academic and industrial settings. Mechanisms of aryldiazonium salt reactions continue to receive attention for both practical and theoretical reasons.

An exciting, recent development in this field is the discovery that arenediazonium ions can be complexed by polyethers. This complexation alters the spectral properties of the aryldiazonium ion and markedly modifies its reactivity. Polyethers are also employed as phase-transfer catalysts which allow reactions of aryldiazonium salts to be carried out in nonhydroxylic media. It is the purpose of this chapter to summarize the presently available information concerning the complexation of aryldiazonium salts by polyethers and the synthetic applications of this phenomenon.

In many studies of aryldiazonium ion complexation, macrocyclic polyethers (crown ethers) are utilized. Therefore, a brief review of crown ether nomenclature is in order. The trivial naming system for crown ethers[7] involves listing, in order: (1) Substituents on the polyether ring, (2) the number of atoms in the polyether ring, (3) the class name crown and (4) the number of oxygen atoms in the polyether ring. Thus, the crown ethers (**1**), (**2**), and (**3**) are dibenzo-18-crown-6, dicyclohexano-18-crown-6 and 18-crown-6, respectively.



(**1**)



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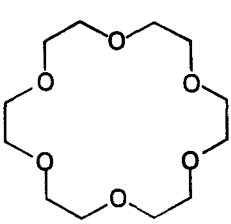

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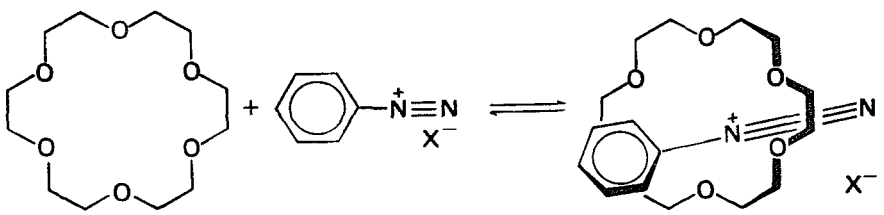
II. DISCOVERY OF THE PHENOMENON

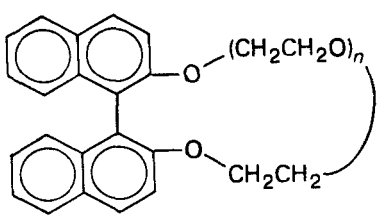
Due to their ionic nature, aryldiazonium salts are usually insoluble in nonhydroxylic organic solvents of low polarity, such as chlorocarbons and hydrocarbons. Using Corey–Pauling–Koltun (CPK) molecular models, Gokel and Cram[8] deduced that crown ethers might complex with aryldiazonium ions by insertion of the positively charged, rod-like diazonium group into the polar cavity of the macrocycle, as illustrated in equation (1). These authors reasoned that the complexation would increase



(1)

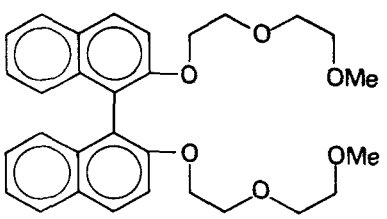
the lipophilicity of the aryldiazonium cation and thereby facilitate the dissolution of aryldiazonium salts in nonpolar organic solvents.

In 1973, Gokel and Cram[8] reported that substituted benzenediazonium tetrafluoroborates can indeed be solubilized in deuteriochloroform by the use of certain crown ethers. Integration of the proton magnetic resonance (PMR) spectrum of a solution which results from contacting a $CDCl_3$ solution of binaphtho-20-crown-6 (**5**) with solid *p*-toluenediazonium tetrafluoroborate reveals that 0.9 mol of the diazonium salt is dissolved per mole of the crown ether. Under the same conditions, the open chain analogue **8** does not solubilize any *p*-toluenediazonium tetrafluoroborate. This suggests the possible requirement of a preformed polyether cavity in order for complexation to occur.



(**4**) $n = 3$ (**6**) $n = 5$

(**5**) $n = 4$ (**7**) $n = 6$



(**8**)

The influence of crown ether cavity size upon the complexation phenomenon has been investigated using *p*-toluenediazonium tetrafluoroborate and the binaphtho crown ether series of **4–7**. For this series of macrocyclic compounds, the crown ether cavity diameters are estimated to be 2.2, 2.7, 3.7 and 5.6 Å, respectively. The observed ratios of moles of diazonium salt solubilized per mole of binaphtho crown ether are 0, 0.9, 0.6 and 0.1 for **4–7**, respectively. As estimated from the X-ray contour map of benzenediazonium chloride[9], the cylindrical diameter of the diazonium group is approximately 2.4 Å. Therefore, the solubilization results indicate that a ratio of cation diameter to crown ether cavity of ~0.8–0.9 produces the greatest complexation. Similar ratios have been noted for the complexation of alkali and alkaline earth cations by crown ethers[10].

Further evidence for the insertion of the diazonium group 'neck' of the benzenediazonium cation into the 'collar' of the crown ether[11] is provided by the observation

that binaphtho-20-crown-6 (**5**) solubilizes one mole of 3,4-dimethylbenzenediazonium tetrafluoroborate per mole of crown ether, but the corresponding 2,6-dimethylbenzenediazonium salt is not measurably solubilized. For the latter diazonium ion, CPK models reveal that insertion of the diazonium group into the crown ether cavity would cause serious steric repulsions between the *ortho* methyl groups and the crown ether ring.

Thus, the research of Gokel and Cram[8,11] provides the first evidence for the complexation of aryldiazonium ions by crown ethers as well as an initial assessment of the structural requirements for the two complexing species.

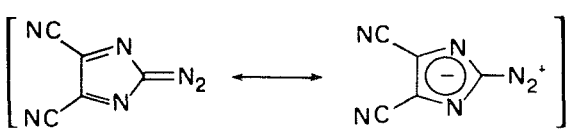
III. SOLID-STATE COMPLEXES OF ARYLDIAZONIUM SALTS AND CROWN ETHERS

A. Isolation

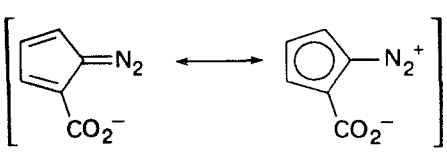
Less than two years after Gokel and Cram[8] had demonstrated the complexation of aryldiazonium tetrafluoroborates by crown ethers in solution, Haymore, Ibers and Meek[12] reported the isolation of the first diazonium-salt–crown-ether complex. When acetone solutions of benzenediazonium hexafluorophosphate and the *cis–anti–cis* isomer of dicyclohexano-18-crown-6 (**2**) are combined and allowed to stand, large, well-formed prisms of the complex are deposited. Alternatively, the complex can be precipitated by a gradual addition of diethyl ether to the acetone solution of the two components. Correct elemental analysis for a one-to-one complex is obtained.

Several complexes of benzenediazonium tetrafluoroborates with 18-crown-6 (**3**) have now been reported[13,14]. Although decomposition points of benzenediazonium salts are notoriously unreproducible, reasonable melting-point behaviour is observed for the complexes of *p*-bromo, *p*-*t*-butyl-, and *p*-chloro-benzenediazonium tetrafluoroborates with **3**.

Diazodicyanoimidazole (**9**) apparently forms a one-to-one complex with 18-crown-6 by complexation through the zwitterionic form[15]. On the other hand, the complex of the potassium salt of diazocyclopentadiene-2-carboxylate (**10**) with dicyclohexano-18-crown-6 appears to involve complexation of the potassium ion rather than the diazonium group[16].



(**9**)



(**10**)

B. X-Ray Diffraction Structure

Very recently, Haymore[17] has determined the structures of benzenediazonium tetrafluoroborate and of the 18-crown-6 complex of benzenediazonium hexafluoro-

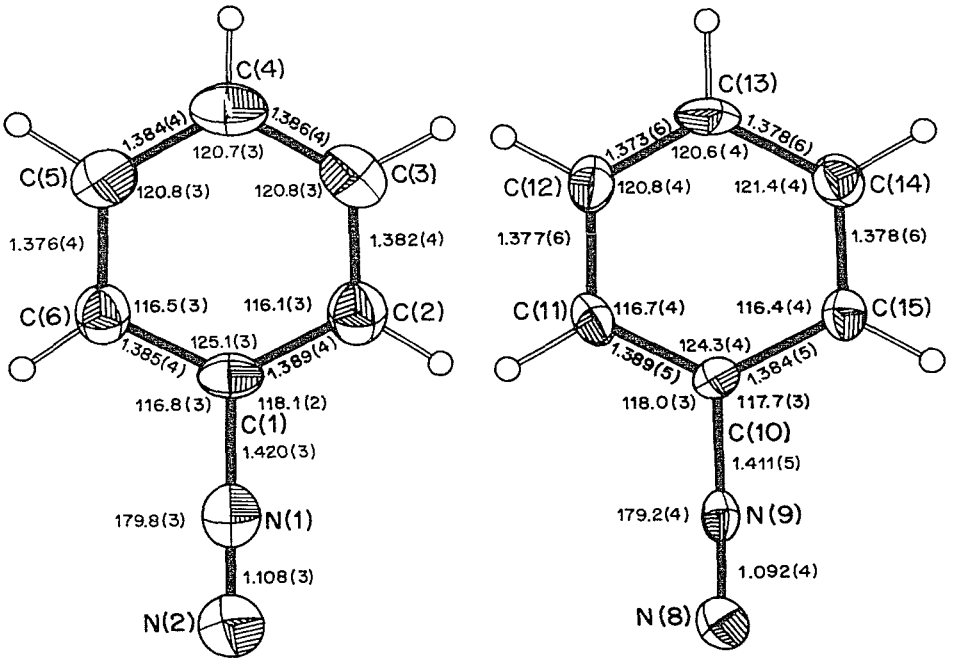


FIGURE 1. ORTEP drawings with measured bond angles and lengths for uncomplexed (left) and 18-crown-6 complexed (right) benzenediazonium ion. Reproduced by courtesy of B. L. Haymore.

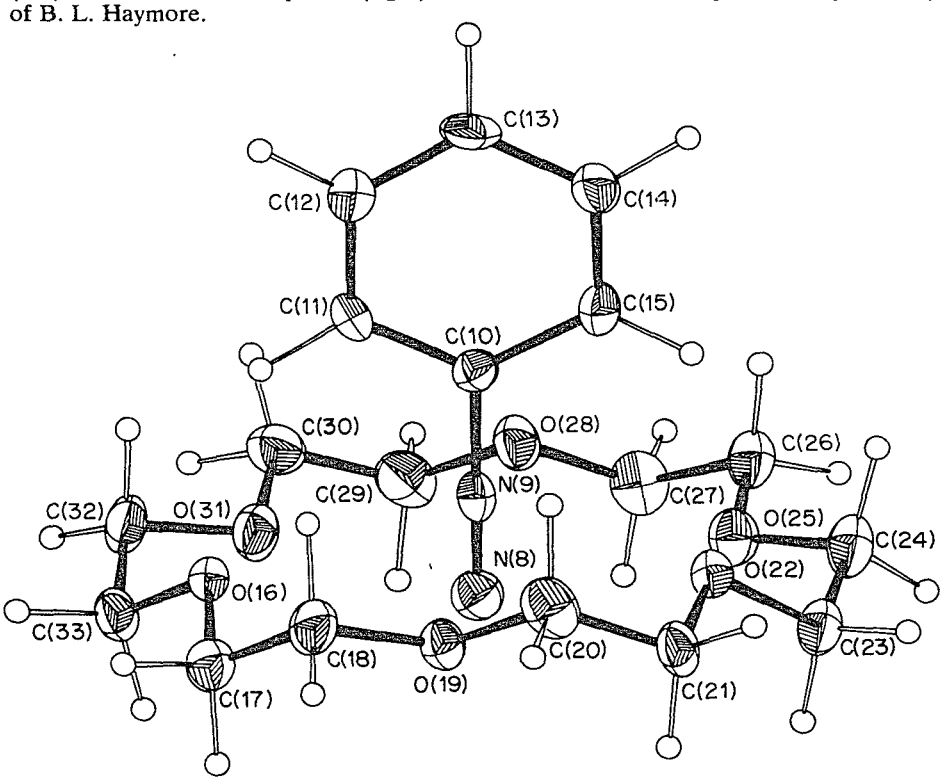


FIGURE 2. ORTEP drawing for the complex of benzenediazonium hexafluorophosphate with 18-crown-6. Reproduced by courtesy of B. L. Haymore.

phosphate by low-temperature X-ray diffraction. The measured bond angles and lengths for the uncomplexed and complexed benzenediazonium ions are recorded on the ORTEP (Oak Ridge Temperature Elipsoid Plotting Program) drawings (Figure 1). The structure of the 18-crown-6 complex of benzenediazonium ion is presented in Figure 2.

Thus, the X-ray diffraction structure verifies the earlier conclusion (Section II) that complexation involves insertion of the diazonium group into the crown ether cavity. The approximate plane formed by the crown ether oxygens roughly bisects the N_α—N_β bond. Further insertion is prevented by steric repulsions between the *ortho* hydrogens of the benzenediazonium ion and methylene hydrogens of the crown ether ring.

Comparison of the structural parameters for the complexed and uncomplexed benzenediazonium cation (Figure 1) reveals a linearity of the C(1)—N_α—N_β bond in both cases. However, both the N_α–N_β and C(1)–N_α bonds are significantly shorter in the complexed diazonium ion.

C. Molecular Orbital Calculations

The interaction of aryldiazonium ions with crown ethers has been probed by Bartsch and Čársky[18] using CNDO/2 calculations. For the uncomplexed diazonium ion, the bond lengths and angles are taken to be those reported for the X-ray crystal structure of benzenediazonium chloride[9]. A complexing crown ether molecule is simulated by three dimethyl ether molecules which are symmetrically arranged about N_α of the benzenediazonium cation and oriented so they match the overall structure of 18-crown-6 in its complexed state[19].

The results of the molecular orbital calculations suggest that complexation of an aryldiazonium ion by an appropriate crown ether involves electrostatic rather than charge-transfer interactions. Comparison of the calculated Wiberg bond indices and atomic charges[20] for the uncomplexed and complexed benzenediazonium ions indicates that upon complexation the multiplicities of both the C(1)—N_α and N_α—N_β bonds increase. This prediction is consistent with the shortening of these bonds upon complexation which is noted in the X-ray diffraction studies (Section III.B). The calculations also predict that complexation increases the positive charges on N_α and C(1), but reduces the amount of positive charge on N_β.

D. Infrared Spectra

When a complex of a crown ether and an aryldiazonium salt is formed as a solid and then mulled with Nujol, a single N≡N stretching absorption band is observed at a

TABLE 1. Infrared spectra of uncomplexed and crown-ether-complexed benzenediazonium salts in the solid state[a]

	$\nu_{N\equiv N}$ (cm^{-1})		
Complex	Complex	Uncomplexed diazonium salt	Reference
$PhN_2^+ PF_6^-$·**2**	2317	2285	12
p-*t*-$BuC_6H_4N_2^+ BF_4^-$·**3**	2306	2277	13
p-$ClC_6H_4N_2^+ BF_4^-$·**3**	2322	2297	14
p-$BrC_6H_4N_2^+ BF_4^-$·**3**	2321	2295	14

[a]Taken as Nujol mulls.

frequency which is different from that for the same vibration in the uncomplexed diazonium salt[12–14] (Table 1). The occurrence of a single, new, absorption band reveals that the complex does not revert to the uncomplexed diazonium salt and crown ether when it is suspended in Nujol. The observed increases in $\nu_{N\equiv N}$ for a benzenediazonium ion upon complexation by a crown ether are unique[12]. Complexation of aryldiazonium cations with other types of ligands produces diminished $\nu_{N\equiv N}$ values[12].

The increase in $\nu_{N\equiv N}$ which results from complexation is consistent with the enhanced $N_\alpha—N_\beta$ bond order predicted by molecular orbital calculations (Section III.C) and the observed $N_\alpha—N_\beta$ bond-shortening noted in the X-ray diffraction structural studies (Section III.B).

E. ESCA Spectra

Bohman and coworkers[21] have measured the ESCA spectra of *p-t*-butylbenzenediazonium tetrafluoroborate and its complex with dibenzo-18-crown-6 (**1**).

In contrast to the previously examined complexation of alkali metal cations by dibenzo-18-crown-6[22], the O1s line (the two types of oxygen exhibit only a single ESCA line) shifts upon complexation with *p-t*-butylbenzenediazonium tetrafluoroborate. This indicates the operation of different relaxation effects for complexed aryldiazonium and alkali metal cations.

Two nonequivalent nitrogen peaks are observed in the N1s spectra of both the uncomplexed and complexed diazonium salts. Simple resonance theory considerations of an uncomplexed benzenediazonium cation predicts that the carbon-bonded nitrogen, N_α, will be more positive than N_β. It should be noted that a recent *ab initio* calculation[23] for the ground state of a free benzenediazonium cation places the main positive charge on N_β. However, such calculations often show large deviations for complex systems. Therefore, unless the positions of the two N1s ESCA peaks are altered by relaxation effects, one expects N_α to have the higher binding energy.

The binding energy difference between the nonequivalent nitrogens decreases from 1.6 eV to 1.2 eV upon complexation[21]. The N1s line at 403.3 eV (interpreted as coming from N_β) shifts by 0.5 eV towards higher binding energy, while the N1s line at 404.9 eV (thought to arise from N_α) remains almost constant.

These results are anomalous since both simple resonance theory and the CNDO/2 calculations of Bartsch and Čársky[18] (Section III.C) predict that the amount of positive charge on N_α should increase upon complexation. One explanation could be that due to unusual relaxation effects N_α has a lower binding energy than N_β in the uncomplexed benzenediazonium ion. If this were the case, the observed binding energy shifts upon complexation would be consistent with the predicted changes in charge density.

The ESCA spectra of *p-t*-butylbenzenediazonium tetrafluoroborate and its complex with dibenzo-18-crown-6 are time-dependent[21]. After extended irradiation, the spectrum for the uncomplexed diazonium ion exhibits another N1s line in addition to the two original N1s lines. The new line appears at the expense of the two original nitrogen lines and is attributed to molecular nitrogen or some kind of symmetrical complex. In contrast, extended irradiation of the dibenzo-18-crown-6-complexed diazonium salt produces only a gradual disappearance of the two original N1s lines.

Comparison of the spectra obtained from the uncomplexed and complexed diazonium salts after 15 hours of irradiation shows that the complex decomposes more rapidly than does the uncomplexed diazonium salt. This result contrasts sharply with the stability enhancements which usually accompany the complexation of aryldiazonium salts by crown ethers (Section V).

IV. SPECTRAL STUDIES OF COMPLEXES OF ARYLDIAZONIUM SALTS AND CROWN ETHERS IN SOLUTION

A. Infrared Spectra

Gokel, Petcavich and their coworkers[14,24] have investigated the effects of crown ether addition upon $\nu_{N\equiv N}$ for benzenediazonium tetrafluoroborates in chlorocarbon solvents. Selected data are presented in Table 2.

TABLE 2. Effect of 18-crown-6 upon the $\nu_{N\equiv N}$ absorption of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$) in chlorocarbon solvents[14,24]

		$\nu_{N\equiv N}$ (cm^{-1})		
X	Solvent	No 18-crown-6	1 equiv. 18-crown-6	5 equiv. 18-crown-6
t-Bu	$CHCl_3$	2272	2271(1)[a], 2308(1.4)	2308
	CH_2Cl_2	2270	2272(1), 2309(1.3)	2309
Et	$CHCl_3$	2270	2271(1), 2307(1.2)	2306
	CH_2Cl_2	2275	2270(1), 2309(1.5)	2310
n-BuO	$CHCl_3$	2245	2245(1), 2294(2.4)	2245[b], 2294
Cl	$CHCl_3$	—[c]	2280(1), 2314(2.4)	2314

[a]Relative intensities of the two bands are given in parentheses.
[b]The 2245 cm^{-1} absorption appears as a weak shoulder.
[c]In the absence of 18-crown-6 the diazonium salt is insoluble in chloroform.

Addition of one equivalent of 18-crown-6 (**3**) to solutions of p-t-butyl-, p-n-butoxy-, and p-ethyl-benzenediazonium tetrafluoroborates in chloroform or dichloromethane gives rise to two $\nu_{N\equiv N}$ absorptions. One occurs at or near the position of the $\nu_{N\equiv N}$ absorption which is observed in the absence of crown ether and a new peak appears in the range of 2300–2325 cm^{-1}. Similarly, two $\nu_{N\equiv N}$ bands are noted for chloroform-insoluble p-chlorobenzenediazonium tetrafluoroborate in the presence of one equivalent of 18-crown-6. For a solution of p-t-butylbenzenediazonium tetrafluoroborate in dichloromethane, addition of one equivalent of 12-crown-4 (whose cavity is too small to accommodate the diazonium group) neither alters the position of the free diazonium ion band nor produces any new band in the 2300–2325 cm^{-1} region. Thus, these results demonstrate that the presence of one equivalent of an appropriately sized crown ether yields a mixture of the complexed and uncomplexed aryldiazonium ion species. In agreement with the observations made for the Nujol mull spectra of the solid-state complexes (Section III.D), $\nu_{N\equiv N}$ is shifted to higher wave number values when a benzenediazonium salt becomes complexed by 18-crown-6 in a chlorocarbon solvent.

Addition of five equivalents of 18-crown-6 converts p-t-butyl-, p-ethyl, and p-chloro-benzenediazonium tetrafluoroborates totally into the complexed form in chloroform and even in the more polar solvent dichloromethane. However, a small amount of uncomplexed p-n-butoxybenzenediazonium ion remains discernible in chloroform even in the presence of seven equivalents of 18-crown-6.

Haymore[17] has probed the influence of the solvent upon the $\nu_{N\equiv N}$ values of p-ethoxybenzenediazonium salts in the uncomplexed and 18-crown-6 complexed states (Table 3). Interestingly, the $\nu_{N\equiv N}$ values for the crown-ether-complexed diazonium ion are found to be independent of the solvent identity even though $\nu_{N\equiv N}$ for the uncomplexed diazonium ion varies considerably as the solvent is changed.

TABLE 3. Infrared spectra for *p*-ethoxybenzenediazonium salts and their complexes with 18-crown-6 in solution[17]

Anion	Solvent	$\nu_{N\equiv N}$ (cm^{-1})	
		Free ion	Complexed ion
BF_4^-	H_2O	2246	2296
PF_6^-	Me_2SO	2257	2297
PF_6^-	MeOH	2249	2297
PF_6^-	Me_2CO	2252	2297
PF_6^-	CH_2Cl_2	2234	2297

Haymore[17] has also determined the $\nu_{N\equiv N}$ values for two benzenediazonium hexafluorophosphates and their complexes with 18-crown-6, 21-crown-7 and 24-crown-8 in acetone (Table 4). Increases in the $\nu_{N\equiv N}$ values upon crown ether complexation are noted to diminish in the order 18-crown-6 > 21-crown-7 > 24-crown-8. As will be shown later (Section VI.A), the complexation of aryldiazonium tetrafluoroborates by 21-crown-7 in chlorocarbon solvents is considerably greater than is that by 18-crown-6 or 24-crown-8. Therefore, there appears to be no correlation between the complexation constants for different crown ethers and the changes in $\nu_{N\equiv N}$ which result when an aryldiazonium salt is complexed.

TABLE 4. Infrared spectra of benzenediazonium hexafluorophosphates (p-$XC_6H_4N_2PF_6$) and their crown ether complexes in acetone[17]

X	$\nu_{N\equiv N}$ (cm^{-1})			
	Free ion	18-Crown-6 complex	21-Crown-7 complex	24-Crown-8 complex
H	2292	2317	2301	2294
EtO	2252	2297	2268	2254

B. Ultraviolet and Visible Spectra

Bartsch and coworkers[13] first reported the shifting of the ultraviolet absorption maximum for benzenediazonium tetrafluoroborates to shorter wavelengths in the presence of an appropriate crown ether. Thus, the absorption maximum of *p*-*t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane decreases from 285 nm in the absence of crown ether to 276 nm in the presence of one equivalent of 18-crown-6. Addition of a large excess of 18-crown-6 results in a further decrease to 268 nm. These results indicate that crown ether complexation of a benzenediazonium ion causes a localization of the π electron system.

In more recent work[25,26], similar decreases of 15–20 nm in the ultraviolet absorption maxima are noted for complexation of a variety of benzenediazonium tetrafluoroborates by 18-crown-6 in 1,2-dichloroethane.

Hashida and Matsui[26] have measured the ultraviolet spectra of *p*-methoxybenzenediazonium tetrafluoroborate in the free ion and the 18-crown-6-complexed forms in seven different solvents. Although complexation always produces a shift of the absorption maximum to shorter wavelengths, no correlation of the magnitude of the shift (4–33 nm) with solvent properties (e.g. dielectric constant, E_T values) is evident.

Complexation of benzenediazonium tetrafluoroborates with binaphtho-20-crown-6(**5**) in chloroform produces yellow to red colours[8,11] which suggests the presence of π–π complexation between the arenediazonium ions (π acids) and a naphthalene ring of the crown ether (π base). The failure to observe such colours in the complexation of *p*-*t*-butylbenzenediazonium tetrafluoroborate with a variety of other crown ethers which also contain aromatic groups[27] suggests that the π–π complexation observed with binaphtho-20-crown-6 is rather unique.

C. Nuclear Magnetic Resonance Spectra

1. The crown ether

For simple crown ethers, the proton magnetic resonance (PMR) spectra of the polyethers exhibit only minor changes in the presence of aryldiazonium salts. Thus, complexation of *p*-toluenediazonium tetrafluoroborate by 18-crown-6 in $CDCl_3$ shifts the methylene singlet from 3.62 to 3.58 ppm[8].

However, larger changes are observed for certain more complicated crown ethers[8]. For example, the four $ArOCH_2$ proton absorption of binaphtho-20-crown-6 (**5**), which appears as an eleven-line multiplet centred at 4.06 ppm, becomes two multiplets (one of six lines centred at 3.89 ppm and one of seven lines centred at 4.21 ppm) when the crown ether complexes *p*-toluenediazonium tetrafluoroborate in $CDCl_3$.

2. The aryldiazonium salt

Considerable insight into the changes which result when benzenediazonium salts are complexed by 18-crown-6 can be obtained from nuclear magnetic resonance spectral studies. The effect upon the aromatic ring is probed using a combination of proton, fluorine and carbon nuclear magnetic resonance spectra. Changes in the diazonium group caused by crown ether complexation are investigated using nitrogen nuclear magnetic resonance spectra. Finally, fluorine nuclear magnetic resonance spectral variations are employed to study the interactions of free and complexed benzenediazonium cations with tetrafluoroborate and hexafluorophosphate counterions.

a. Aromatic ring substituents. Juri and Bartsch[28] have detected a small, but real, upfield PMR shift of benzenediazonium cation *ortho* hydrogens upon crown ether complexation. Thus, the *ortho* hydrogen absorptions (of the A_2B_2 pattern) of *p*-*t*-butylbenzenediazonium tetrafluoroborate and hexafluorophosphate in deuterated dimethyl sulphoxide shift upfield by 0.07 and 0.08 ppm, respectively, in the presence of one equivalent of 18-crown-6. Neither the chemical shifts for the *meta* hydrogens (of the A_2B_2 pattern) nor those for the hydrogens of the *t*-butyl group are affected by crown ether complexation.

Changes in the ^{19}F-NMR chemical shifts of *p*-, *m*-, and *o*-fluorobenzenediazonium salts caused by the addition of 18-crown-6 have been investigated by Gokel and coworkers[24]. For the ring-bound fluorine of *p*-fluorobenzenediazonium tetrafluoroborate dissolved in acetonitrile, acetone and methanol, upfield shifts of the fluorine resonance by approximately 4 ppm are observed when one equivalent of 18-crown-6 is added. In contrast, for *m*-fluorobenzenediazonium tetrafluoroborate in the same three solvents there is very little influence of 18-crown-6 upon the ^{19}F-NMR absorption position. For neither *p*- nor *m*-fluorobenzenediazonium tetrafluoroborate is any effect of crown ether discernible in water, a solvent in which only weak complexation is expected (Section VI.D).

When $CDCl_3$-soluble *p*-, *m*- and *o*-fluorobenzenediazonium chlorides are prepared

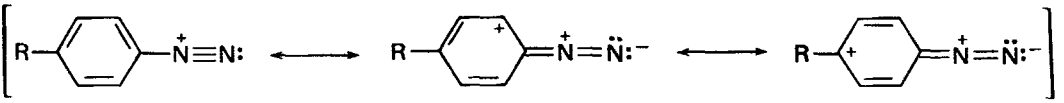
by counterion interchange from the corresponding tetrafluoroborates[29], the addition of one equivalent of 18-crown-6 causes upfield ^{19}F-NMR absorption shifts of 2.3, 0.2 and 3.2 ppm, respectively[24].

When taken together the PMR and ^{19}F-NMR studies indicate that complexation by an appropriate crown ether significantly influences the environments of *ortho* and *para*, but not *meta*, substituents.

b. Aromatic ring carbon atoms. Changes in the ^{13}C-NMR spectra of *p-t*-butyl-benzenediazonium tetrafluoroborate in dichloromethane[14] and of 4-*n*-butyl- and 4-*n*-butoxy-benzenediazonium tetrafluoroborates in $CDCl_3$[24] caused by adding one equivalent of 18-crown-6 are recorded in Table 5. Additional amounts of 18-crown-6 produce further shifts in the same direction but of lesser magnitudes.

For all three benzenediazonium salts, the addition of 18-crown-6 produces an approximately 3 ppm downfield shift in the C(1) absorption and upfield shifts of 2–3 ppm for the *ortho* and *para* carbons. Chemical shift changes for the *meta* carbons are considerably smaller.

The ^{13}C-NMR spectral changes may be rationalized by the following resonance theory argument[31]. Consider that the resonance hybrid for the benzenediazonium cation is comprised of contributions from the diazonium and diazo resonance forms **11–13**. In the presence of crown ether the contribution of the diazonium resonance



(11) **(12)** **(13)**

form **11** to the hybrid should be enhanced by interactions of the crown ether with the localized positive charge.Therefore, crown ether complexation should increase the amount of positive charge on the diazonium group and reduce the positive charges on the *ortho* and *para* carbons because of the decrease in charge dispersal by resonance. According to this rationalization, there should be an upfield shift for the *ortho* and *para* carbons and C(1) should be deshielded due to the increased positive charge on the diazonium group and shift downfield. These predictions are in agreement with the observed spectral shifts. The downfield chemical shift for C(1) caused by crown ether complexation is also consistent with the results of CNDO/2 molecular orbital calculations (Section III.C) which indicate that the amount of positive charge on C(1) will increase in the crown-ether-complexed form[18].

Chemical shift values for C(1) in five 18-crown-6-complexed, *para*-substituted benzenediazonium salts have now been determined[14,24,30] (Table 5). The C(1) chemical shifts for benzenediazonium ions with *p*-hydroxy and *p-n*-butoxy substituents are 9–11 ppm upfield from those with *p*-methyl, *p-t*-butyl, and *p-n*-butyl groups. If contributions from both diazonium and diazo resonance forms are again considered, the relative contribution of diazo forms to the hybrid should be greater for the substituent Y due to the supplemental resonance interactions illustrated by **14** and **15**. Therefore

(14) **(15)**

TABLE 5. Effect of 18-crown-6 upon the ^{13}C-NMR chemical shifts of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$)[14,24,30]

			^{13}C-NMR chemical shift (ppm)[a]							
							X group			
X	Solvent	No. equiv. 18-crown-6	C(1)	*Ortho*	*Meta*	*Para*	C_α	C_β	C_γ	C_δ
t-Bu	CH_2Cl_2	0	110.19	132.43	128.87	167.33	36.66	30.08	—	—
t-Bu	CH_2Cl_2	1	113.58	130.29	128.43	164.54	36.19	30.14	—	—
n-Bu	$CDCl_3$	0	110.39	132.47	131.25	159.10	36.42	32.23	22.14	13.56
n-Bu	$CDCl_3$	1	113.19	130.63	129.87	156.23	35.62	31.78	22.65	13.14
n-BuO	$CDCl_3$	0	101.26	135.64	117.50	168.87	70.13	30.43	18.77	13.48
n-BuO	$CDCl_3$	1	104.49	133.40	116.80	167.05	[b]	30.00	18.30	13.05
HO	$CHCl_3$	1.2–1.8	102.1	—	—	—	—	—	—	—
Me	$CHCl_3$	1.2–1.8	113.3	—	—	—	—	—	—	—

[a]Downfield from TMS.
[b]Obscured by a large peak due to 18-crown-6.

TABLE 6. Effect of 18-crown-6 upon the ^{15}N-NMR chemical shifts of benzenediazonium tetrafluoroborates (p-$XC_6H_4N_2BF_4$)[30,32]

X	Solvent	No. equiv. 18-crown-6	^{15}N-NMR chemical shift (ppm)[a]	
			N_α	N_β
t-Bu	CH_2Cl_2	0	143.8	58.3
t-Bu	CH_2Cl_2	1	148.9	56.8
t-Bu	CH_2Cl_2	5	149.9	56.4
NO_2	$CDCl_3$	1.2–1.8	152.2	57.1
H	$CDCl_3$	1.2–1.8	150.2	57.2
Me	$CDCl_3$	1.2–1.8	149.4	56.9
MeO	$CDCl_3$	1.2–1.8	148.5	53.2
HO	$CDCl_3$	1.2–1.8	146.8	50.8

[a]Upfield from external 1M $H^{15}NO_3$.

the diazonium group is less deshielding when the *para* substituent possesses an unshared electron pair and the C(1) resonance moves upfield[30].

c. The diazonium group. ^{15}N-NMR chemical shifts for the two nitrogen atoms of five benzenediazonium tetrafluoroborates which were solubilized in $CDCl_3$ by 18-crown-6 have been reported by Duthaler, Förster and Roberts[30]. Very recently, Casewit and Roberts[32] have measured these chemical shifts for chlorocarbon-soluble p-t-butylbenzenediazonium tetrafluoroborate in dichloromethane in the absence and presence of 18-crown-6. These data are collected in Table 6.

For p-t-butylbenzenediazonium tetrafluoroborate, complexation by 18-crown-6 produces an upfield chemical shift for N_α, and a smaller downfield shift for N_β. This finding is completely consistent with the results of CNDO/2 molecular orbital calculations (Section III.C) which predict that complexation will enhance the positive charge density on N_α, but decrease the amount of positive charge on N_β.

For the five benzenediazonium tetrafluoroborates which were solubilized in $CDCl_3$ by adding 1.2–1.8 equivalents of 18-crown-6, a general downfield shift for both N_α and N_β is noted as the electron-releasing character of the *para* substituent is enhanced. Electron release by a *para* substituent should lead to larger contributions of structures such as **13** and **15** to the resonance hybrid[30]. The resulting increase in the diazo character of the resonance hybrid should produce downfield shifts for both nitrogens, as is observed. The only anomalous feature of these data is the absence of an anticipated change in the N_β chemical shift in going from the p-nitrobenzenediazonium ion to the benzenediazonium ion[30].

d. The anion. Juri and Bartsch[28] have determined the ^{19}F-NMR chemical shifts for p-t-butylbenzenediazonium tetrafluoroborate and hexafluorophosphate dissolved in 1,2-dichloroethane in the absence and presence of 18-crown-6. The addition of one equivalent of 18-crown-6 causes an upfield shift of 2.5 ppm for the tetrafluoroborate and 1.4 ppm for the hexafluorophosphate anions. A control experiment has demonstrated that the ^{19}F-NMR chemical shift of tetra-n-butylammonium tetrafluoroborate is unaffected by the presence of 18-crown-6.

These results provide evidence for ion-pairing interactions of benzenediazonium ions with even such charge-dispersed anions as tetrafluoroborate and hexafluorophosphate in solvents of low polarity. The somewhat greater change in chemical shift which is observed when 18-crown-6 is added to the diazonium tetrafluoroborate is ascribed to tighter ion pairing in the uncomplexed diazonium tetrafluoroborate than in the hexafluorophosphate.

V. MODIFIED REACTIVITY OF CROWN-ETHER-COMPLEXED ARYLDIAZONIUM SALTS

Complexation with a crown ether modifies the reactivity of an aryldiazonium salt. As discussed earlier (Section III.E), the complex of *p*-*t*-butylbenzenediazonium tetrafluoroborate and dibenzo-18-crown-6 is decomposed by X-ray irradiation more rapidly than is the uncomplexed diazonium salt. However, this behaviour is atypical, since in a variety of other situations the crown-ether-complexed diazonium salt is more stable. In this section, the reduced reactivity of crown-ether complexed diazonium salts will be surveyed.

A. Thermal Stabilization in Solution

Bartsch and coworkers[13] reported the first evidence for diminished arenediazonium ion reactivity upon complexation by crown ethers. To examine the influence of crown ethers upon the thermal decomposition of aryldiazonium ions, these authors employed a special modification of the Schiemann reaction. The thermal decomposition of an aryldiazonium salt in an organic solvent of low polarity may be studied under homogeneous conditions using chlorocarbon-soluble *p*-*t*-butylbenzenediazonium tetrafluoroborate[33] (equation 2). Kinetics are followed by measuring the rate of disappearance of the diazonium ion ultraviolet absorption.

$$p\text{-}t\text{-}BuC_6H_4N_2^+BF_4^- \xrightarrow[ClCH_2CH_2Cl]{50^\circ C} \underset{39\%}{p\text{-}t\text{-}BuC_6H_4F} + \underset{61\%}{p\text{-}t\text{-}BuC_6H_4Cl} \qquad (2)$$

Although the presence of 18-crown-6 has no effect upon the thermolysis products, the rate of decomposition of the diazonium salt is markedly decreased. The observed retardations are rationalized in terms of specific diazonium salt complexation by the crown ether, as depicted in equation (3) where O represents the crown ether. For this

$$\begin{array}{ccc} ArN_2^+\,BF_4^- + \bigcirc & \overset{K}{\rightleftharpoons} & Ar\overset{\frown}{(}N_2^+\,BF_4^- \\ \downarrow k_1 & & \downarrow k_2 \\ \text{products} & & \text{products} \end{array} \qquad (3)$$

scheme, appropriate kinetic derivation[13] reveals that a plot of $1/(k_1 - k_{obs})$ vs. $1/[18\text{-crown-6}]$ should be linear with a slope of $1/(k_1 - k_2)K$ and an intercept at $1/[18\text{-crown-6}] = 0$ of $1/(k_1 - k_2)$ under the condition that $[18\text{-crown-6}] \gg [ArN_2^+\,BF_4^-]$. In the absence of crown ether, the value of k_1 at 50°C is 2.51×10^{-4} s^{-1} [28]. A plot of the rate data obtained with different crown ether concentrations is strictly linear with an intercept of $1/(2.49 \times 10^{-4})$ s^{-1}. Therefore, k_1 must be at least one hundred times greater than k_2.

This kinetic analysis establishes that the crown-ether-complexed *p*-*t*-butylbenzenediazonium ion is thermally stable under conditions which converts the uncomplexed diazonium salt into products. Thus, complexation with crown ethers represents a new method of stabilizing arenediazonium ions.

From the slope of the linear plot, a complexation constant of 1.71×10^4 M^{-1} is calculated for the association of 18-crown-6 with *p*-*t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane at 50°C.

More recently, Kuokkanen and Virtanen[25] have applied a similar kinetic analysis to the thermal decomposition of seven benzenediazonium tetrafluoroborates in 1,2-dichloroethane at 50°C. For *p*-acetyl-, *m*-acetyl-, *p*-methyl, and *m*-methylbenzenediazonium ions as well as benzenediazonium ion itself, values of $k_1 - k_2$ are close to the value of k_1, so $k_1 \gg k_2$. For *p*-chlorobenzenediazonium ion, k_2 is approximately 15% of k_1. However, for the *o*-methylbenzenediazonium ion, which should complex with 18-crown-6 only weakly due to steric factors, the crown-ether-complexed diazonium ion is almost as reactive as the uncomplexed species.

Thus, with the exception of *ortho*-substituted compounds it appears that the thermolysis of benzenediazonium ions in 1,2-dichloroethane in the presence of 18-crown-6 proceeds almost exclusively via the uncomplexed diazonium ion form. Extension of these studies to include a wider range of substituents as well as solvents in which the complexation of diazonium ions by crown ethers is weaker (Section VI.D) would be most useful.

B. Thermal Stabilization in the Solid State

A quantitative investigation of the influence of 18-crown-6 upon the thermal stability of benzenediazonium tetrafluoroborate has been conducted by Bartsch and Shiu[34]. Small samples of the diazonium salt and its one-to-one complex with 18-crown-6 are sealed in glass ampoules and placed in a 50°C constant-temperature bath. At appropriate time intervals, ampoules are removed and the remaining diazonium ion is converted into an azo dye whose concentration is determined spectrophotometrically.

The uncomplexed diazonium salt exhibits thermal stability for approximately two hours. A rapid decomposition then commences and after five hours the diazonium salt is completely decomposed. The complex of the diazonium salt and 18-crown-6 can be heated for 20 hours before the onset of decomposition. Also, the decomposition itself proceeds more slowly than does that of the uncomplexed salt. After 30 and 45 hours, 90% and 50%, respectively, of the diazonium activity remains.

C. Photochemical Stabilization in the Solid State

Somewhat less familiar than the thermal Schiemann reaction is the preparation of fluoroarenes by the photolysis of arenediazonium tetrafluoroborates and hexafluorophosphates[35]. In several instances, considerably higher yields of aromatic and heteroaromatic fluorides are realized from the photochemical Schiemann reaction than from analogous thermal processes[35–39].

Using the technique developed by Petterson and coworkers[35], Bartsch, Haddock and McCann[40] have demonstrated that complexation of benzenediazonium tetrafluoroborate with 18-crown-6 produces dramatic photochemical stabilization when compared with the uncomplexed diazonium salt.

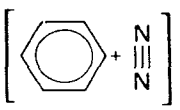
Irradiation (3500 Å lamps) of thin films of solid benzenediazonium tetrafluoroborate deposited on the walls of borosilicate glass tubes produces 73–80% yields of fluorobenzene and 1.9–2.0 equivalents of gas (N_2 + BF_3). Evaporation of an equimolar acetone solution of the diazonium salt and 18-crown-6 also deposits a thin, solid, film on the walls of a borosilicate glass tube. Irradiation of this solid film for the same period of time as before produces only a 4% yield of fluorobenzene and slight gas evolution. Since mostly undecomposed aryldiazonium salt remains after the irradiation, the function of the crown ether is photochemical stabilization rather than the diversion of a photointermediate to form other products.

D. Reduced Shock Sensitivity in the Solid State

Shephard and coworkers[15] have demonstrated a reduced shock sensitivity of diazonium compounds when complexed with crown ethers. As a dry solid, diazodicyanoimidazole (**9**) is shock-sensitive and detonates on impact. In contrast, the crystalline, one-to-one complex of **9** and 18-crown-6 can be handled with ease and does not detonate under the conditions of several standard impact tests.

E. Diminished N_α, N_β, Interchange During Solvolysis

That N_α, N_β interchange may accompany the reactions of aryldiazonium ions was first established by Lewis and Insole[41]. More recent studies by Lewis[42,43], Swain[42,43], and especially by Zollinger[44,45] have revealed that the interchange involves a phenyl-cation–nitrogen-molecule ion pair **16** which either recombines or dissociates to form the free phenyl cation.



(16)

As part of a mechanistic study of the N_α, N_β interchange reaction which occurs when (β-^{15}N) benzenediazonium tetrafluoroborate is solvolysed in 2,2,2-trifluoroethanol, Tröndlin, Medina and Rüchardt[46] have determined the influence of dibenzo-18-crown-6 upon the solvolysis rate and extent of N_α, N_β interchange in the reactant recovered from incomplete reaction. The presence of 4.4 equivalents of dibenzo-18-crown-6 reduces the solvolysis rate to 22% of its value in the absence of crown ether. Such rate reductions are anticipated if the crown ether partially converts the diazonium salt into a less reactive complex (Section V.A).

Interruption of the solvolysis reaction after 70% completion and recovery of the unreacted diazonium salt shows 6.9 ± 0.1% of ^{15}N inversion in the absence of crown ether, but only 5.7 ± 0.1% inversion when the crown ether is present. Although the reason for the 17% decrease in the N_α, N_β interchange is currently unknown, it is clear that the presence of crown ether does influence the exchange reaction.

F. Deactivation of Azo Coupling

The presence of crown ethers retards the azo coupling of aryldiazonium ions with electron-rich aromatic compounds in both homogeneous and two-phase reaction systems.

Butler and Shepherd[47] have studied the effect of varying concentrations of dicyclohexano-18-crown-6 upon the reaction rate of *p*-methoxybenzenediazonium tetrafluoroborate with pyrrole in 1,2-dichloroethane. In the presence of 1–5 equivalents of the crown ether, an approximately linear decrease in the azo coupling rate is noted as the crown ether concentration is increased. This suggests that both uncomplexed and crown-ether-complexed diazonium ions are present, but only the former are reactive.

Juri and Bartsch[48] have reported that the coupling of *p*-*t*-butylbenzenediazonium tetrafluoroborate with *N,N*-dimethylaniline in 1,2-dichloroethane is diminished by the presence of one equivalent of 18-crown-6 to a rate which is approximately 10% of that found under comparable conditions but in the absence of crown ether.

The azo coupling rate of *p*-nitrobenzenediazonium chloride with *N*-ethylcarbazole in the two-phase solvent system of dichloromethane–water decreases by 78% in the presence of 0.05 equivalents of 18-crown-6[49].

Further evidence for the unreactivity of crown-ether-complexed aryldiazonium ion is provided by the observance of only normal azo coupling products in the three studies referenced above as well as that by Gokel and Cram[8]. Formation of azoarene–crown-ether rotaxanes (axle-in-wheel type of compounds[50]) from crown-ether-complexed aryldiazonium ions may be prohibited by steric factors or by a reduced electrophilicity of the complexed diazonium ion.

G. Diminished Nucleophilic Attack *Para* to the Diazonium Group

The diazonium group is strongly activating for nucleophilic aromatic substitution because of its positive charge. Gokel, Korzeniowski and Blum[51] have probed the influence of crown ether complexation upon nucleophilic aromatic substitution reactions of the *p*-bromobenzenediazonium ion.

Reaction of *p*-bromobenzenediazonium tetrafluoroborate with benzyltrimethylammonium chloride in chloroform produces a 55% yield of the nucleophilic halogen displacement (Cl for Br) product. Under the same conditions but in the presence of one equivalent of 18-crown-6, the reaction is incomplete and only a 30% yield of the halogen displacement product is obtained. Thus, the activating effect of the diazonium group is diminished by crown ether complexation.

VI. FACTORS WHICH AFFECT THE COMPLEXATION OF ARYLDIAZONIUM SALTS BY POLYETHERS

Thus far in the discussion, the qualitative solubilization studies (Section II) provide the only information regarding the effect of crown ether structure upon the complexing efficiency for aryldiazonium ions. In this section the available information concerning the influence of the crown ether structure, the aryldiazonium ion substituent, the anion and the solvent is summarized. In addition, the complexing abilities of crown ethers and acyclic polyethers for aryldiazonium ions are compared.

A. The Crown Ether

Limited information regarding the relationship between the cavity size of a crown ether and its ability to complex an arenediazonium ion is provided by the solubilization studies of Gokel and Cram[8] which utilize the binaphtho crown ethers **4–7**. The results (Section II) suggest that a crown ether cavity size of approximately 2.7 Å should be optimal.

To more completely probe the effects of structural variation within the crown ether upon the capacity for aryldiazonium ion complexation, Bartsch and Juri[27] have undertaken a screening study the results of which allow the relative complexing abilities of approximately 40 macrocyclic multidentate compounds to be compared.

The relative complexing abilities are determined by measuring the rates of decomposition of *p-t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane in the presence of one equivalent of the macrocyclic compounds. As described in Section V.A, it has been established that for 18-crown-6 the entire thermolysis reaction proceeds via the uncomplexed diazonium ions species (equation 4). Based upon the assumption that other crown ethers similarly convert the diazonium salt into a thermally stabilized complex, the reduced decomposition rate caused by one equivalent of a crown ether provides a qualitative measure of the complexing ability. A larger complexation constant K is manifested by a greater rate retardation. Rate data for selected crown ether compounds are presented in Table 7.

TABLE 7. Observed first-order rate constants for the thermolysis of *p-t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane at 50°C in the presence of one equivalent of crown ether[27]

Entry	Crown ether	$k_{obs} \times 10^4$ (s^{-1})
1	None	2.51
2	12-Crown-4	2.48
3	15-Crown-5	2.22
4	18-Crown-6	1.35
5	21-Crown-7	0.13
6	Dicyclohexano-18-crown-6	1.34
7	Dicyclohexano-21-crown-7	0.76
8	Dicyclohexano-24-crown-8	1.33
9	Dibenzo-18-crown-6	1.94
10	Dibenzo-21-crown-7	0.54
11	Dibenzo-24-crown-8	0.86
12	Benzo-18-crown-6	1.68
13	3-Methylbenzo-18-crown-6	1.56
14	3-Formylbenzo-18-crown-6	1.99

$$ArN_2^+ BF_4^- + \text{complexing agent} \underset{}{\overset{K}{\rightleftharpoons}} \text{complex} \qquad (4)$$

$$\downarrow k_1$$

products

The presence of 12-crown-4 does not change the thermolysis rate from that observed in the absence of crown ether. This is consistent with a crown ether cavity[52] (Table 8) which is too small to accommodate a diazonium group with an estimated[8] cylindrical diameter of ~2.4 Å. The slight rate retardation noted with 15-crown-5 indicates only weak complexation. For 18-crown-6 there should be a good match between the crown ether cavity diameter and the diazonium group and the thermolysis rate is reduced by approximately 50%.

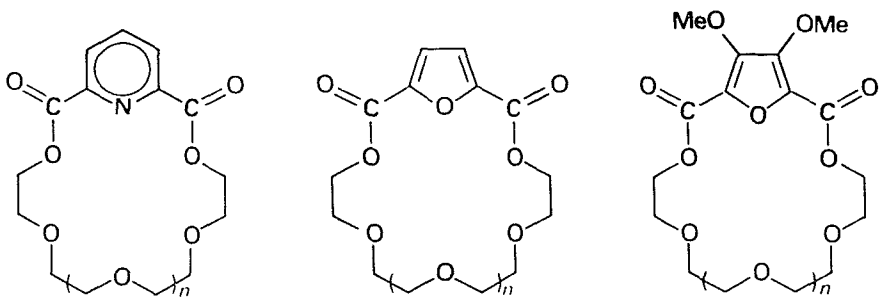
Considering only the relative diameters of the crown ethers and the diazonium group, it would be anticipated that 21-crown-7 should be a poorer complexing agent that 18-crown-6. Since the rate data reveals that 21-crown-7 complexes the diazonium ion more strongly, some additional factor must be important. Bartsch and Juri[27] suggest that this factor is a greater flexibility of the larger ring which relieves steric interactions between the *ortho* hydrogens of the benzenediazonium cation and the crown ether framework. Of the approximately 40 macrocyclic compounds examined, 21-crown-7 is the strongest complexing agent for the aryldiazonium ion. The series

TABLE 8. Estimated cavity diameters for crown ethers[52]

Crown ether	Cavity diameter (Å)
12-Crown-4	1.2–1.5
15-Crown-5	1.7–2.5
18-Crown-6	2.6–3.2
21-Crown-7	3.4–4.3

could not be extended to include 24-crown-6 because of difficulties in obtaining the crown ether in a pure state.

For both the dicyclohexano and dibenzo crown ether series (Table 7, entries 6–8 and 9–11, respectively) the 21-membered macrocycle provides stronger complexation than either of the corresponding 16- or 24-membered ring compounds. Strongest complexation with the 21-membered ring macrocycle is also observed for three series of pyridyl, furanyl and dimethoxyfuranyl crown ether esters, **17**, **18** and **19**, respectively.



(17) **(18)** **(19)**

n = 1, 2, 3

The rate data for benzo-18-crown-6 compounds (Table 7, entries 12-14) demonstrates that electron-donating substituents on the crown ether enhance complexation, but electron-withdrawing groups diminish it.

Krane and Skjetne[53] have reported the use of low-temperature NMR techniques to assess the ring-size effect in the complexation of *p*-toluenediazonium tetrafluoroborate by 18-crown-6, 21-crown-7 and 24-crown-8 in $CHCl_2F$. Of these three crown ethers, 21-crown-7 provides the strongest complexation of the aryldiazonium salt.

Complexation constants for the association of *p*-ethoxybenzenediazonium hexafluorophosphate with six crown ethers in acetone have been determined by Haymore[17] using infrared spectroscopy. Results are recorded in Table 9. Preferred complexation with 21-crown-7 is again observed. The weaker complexation noted in going from 18-crown-6 to *cis*-cyclohexano-18-crown-6 to *cis–syn–cis*-dicyclohexano-18-crown-6 to *cis–anti–cis*-dicyclohexano-18-crown-6 probably results from increasing levels of steric interactions of the crown ether with the *ortho* hydrogens of the benzenediazonium ion.

TABLE 9. Association constants for *p*-ethoxybenzenediazonium hexafluorophosphate with crown ethers in acetone[17]

Crown ether	log K (M^{-1})
12-Crown-4	—[a]
15-Crown-5	—[a]
18-Crown-6	2.0
21-Crown-7	3.1
24-Crown-8	1.9
cis-Cyclohexano-18-crown-6	1.8
cis–syn–cis-Dicyclohexano-18-crown-6	1.5
cis–anti–cis-Dicyclohexano-18-crown-6	1.2

[a]No measurable complexation.

B. Ring Substituents of the Aryldiazonium Ion

The influence of aromatic ring substituents upon the complexation of benzenediazonium salts by 18-crown-6 has been investigated in three solvents by four research groups using four different experimental methods.

By titration calorimetry Izatt and coworkers[54,55] have determined log K, ΔH and $T\Delta S$ values for the association of eight benzenediazonium tetrafluoroborates with 18-crown-6 in methanol. A good linear correlation between log K and $\sigma\rho^+$ with $\rho^+ = 0.65$ is observed. From association constant determinations using ultraviolet spectroscopy, Hashida and Matsui[26] have reported $\rho = 0.98$ for the correlation of σ constants vs. log K values for interactions of eight *meta*- and *para*-substituted benzenediazonium tetrafluoroborates with 18-crown-6 in methanol. Examination of the data reveals that the difference in the magnitudes of the ρ values in these two studies results entirely from the choice of σ substituent constants.

It is clear that electron-withdrawing aromatic ring substituents enhance the complexation of the benzenediazonium ion by a crown ether and electron-donating substituents disfavour the association. This is entirely consistent with the electrostatic interactions between the diazonium ion and the crown ether predicted by the CNDO/2 calculations (Section III.C). However, when compared with diazo systems which involve cation–anion association, such as arenediazocyanides[56] ($\rho = 3.53$), arenediazosulphones[57] ($\rho = 3.76$) arenediazosulphonate[58] ($\rho = 5.5$) and arenediazotate formation[56] ($\rho = 6.58$), the ρ value for the complexation of benzenediazonium ions by the neutral crown ether is quite low.

Using infrared spectroscopy and a limited number of compounds, Haymore[17] has observed that log K values for the association of benzenediazonium hexafluorophosphates with 18-crown-6 are identical to those reported[54,55] for the complexation of the corresponding tetrafluoroborate salts in methanol. Thus, the change from methanol to acetone does not measurably affect the ρ value.

Compared with these results, a small increase in ρ was noted ($\rho = 1.19$) when Kuokkanen and Virtanen[25] determined the association constants for seven benzenediazonium tetrafluoroborates with 18-crown-6 in 1,2-dichloroethane using a kinetic technique. An enhancement of the sensitivity of complexation to substituent effects with diminishing solvent polarity was indicated.

A quantitative assessment of the effects of *ortho* substituents upon the complexation of benzenediazonium tetrafluoroborates by 18-crown-6 has been made by two groups. When compared with *p*-methylbenzenediazonium ion, movement of the methyl group to an *ortho* position decreased the association constant by approximately a factor of ten[26]. Introduction of a second methyl group causes an additional diminution by a factor of 100. For benzenediazonium ions with acetyl groups[25], a change of the substituent position from *para* to *ortho* produces a 10^5 decrease in K. Such behaviour undoubtedly results from steric interactions of the *ortho* substituents with the crown ether framework.

Compared with anilinium ions, aryldiazonium ions are much more sensitive to the steric effects of *ortho* substituents because of the markedly different geometries of the complexes[53].

C. The Anion of the Aryldiazonium Salt

In solvents of low polarity, the association of aryldiazonium salts with crown ethers is disfavoured by anions which exhibit ion pairing with the uncomplexed anion. Thus, from several lines of evidence, Juri and Bartsch[28] conclude that complex formation for *p-t*-butylbenzenediazonium hexafluorophosphate with 18-crown-6 in 1,2-dichloroethane is greater than for the corresponding tetrafluoroborate salt.

TABLE 10. Anion and concentration effects upon log K for the complexation of p-ethoxybenzenediazonium salts by 18-crown-6 in dichloromethane at 35°C[17]

Diazonium salt concentration (mmol)	Apparent log K (M^{-1})	
	Tetrafluoroborate	Hexafluorophosphate
1000	1.94	2.31
100	2.86	3.17
10	3.43	3.61
1	3.58	3.69

Very recently, Haymore[17] has obtained more quantitative data concerning anion and concentration effects for the complexation of p-ethoxybenzenediazonium tetrafluoroborate and hexafluorophosphate in dichloromethane using an infrared spectroscopic method. Results are recorded in Table 10.

Increases in log K with diminishing diazonium ion concentrations result from reduced ion pairing of the uncomplexed diazonium salt with the anion. However, at all concentrations a greater complexation of the hexafluorophosphate salt is evident.

D. The Solvent

The effect of solvent upon the association constants for 18-crown-6 with p-methoxybenzenediazonium tetrafluoroborate[26] and p-ethoxybenzenediazonium hexafluorophosphate[17] is shown in Table 11. The data obtained for the latter suggest a possible inverse correlation between solvent polarity and the magnitude of the association constant. However, the data for the former which include a larger number of low polarity solvents reveal that there is no simple relationship between log K and the dielectric constant or E_T value of the solvent[26].

TABLE 11. Log K values for the association of benzenediazonium salts with 18-crown-6 in different solvents[17,26]

Solvent	ε	E_t	log K (M^{-1})	
			p-$MeOC_6H_4N_2BF_4$[a]	p-$EtOC_6H_4N_2PF_6$[b]
H_2O	78	—	—	−0.5[c]
Me_2SO	47	—	—	0.5
MeOH	33	—	2.09	1.7
Acetone	21	42.2	2.56	2.0
$ClCH_2CH_2Cl$	10	41.9	4.67	—
CH_2Cl_2	9	41.1	3.23	3.7
THF	8	37.4	2.27	—
$CHCl_3$	5	39.1	3.45	—
Dioxane	2	36.0	1.87	—

[a]At 15°C.
[b]At 35°C.
[c]The anion was tetrafluoroborate.

E. Acyclic Polyethers

Interactions of arenediazonium ions with acyclic polyethers have been probed by Bartsch and coworkers for individual glymes from diglyme to decaglyme[59] and for

TABLE 12. Log K values for the complexation of *p-t*-butylbenzenediazonium tetrafluoroborate by acyclic polyethers in 1,2-dichloroethane at 50°C[59]

Polyether	log K (M^{-1})
Diglyme	2.26
Triglyme	2.19
Tetraglyme	2.35
Pentaglyme	2.73
Hexaglyme	2.90
Heptaglyme	3.00
Octaglyme	2.65
Nonaglyme	2.77
Decaglyme	3.14

oligoethylene glycols, $HO(CH_2CH_2O)_nH$, and their monomethyl and dimethyl ethers[60]. The retarding influence of the acyclic polyethers upon the thermal decomposition rate of *p-t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane is measured. The rate retardations are considered to result from the conversion of the diazonium ion into an unreactive form upon complexation (equation 5) as has earlier been established for the crown ether 18-crown-6[13].

$$ArN_2^+ BF_4^- + \text{acyclic polyether} \underset{}{\overset{K}{\rightleftharpoons}} \text{complex} \qquad (5)$$

$$\downarrow k_1$$

products

Using this assumption and an excess of the acyclic polyether, complexation constants may be calculated directly from the observed first-order rate constants for the diazonium ions thermolysis in the presence and absence of the potential complexing agent. Log K values for the individual glymes are recorded in Table 12.

The log K values are essentially the same for diglyme, triglyme and tetraglyme and then increase monotonically for pentaglyme, hexaglyme and heptaglyme as the ability of the polyether to form a pseudo-cyclic cavity is enhanced. For octaglyme and nonaglyme, the pseudo-cyclic cavity can contain only a portion of the ether oxygens because of repulsions of the polyether chain-ends. Therefore, weaker complexation is observed. CPK models indicate that, for decaglyme, seven or eight oxygens may form a pseudo-cavity with the remaining oxygens in an arm which passes over the face of the cavity. Thus when complexed with the benzenediazonium ion, decaglyme appears to assume a conformation which is not only crown-ether-like, but also cryptand-like.

To determine the increase in complexation efficiency that is derived by preforming the cyclic cavity of the polyether ('the macrocyclic effect'), complexation constants for acyclic and cyclic polyethers with the same number of oxygen atoms have been compared. From comparison of K values for the association of pentaglyme and of 18-crown-6 with *p-t*-butylbenzenediazonium ion in 1,2-dichloroethane at 50°C, a macrocyclic effect of approximately 30 has been calculated[59].

Based upon the same two polyethers, a macrocyclic effect of 18,700 has been reported for the complexation of *t*-butylammonium thiocyanate in chloroform[61]. Thus, the magnitude of the macrocyclic effect is shown to be highly dependent upon the nature of the cationic species which is being complexed.

In further research, the complexing ability of commercially available oligoethylene glycols and oligoethylene glycol monomethyl ethers as well as synthesized oligoethylene glycol dimethyl ethers for *p*-*t*-butylbenzenediazonium tetrafluoroborate in 1,2-dichloroethane has been assessed[60]. Oligoethylene glycols with methylated end-groups offer no significant advantage over the corresponding unmethylated compounds. Polyethylene glycols 1000 and 1500 complex arenediazonium salts about 10% as efficiently as 18-crown-6. These findings raise the possibility of substituting inexpensive, commercially available polyethylene glycols for crown ethers as solubilizing and stabilizing agents for aryldiazonium salts.

VII. POLYETHERS AS PHASE-TRANSFER CATALYSTS FOR ARYLDIAZONIUM SALT REACTIONS IN SOLVENTS OF LOW POLARITY

Gokel and Cram[8] reported the first use of crown ethers as phase-transfer catalysts for aryldiazonium salt reactions in nonpolar organic solvents in 1973. Descriptions of several phase-transfer-catalysed reactions of a variety of aryldiazonium salts by cyclic and acyclic polyethers have now appeared and are summarized in this section.

These reactions are categorized according to the systemic nomenclature for substitution reactions proposed by Bunnett[62]. The name of the group (or atom) which is introduced is given first. This is followed by de- and the name of the leaving group. For example, an arenediazonium salt reaction in which N_2 is replaced by H is a protodediazoniation.

A. Proto- and Deuterio-dediazoniation

Using 10 mole % of dicyclohexano-18-crown-6 as a phase-transfer catalyst, Hartman and Biffar[63] have reported that benzenediazonium tetrafluoroborates with electron-withdrawing groups are readily reduced by powdered copper in dichloromethane. No reaction occurs in the presence of 15-crown-5 or in the absence of crown ether. From benzene- and *p*-toluene-diazonium tetrafluoroborates mixtures of proto- and fluorodediazoniation products are obtained.

Korzeniowski and Gokel[29] have noted a quantitative protodediazoniation of *p*-bromobenzenediazonium tetrafluoroborate when the diazonium salt is stirred with two equivalents of potassium acetate and 5 mole % of 18-crown-6 in chloroform for one hour at room temperature. Use of deuteriochloroform as the solvent gives 4-deuteriobromobenzene in quantitative yield. A mechanism in which aryl radicals (equation 6) abstract hydrogen atoms is proposed.

$$\begin{aligned} ArN_2^+\ BF_4^- + AcO^- &\longrightarrow Ar{-}N{=}N{-}OAc \\ Ar{-}N{=}N{-}OAc + AcO^- &\longrightarrow Ar{-}N{=}N{-}O^- + Ac_2O \\ Ar{-}N{=}N{-}O^- + ArN_2^+ &\longrightarrow (ArN{=}N)_2O \\ (ArN{=}N)_2O &\longrightarrow Ar{-}N{=}N{-}O\cdot + N_2 + Ar\cdot \end{aligned} \qquad (6)$$

B. Halodediazoniation

An alternative to the Sandmeyer reaction for the preparation of aryl bromides and iodides from aryldiazonium salts has been developed by Korzeniowski and Gokel[64]. The halodediazoniations are conducted by stirring a benzenediazonium salt with potassium acetate and a moderate excess of a halogen atom source (bromotrichloromethane, iodomethane or molecular iodine) in chloroform at room temperature in the

presence of a catalytic amount of 18-crown-6. Yields of aryl bromides and iodides are good-to-excellent from benzenediazonium tetrafluoroborates which possess either electron-donating or electron-withdrawing substituents in *meta* and *para* positions. When *ortho* substituents are present, lower aryl halide yields are obtained.

The bromodediazoniation reactions also produce significant amounts of hexachloroethane. Presumably this product arises by the coupling of trichloromethyl radicals which result when aryl radicals (equation 6) abstract bromine atoms from bromotrichloromethane.

Bartsch and Yang[65] have demonstrated that the substitution of polyethylene glycol 1000 for 18-crown-6 as the phase-transfer agent provides yields of halodediazoniation products which equal or surpass those obtained using the crown ether. Although a considerably higher concentration of polyethylene glycol 1000 must be employed, the very low cost of this acyclic polyether is an important compensating factor.

C. Aryldediazoniation

Good-to-excellent yields of a wide variety of mixed biaryls may be prepared by a phase-transfer catalytic Gomberg–Bachman reaction. Korzeniowski, Blum and Gokel[66] have employed 18-crown-6 as a phase-transfer catalyst for the reactions of *ortho*-, *meta*- and *para*-substituted benzenediazonium tetrafluoroborates with potas-

$$ArN_2^+ BF_4^- + KOAc + 18\text{-crown-6} \xrightarrow[\text{r.t. 1.5 h}]{C_6H_6} ArPh \quad 60-85\% \qquad (7)$$

sium acetate in benzene (equation 7). Intermediate aryl radicals (equation 6) attack the solvent to form the unsymmetrical biaryls. Extended reaction periods are required to obtain appreciable biaryl yields in the absence of crown ethers. With polyethylene glycol 1000 as the phase-transfer catalyst[65], somewhat lower biaryl yields are realized than with 18-crown-6.

Other aromatic or heteroaromatic compounds may be used in place of benzene[66]. Thus mixed biaryls are also obtained using mesitylene and thiophene as solvents.

D. Azocyanide Formation

Ahern and Gokel[67] have reported the facile synthesis of *trans*-arenediazocyanides by the phase-transfer-catalysed reactions of *meta*- and *para*-substituted benzenediazonium tetrafluoroborates with potassium cyanide in dichloromethane in the presence of 18-crown-6 (equation 8). The azocyanides serve as dieneophiles for the synthesis of novel heterocyclic compounds by Diels–Alder reactions.

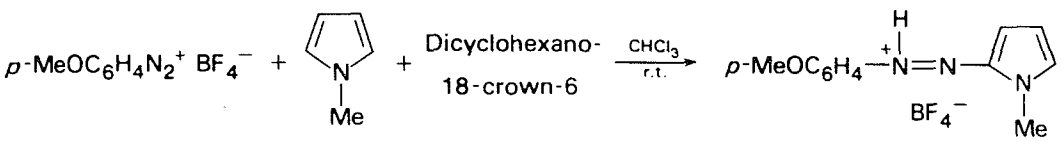
$$ArN_2^+ BF_4^- + KCN + 18\text{-crown-6} \xrightarrow[\text{r t 6 h}]{CH_2Cl_2} Ar{-}N{=}N{-}CN \quad 80-95\% \qquad (8)$$

Recent results by Bartsch and Yang[68] have demonstrated that polyethylene glycol 1000 may also be used as the phase-transfer catalyst for this reaction. The acyclic polyether appears to offer the special advantage that *ortho*-substituted benzenediazonium ions may also be converted into the corresponding *trans*-arenediazocyanides.

E. Azo Coupling

Phase-transfer catalysis of the azo coupling reaction of aryldiazonium salts by a crown ether was first reported by Gokel and Cram[8]. A quantitative yield of the azo coupling product is obtained from the reaction of *p*-chlorobenzenediazonium tetrafluoroborate with *N,N*-dimethylaniline in dichloromethane at −78°C in the presence of 18-crown-6. Attempts to form azoarene–crown ether rotaxanes by treating binaphtho-20-crown-6(5)-solubilized *p*-toluenediazonium tetrafluoroborate with several organometallic reagents have yielded only nonencircled, conventional azo coupling products.

Crown-ether-catalysed reactions of aryldiazonium salts with pyrroles in chloroform have been described by Shepherd[47]. Treating a chloroform solution of 1-methylpyrrole with solid *p*-methoxybenzenediazonium tetrafluoroborate at room temperature gives no apparent reaction due to the insolubility of the diazonium salt. However, after the addition of dicyclohexano-18-crown-6, complete reaction occurs within 15 minutes. The precipitated reaction product is not the anticipated azopyrrole, but the analytically pure tetrafluoroborate salt of the protonated azopyrrole (equation 9). The free azopyrrole is liberated by treatment of the tetrafluoroborate salt with



(9)

aqueous ammonia. Similar results are obtained when benzenediazonium tetrafluoroborate is the electrophile.

If the 2- and 5-positions of the pyrrole are blocked, electrophilic attack of the aryldiazonium ion occurs at the 3-position.

F. Nucleophilic Substitution *Para* to the Diazonium Group

Gokel, Korzeniowski and Blum[51] have reported stirring *p*-bromobenzenediazonium tetrafluoroborate with potassium chloride in chloroform in the presence of one equivalent of 18-crown-6 for 24 hours at 30°C. Following reduction of the diazonium group prior to analysis, a 55% yield of chlorobenzene is obtained. This result demonstrates a rather facile nucleophilic substitution on the activated aryl bromide.

VIII. CONCLUSIONS

The complexation of aryldiazonium salts by polyethers adds a new dimension to the chemistry of this important chemical species. As has been illustrated, substantial spectral and reactivity changes result when the diazonium group 'neck' of the aryldiazonium ion is inserted into the 'collar' of an appropriately sized crown ether. Several reactions which utilize polyethers as phase-transfer catalysts for aryldiazonium salt reactions in nonhydroxylic solvents of low polarity have also been described. Due to an uncommonly small 'macrocyclic effect' in the complexation of aryldiazonium ions by polyethers, inexpensive, environmentally safe, polyethylene glycols may often be substituted for crown ethers in these reactions.

For the future, it is anticipated that additional phase-transfer-catalysed reactions of aryldiazonium salts which utilize polyethers will be developed. Also, the stability enhancements observed for crown-ether-complexed aryldiazonium ions may find application in improving diagnostic reagents for clinical chemistry and for advances in

photoreproduction and polymerization processes. It also seems reasonable that stability enhancements similar to those noted for crown ether complexation of aryldiazonium ions may also be realized for less stable diazonium ion species, such as heteroaromatic, vinylic and perhaps even alkyldiazonium ions.

Hopefully, the summary provided in this chapter will serve as a catalyst for further developments in the chemistry of diazonium ions complexed by polyethers.

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CHAPTER 22

Poly(diacetylenes) and polyyne polymers containing transition-metal atoms in the main chain

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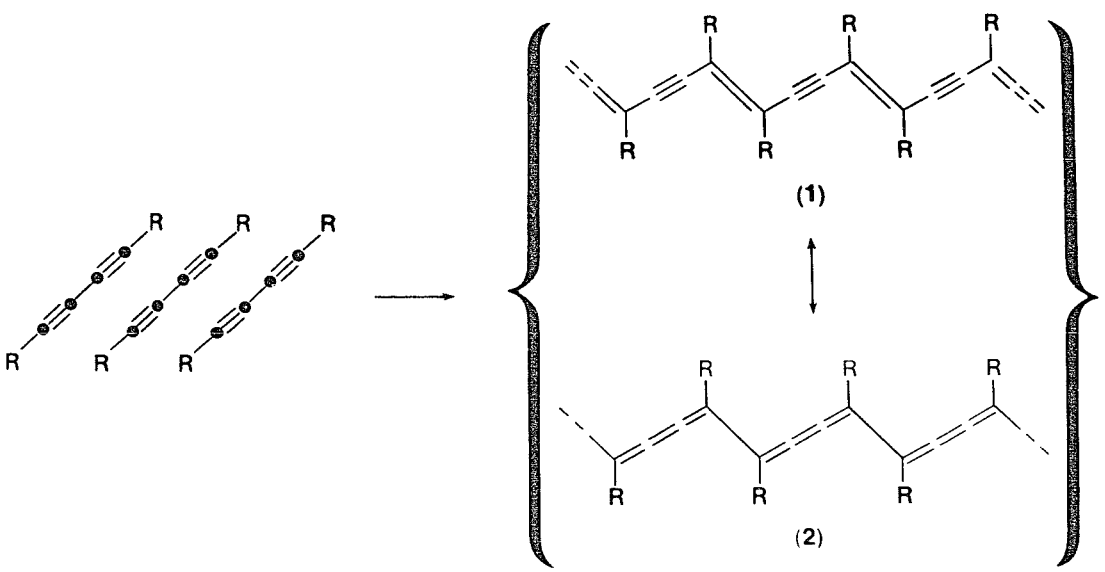
I. POLY(DIACETYLENES)

A. Introduction

The solid-state polymerization of conjugated diynes, first characterized by Wegner[1], has attracted widespread attention from both physicists and chemists. The reaction, illustrated in Scheme 1, involves successive 1,4-addition of neighbouring diyne units and yields a polymer with a conjugated backbone. Two contributing structures **1** and **2** can be drawn for the polymer backbone, but the acetylenic structure **1** appears to be the principal contributor, and a reasonably accurate representation of the true structure.

With only one known exception[2], those derivatives that show reactivity in the polymerization reaction have a monomer crystal structure in which the diyne 'rods' are stacked parallel to each other. During the polymerization successive diyne molecules tilt toward the stacking axis so that the terminal acetylenic carbons of adjacent



SCHEME 1

molecules move within bonding range. The four carbons of the diyne unit retain their linear arrangement in the polymer, and the major geometrical change that occurs during polymerization is a change in the bonding angle to the side-group.

Often the polymer and monomer form stable solid solutions over the entire conversion range, in which case it is possible to obtain large, essentially perfect, polymer crystals. It is also possible to prepare molecularly thin films of certain poly(diacetylenes) by solid-state polymerization of monomers in mono- or multi-layers[3].

The polymer chains, which may contain several thousand monomer units[4a,b], are arranged parallel to each other, thus providing polymer crystals with optical, electrical and mechanical properties in the chain direction which differ drastically from those measured in a direction perpendicular to the chain. Dramatic colour changes occur during the polymerization – from colourless, through red or blue at intermediate stages, and finally a deep reddish-gold, blue or green for the final polymer. The polymer crystals exhibit a distinct metallic lustre. The discovery of metallic conduction in doped poly(acetylene)[5] has stirred interest in the possibility of finding the same behaviour for the poly(diacetylenes), but to date only limited success has been realized[6].

Initiation of polymerization has been accomplished by heat, radiation (visible, ultraviolet, X-ray and gamma) and by subjecting monomer crystals to mechanical stress. Some monomers are polymerized by heat as well as by all of the forms of radiation, but more commonly a given monomer is sensitive to a limited number of modes of initiation. The same polymer is formed from a given monomer irrespective of the mode of initiation, although minor differences have been noted in some cases[7].

Diynes, both symmetrical and unsymmetrical, with a wide variety of substituent groups, have been found to be reactive. It is the substituent groups that determine the packing of the monomer molecules in the crystal, and this is the crucial factor in determining reactivity. Electronic interactions between substituent groups and the diyne function apparently play only a minor role. Spectacular differences in reactivity have been observed for different crystalline modifications of the same monomer[8–10].

Recently, it has been shown that some unreactive monomers will participate in copolymerization in mixed crystals containing the 'unreactive' monomer and a reactive diyne[11–13]. It has also been found that some unreactive diynes are activated by exposing the crystals to the vapour of certain organic solvents[2].

B. Monomer Crystal Packing Requirements

Determination of the crystal structure of monomers possessing moderate-to-high reactivity is hampered by the fact that polymerization is initiated by X-radiation. However, if the diffraction is carried out at low temperatures, the polymerization may be slow enough to permit structure determination. For example, the *p*-toluenesulphonate ester of 2,4-hexadiyne-1,6-diol(**3**) the most widely studied of all

$$p\text{-}MeC_6H_4SO_3CH_2C{\equiv}C{-}C{\equiv}CCH_2OSO_2C_6H_4Me\text{-}p$$

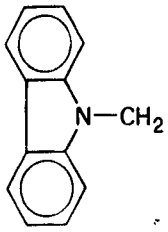
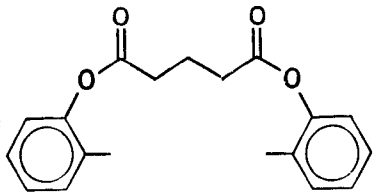
(3)

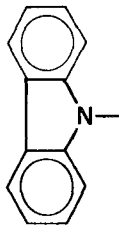
the diacetylene monomers, is polymerized rapidly by X-rays at room temperature, but at 120 K, the reaction is slow enough to allow the structure determination[14,15].

Data for a variety of monomer crystals are summarized in Table 1. Structures of the side-groups are given in the second column; with the exception of the last compound (entry 14) the diynes have symmetrical structures. The significance of the intermolecular distances and angles given in columns 3–6 can be seen in Scheme 2. The polymer chains form in the direction of the stacking axis, *S*, and the angle between this axis and

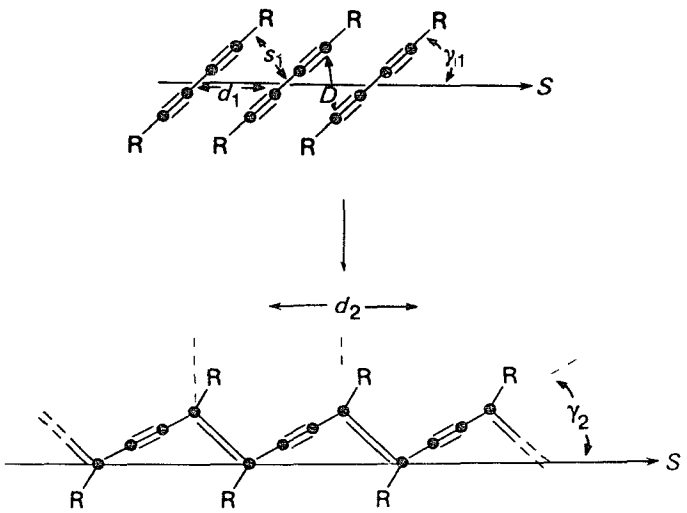
TABLE 1. Intermolecular distances and angles in diacetylene crystals

$R^1C{\equiv}C{-}C{\equiv}C{-}R^2$

Entry	R^1, R^2	d_1 (Å)[a]	γ_1 (deg.)[a]	s_1 (Å)[a]	D^*(Å)[a]	Reactivity[b]	References
	$R^1 = R^2$						
1	p-$MeC_6H_4SO_3CH_2$	5.11	45	3.61	3.62	+	14, 15
2	$HOCH_2$	5.34	41	3.50	3.51	+	16, 17, 18
3	$HOCH_2CH_2$	4.85	48	3.60	3.65	+	19
4	$PhNHCO_2(CH_2)_4$	5.23	42	3.50	3.52	+	20, 21
5		4.55	60	3.94	4.22	+	22, 23
6	$PhCO_2CH_2$[c]	4.35 8.48	59 40	3.73 5.45	4.03 6.10	+[d] −	24
7	R^1R^2 = 	4.93 5.42	46 90	3.55 5.42	3.58 5.42	+ −	25

8	p-$MeOC_6H_4SO_3CH_2$	5.80	62	5.12	5.23	–[e]	26
9	p-$ClC_6H_4SO_3CH_2$	5.03	67	4.63	4.96	–[e]	27
10	2-$C_{10}H_7SO_3CH_2$	5.42	62	4.79	4.94	–	28
11	$PhOCH_2$[c]	8.53	77	8.31	8.51	–	29
		7.47	73	7.14	7.31	–	
12	Ph	6.04	51	4.69	4.69	–	16, 30
13		4.66	90	4.66	5.98	–	31
14	R^1 = Me, R^2 = CH_2OH	4.87	49	3.68	3.72	+	32

[a] See Scheme 2.
[b] + and – signify that polymerization has or has not been observed, respectively. No attempt has been made to classify in terms of rate or extent of polymerization although semiquantitative data are given in some of the references cited.
[c] Two crystalline forms.
[d] Polymerizes under pressure.
[e] A second reactive modification of unknown structure has been reported recently. See References 33 and 34.



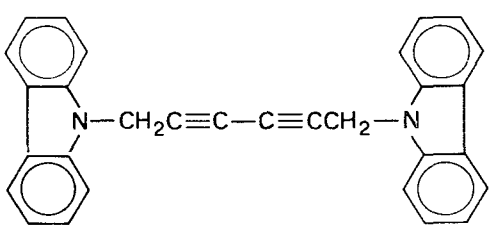
SCHEME 2

the diyne rods is γ_1. The separation of the diyne units in the direction of S is d_1, while the perpendicular distance, $d_1 \sin \gamma_1$, is designated s_1. The distance between the carbons that become bonded during polymerization is D. In the polymer the repeat distance, d_2, is 4.9 ± 0.1 Å and γ_2, the angle made by the backbone carbons with the chain direction, is ca. 12–13°.

Optimum and limiting values for the monomer parameters have been specified by Baughman[17] and by Wegner[35]. For significant reactivity, it is specified that s should be in the range 3.4–4.0 Å and γ_1 should be ca. 45°[35]. Examination of Table 1 shows that the reactive diynes satisfy these requirements for the most part. The largest deviations are found for the benzoate **4** (entry 6) and 1,6-bis(9-carbazolyl)-2,4-hexadiyne (**5**, entry 5) where γ_1 is 59° and 60°, respectively. The latter compound does show very

$PhCO_2CH_2C{\equiv}C{-}C{\equiv}CCH_2OCOPh$

(4)



(5)

low reactivity, the rate of polymerization being low enough to permit X-ray structure determination of the monomer crystal at room temperature[22,23]. Polymerization of **4** occurs only when the pressure is applied to the crystal, and this may distort the lattice to one with more favourable parameters[17].

The distance D is determined by both d_1 and γ_1 and probably is the most significant of the three parameters. The upper limit quoted for D is 5 Å[17], but the value for **5**, 4.22 Å, is the largest value that has been found for a diyne which still shows measurable activity. In view of the very low reactivity of this compound, it seems likely that the upper limit for D is not substantially greater than 4.3 Å.

For the cases where structures have been determined for two crystalline modifica-

tions of the same compound, entries **6** and **7**, values of s_1 and D for the unreactive forms fall outside the designated limits.

In contrast to the tosylate **3**, which exhibits high reactivity, esters **6**, **7** and **8** (entries

$$ArSO_2OCH_2C{\equiv}C{-}C{\equiv}CCH_2OSO_2Ar$$

(**6**) Ar = *p*-$MeOC_6H_4$
(**7**) Ar = *p*-ClC_6H_4
(**8**) Ar = 2-$C_{10}H_7$

8, 9 and 10) are unreactive in their common crystalline forms, although reactive modifications of **6** and **7** have been reported recently[33,34]. For the unreactive modifications of **6**, **7** and **8** the crystal structures show that the side-groups are arranged in conformations such that interference between side-groups on neighbouring molecules prevents the diyne units from moving into favourable bonding orientations[26–28]. Mixed crystals of **7** with the tosylate **3** can be prepared which contain up to 20% **7**, and which can be polymerized to 100% conversion[12]. The *p*-chlorobenzenesulphonate **7** enters the polymer in the same proportion as is present in the monomer crystal.

One case is known of a reactive diacetylene in which neighbouring diyne units are not parallel; this is the bis(*m*-tolylcarbamate) of 2,4-hexadiyne-1,6-diol (**9**)[2]. In one of

$$m\text{-}MeC_6H_4NHCO_2CH_2C{\equiv}C{-}C{\equiv}CCH_2OCONHC_6H_4Me\text{-}m$$

(**9**)

the crystalline phases of this compound the diyne axes of adjacent molecules are *crossed* at an angle of 72°, yet it polymerizes, albeit partially, under the influence of X-radiation! However, distances as short as 3.607 Å are found between terminal acetylenic carbons of neighbouring molecules. This distance, which corresponds to the D parameter for crystals with parallel diyne units, is well within the range for bond formation.

C. Molecular Structure of Monomers

The polymerization of a large number of diacetylenes with a variety of attached functional groups has been studied, and the results are summarized in Table 2. An attempt has been made to group together similar types of molecules in the different parts, (a)–(r), of the table. In the reactivity column, + and − simply signify that detectable polymerization has or has not been observed. In many of the reports the polymer itself was not characterized, but the development of a deep red or blue colour upon heating or irradiation is sufficient evidence for the occurrence of the type of polymerization under consideration in this chapter. No attempt has been made to compare relative rates of polymerization or final polymer conversions for the various monomers. Numerous papers have appeared for some of the compounds, and the references in the table are not meant to be complete, but merely serve to locate leading sources.

For the most part, the synthetic methods used for the monomers are standard, straightforward procedures and are generally obvious. Consequently, discussions of synthetic methods are not included in the pages that follow, except where unusual methods have been used.

Simple alkadiynes with unbranched side-groups undergo solid-state polymerization, as can be seen in part (a) of Table 2. The compounds are particularly sensitive to

TABLE 2. Alkadiynes and derivatives which have been studied in solid-state polymerizations

(a) Alkadiynes, $RC{\equiv}C{-}C{\equiv}C{-}R$

R	Reactivity	References
Me	+	17
n-$C_{10}H_{21}$	+	36
n-$C_{12}H_{25}$	+	37, 38
n-$C_{13}H_{27}$	+	37, 38
$PhCH_2$	−	1
9-$AnCH_2$[a]	−	25, 34

(b) Alkadiynols and derivatives, $R^1C{\equiv}C{-}C{\equiv}CR^2$

R^1	R^2	Reactivity	References
Me	CH_2OH	+	10, 32, 39
Me	$CH_2OCONHPh$	+	39, 40
Me	$CH_2OCONHEt$	+	39
Me	$CH_2CH(Et)OCONHPh$	+	39
n-$C_{10}H_{21}$	$(CH_2)_9OH$	+	34
n-$C_{12}H_{25}$	CH_2OH	+	38
$HC{\equiv}C(CH_2)_2$	CH_2OCOPh	+	41
$HC{\equiv}C(CH_2)_2$	$CH_2OCONHMe$	+	41
$HC{\equiv}C(CH_2)_2$	CH_2OTs	+	41

(c) Alkadiynediols, $RCH(OH)(CH_2)_nC{\equiv}C{-}C{\equiv}C(CH_2)_nCH(OH)R$

R	n	Reactivity	References
H	0	+	16, 42, 43
Me	0	+	39, 44
H	1	+	19, 39, 45

(d) Carboxylate esters of 2,4-hexadiyne-1,6-diol, $RCO_2CH_2C{\equiv}C{-}C{\equiv}CCH_2OCOR$

R	Reactivity	References
n-C_5H_{11}	−	45, 46
n-C_7H_{15}	+	46
n-C_9H_{19}	+	46
n-$C_{11}H_{23}$	+	46
n-$C_{13}H_{27}$	+	46
n-$C_{15}H_{31}$	+	46
n-$C_{17}H_{35}$	+	46
Ph	+[b]	1, 24
PhO	−	1
o-$(HO_2C)C_6H_4$	+	1

TABLE 2. *continued*

(e) Sulphonate esters of alkadiynediols, $RSO_3(CH_2)_nC{\equiv}C{-}C{\equiv}C{-}(CH_2)_nOSO_2R$

R	*n*	Reactivity	References
Ph	1	+	33
p-MeC_6H_4	1	+	47[c]
p-FC_6H_4	1	+	48, 49
p-ClC_6H_4	1	+[d]	27, 34, 50
p-BrC_6H_4	1	+[d]	13, 33, 50
p-$MeOC_6H_4$	1	+[d]	26, 33
m-$CF_3C_6H_4$	1	+	49
2-$C_{10}H_7$	1	−[e]	28
Me	3	+	51

(f) Symmetrical urethane derivatives of alkadiynediols,

$RNHCO_2(CH_2)_nC{\equiv}C{-}C{\equiv}C(CH_2)_nOCONHR$

R	*n*	Reactivity	References
Et	1	+	39
n-Bu	1	+	1
n-C_6H_{13}	1	+	39, 52
n-C_8H_{17}	1	+	39
n-$C_{12}H_{25}$	1	+	39
cyclo-C_6H_{11}	1	+	1
Ph	1	+	1, 39
p-MeC_6H_4	1	+	1
m-MeC_6H_4	1	+	2
o-ClC_6H_4	1	+	2
m-ClC_6H_4	1	+	1
p-ClC_6H_4	1	+	1, 2
o-$MeOC_6H_4$	1	+	2
3-Thienyl	1	+	34
Me	2	+	39
Et	2	+	39
Ph	2	+	39, 44
1-$C_{10}H_7$	2	+	39
Et	3	+	39
Ph	3	+	39, 51, 53a
$EtOCOCH_2$	3	+	54, 55, 56, 57
$BuOCOCH_2$	3	+	54, 55, 56, 57
Me	4	+	58
Et	4	+	59
i-Pr	4	+	60
n-C_6H_{13}	4	+	61
$EtOCOCH_2$	4	+	54, 55, 56, 57
$BuOCOCH_2$	4	+	54, 55, 56, 57
Ph	4	+	34, 53a

(g) Unsymmetrical urethane derivatives of 2,4-hexadiyne-1,6-diol,

$R^1NHCO_2CH_2C{\equiv}C{-}C{\equiv}CCH_2OR^2$

R^1	R^2	Reactivity	References
Ph	H	+	40
Ph	MeNHCO	+	39, 40

TABLE 2. *continued*

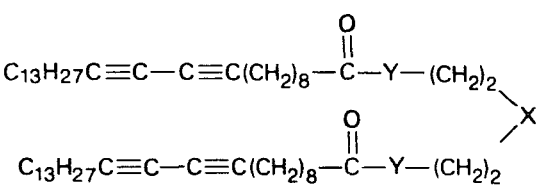
(h) Alkadiynoic acids, $RC{\equiv}C{-}C{\equiv}C(CH_2)_nCO_2H$[f]

R	*n*	Reactivity	References
n-$C_{12}H_{25}$	0	+	34, 62
n-$C_{16}H_{33}$	0	+	34
n-$C_{12}H_{25}$	3	+	34
Et	8	+	6
n-C_5H_{11}	8	+	63, 64a
n-C_6H_{13}	8	+	63
n-C_8H_{17}	8	+	63
n-C_9H_{19}	8	+	34, 64a
n-$C_{10}H_{21}$	8	+	34, 63, 64a
n-$C_{12}H_{25}$	8	+	34, 63, 65, 66
n-$C_{14}H_{29}$	8	+	34, 63
n-$C_{16}H_{33}$	8	+	63

(i) Amide derivatives of alkadiynoic acids, $R^1C{\equiv}C{-}C{\equiv}C(CH_2)_8CONHR^2$

R^1	R^2	Reactivity	References
n-$C_{12}H_{25}$	$PhCH(CH_3)$[g]	+	67
$2,4(NO_2)_2C_6H_3OCH_2$	$PhCH(CH_3)$[g]	+	67

(j) Ester and amide derivatives of 10,12-hexacosadiynoic acid,



Y	X	Reactivity	References
O	O	+	64a
O	NMe	+	64a
NH	O	+	64a
O	$\overset{+}{N}Me_2Br^-$	+	68

(k) Alkadiynedioic acids and their salts, $MO_2C(CH_2)_nC{\equiv}C{-}C{\equiv}C(CH_2)_nCO_2M$

n	M	Reactivity	References
5	K	+	69
8	H	+	10
8	Ba/2	+	10

TABLE 2. *continued*

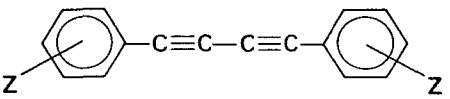
(l) Ester and amide derivatives of alkadiynedioic acids, $ZCO(CH_2)_nC{\equiv}C{-}C{\equiv}C(CH_2)_nCOX$

Z	*n*	X	Reactivity	References
MeO	5	OH	+	69
MeO	5	MeO	+	69
MeO	8	OK	+	69
MeO	8	OH	+	51, 70, 71
MeO	8	OMe	+	69
neo-$C_5H_{11}O$	8	=Z	+	69
cyclo-$C_6H_{11}O$	8	=Z	+	69
cyclo-$C_6H_{11}O$	8	OH	+	69
$PhCH_2O$	8	=Z	+	69
$PhCH_2O$	8	OH	+	69
$HOCH_2CH_2O$	8	OMe	+	72
p-AcC_6H_4O	8	OMe	+	73
p-BzC_6H_4O	8	OMe	+	73
p-BzC_6H_4O	8	=Z	+	73
p-$BrC_6H_4COCH_2O$	8	=Z	+	73
p-$(PhCH{=}CHCO)C_6H_4O$	8	OMe	+	73
p-$(PhCOCH{=}CH)C_6H_4O$	8	OMe	+	73
o-BzC_6H_4NH	8	OMe	+	73
p-BzC_6H_4NH	8	OMe	+	73
$HOCH_2CH_2NH$	8	OMe	+	73
$MeOCH_2CH_2NH$	8	=Z	+	74
n-$C_6H_{13}\dot{N}H_3\bar{O}$	8	NHC_6H_{13}	+	75
$PhCH(CH_3)NH^g$	8	=Z	+	67
n-$C_6H_{13}NH$	8	OH	+	73
MeO	9	OMe	+	36, 69
MeO	9	OH	+	69
EtO	9	OEt	+	69
EtO	9	OH	+	69

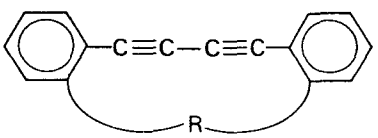
(m) Miscellaneous derivatives, $R^1C{\equiv}C{-}C{\equiv}CR^2$

R^1	R^2	Reactivity	References
$PhOCH_2$	$=R^1$	−	29
2,4-$(NO_2)_2C_6H_4OCH_2$	$=R^1$	+	76
$PhNHCO_2CHMe$	$=R^1$	$+^b$	44
$PhNHCO_2CMe_2$	$=R^1$	−	10
$MeC{\equiv}C{-}C{\equiv}CHg$	Me	+	77
Carbaz^h	$=R^1$	−	51
Carbaz$-CH_2{}^h$	$=R^1$	+	22, 34, 78, 79
Carbaz$-(CH_2)_3{}^h$	$=R^1$	+	80
Carbaz$-CH_2{}^h$	*n*-$C_{12}H_{25}$	+	80
3-BrCarbaz$-CH_2{}^i$	$=R^1$	+	80
n-$C_{13}H_{27}$	$(CH_2)_9OPO(CH_2)_2\dot{N}H_3$ (O, O^-)	+	68
MeCH(OTs)	$=R^1$	−	41

TABLE 2. *continued*

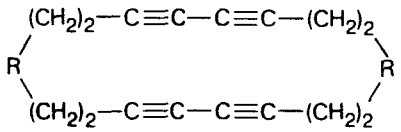
(n) Diarylbutadiynes, 

Z	Reactivity	References
H	−	16, 81
o-NO_2	+	81
m-NO_2	+	81
p-NO_2	−	81, 82
o-NH_2	−	81
m-NH_2	−	81
p-NH_2	−	81
o-AcNH	+	81
m-AcNH	+	81
p-AcNH	−	81
o-BzNH	+	81
m-BzNH	+	81
p-BzNH	−	81
o-PhNHCONH	+	81
m-PhNHCONH	+	81
p-PhNHCONH	−	81

(o) Cyclic diarylbutadiynes, 

—R—	Reactivity	References
$-OCH_2-C\equiv C-CH_2O-$	+	83
$-O(CH_2)_3O-$	+	83
$-O(CH_2)_4O-$	−	83
$-O(CH_2)_5O-$	−	83
$-O(CH_2)_6O-$	−	83
$-OCH_2CH=CHCH_2O-$ (*cis*)	+	83
$-OCH_2CH=CHCH_2O-$ (*trans*)	+	83
$-OCH_2(o\text{-}C_6H_4)CH_2O-$	+	83
$-OCO(CH_2)_3COO-$	+	25, 84, 85
$-OCO(CH_2)_4COO-$	−	85
$-OCO(CH_2)_5COO-$	−	85
$-OCO(CH_2)_6COO-$	−	85

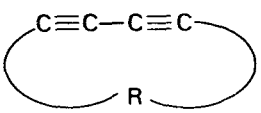
TABLE 2. *continued*

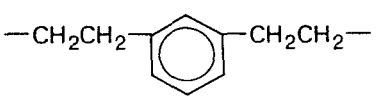
(p) Miscellaneous cyclic polyacetylenes, 

—R—	Reactivity	References
o-C_6H_4	–	86
m-C_6H_4	–	86
p-C_6H_4	–	86

$[-(CH_2)C{\equiv}C-C{\equiv}C-(CH_2)_2-]_n$

n	Reactivity	References
2	–	87
3	–	87
4	+	87–89



R	Reactivity	References
	+	86

(q) Alkatriynediols, alkatetraynediols and derivatives, $ROCH_2(C{\equiv}C)_nCH_2OR$

R	*n*	Reactivity	References
H	3	+	90
Bz	3	+	90
Ts	3	+	90
BuNHCO	3	+	90
PhNHCO	3	+	90
EtNHCO	4	+	40

TABLE 2. *continued*

(r) Miscellaneous alkapolyynediols and derivatives, $ROCH_2(C{\equiv}C)_2[CH_2CH_2(C{\equiv})_2]_nCH_2OR$

R	*n*	Reactivity	References
Bz	1	+	41
MeNHCO	1	+	41
Ts	1	+	41
Bz	2	+	41
MeNHCO	2	+	41
PhNHCO	2	+	41
Ts	2	+	41

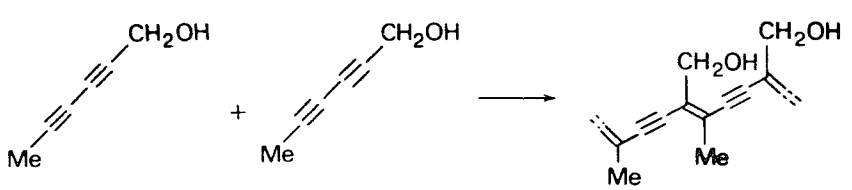
[a] 9-$AnCH_2$ = 9-Anthrylmethyl.
[b] Polymerizes under pressure.
[c] Numerous references, see text.
[d] The common crystalline form fails to polymerize, but a reactive crystalline form has been reported.
[e] Mixed crystals with the tosylate do polymerize[7].
[f] Salts of the acids, particularly cadmium salts, are often used instead of the free acids.
[g] *R* configuration.
[h] Carbaz = 9-carbazolyl.
[i] 3-BrCarbaz = 3-bromo-9-carbazolyl.

ultraviolet light[36]. The polymer from 2,4-hexadiyne is highly amorphous, presumably because the monomer molecules are arranged in the crystal so that polymer chain growth can occur in more than one direction[17]. Symmetrical diynes with an even number of carbons in the side-chains are more reactive than those with an odd number[37]. Highly branched side-chains as in **10** prevent close approach of neighbouring diyne units, and this compound as well as related, highly branched compounds fail to polymerize.

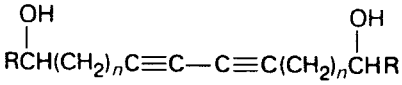
t-BuC≡C—C≡C Bu-*t*

(10)

Simple alkadiynols and their derivatives are summarized in part (b). The distances and angles in the 2,4-hexadiyn-1-ol crystal (Table 1, entry 14) are close to the values for optimum reactivity, and polymerization does occur readily on exposure to light or under pressure[32]. The monomer units are stacked in a fashion that leads to head-to-tail polymerization as shown in Scheme 3. When polymerization reaches ca. 30%, cracks begin to appear in the crystal and soon after this occurs the reaction ceases. The strain that develops in the polymer and causes fracturing is attributed to hydrogen bonding between neighbouring hydroxymethyl side-groups which leads to asymmetric intermolecular forces[32].



SCHEME 3



(**11**) R = H, $n = 0$
(**12**) R = H, $n = 1$
(**13**) R = Me, $n = 0$

Alkadiynediols are listed in part (c). The simplest member, 2,4-hexadiyne-1,6-diol (**11**) polymerizes at 90–100°C[42]. The polymer formed in the initial stages has the red colour typical of long-chain poly(diacetylenes) but after ca. 40 h the colour shifts to light brown and then slowly darkens. It was suggested originally that the change in colour was caused by a drastic reduction in polymer chain length in the later stages of the reaction, but it seems more likely that conformational changes of the type discussed in Section I.F.3.a are involved. These changes lead to a decrease in effective conjugation length without changing the overall length of the polymer chain.

The next homologue, **12**, is polymerized by ultraviolet or γ-radiation or by thermal annealing, without phase separation[91], and it has been proposed that the longer side-chains in **12** provide sufficient freedom for reorientation of the diyne units without disrupting the hydrogen bonds between side-chains[19].

3,5-Octadiyne-2,7-diol (**13**) fails to polymerize thermally at atmospheric pressure and temperatures up to 100°C, but it does polymerize at room temperature under 30 kbar pressure[44].

Carboxylate esters of 2,4-hexadiyne-1,6-diol are contained in part (d) of Table 2. The relative reactivities of a series of fatty acid esters, **14a–g**, have been measured and the results are presented in Scheme 4[46]. Thermal polymerization of these compounds

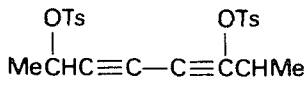
	n	% Polymerization[a]		n	% Polymerization[a]
14a	5	0	**14e**	13	20
14b	7	1	**14f**	15	17
14c	9	32	**14g**	17	6
14d	11	26			

[a]% Polymer after UV irradiation for 30 min.

SCHEME 4

is very slow, measurable conversions occurring only for the caprate, **14c**, and laurate, **14d**, and even with these the conversion to polymer amounts to only 1–2% for samples which had been heated for several days at temperatures just below the melting point. Polymerization by ultraviolet light is faster, and the extent of conversion after 30 min is summarized in Scheme 4. Although the caproate ester, **14a**, is inert, the remaining homologues show activity which reaches a maximum with the caprate ester, **14c**. Evaluation of reactivity in photopolymerization of diacetylenes is difficult because initial polymer formation occurs on the surface of the monomer crystal, and the polymer, which has a very high absorption coefficient in the ultraviolet region, acts as a filter, preventing penetration of radiation beyond 10^{-4} to 10^{-5} cm.

Sulphonate esters of alkadiynediols, Table 2, part (e), have been studied extensively. To date it has not been possible to grow reactive crystals of the 2-napthalenesulphonate, **8**, of 2,4-hexadiyne-1,6-diol or the tosylate of 3,5-octadiyne-2,7-diol, **15**, but mixed crystals of the former with **3** do undergo copolymerization[11,13].



(15)

(16) Ar = *p*-BrC_6H_4
(17) Ar = *p*-FC_6H_4

The *p*-bromobenzenesulphonate, **16**, exhibits behaviour similar to that mentioned in Section I.B for the *p*-chloro and *p*-methoxy analogues, i.e. the crystalline form that is obtained by customary recrystallization procedures is unreactive, but by crystallization from highly supersaturated solutions. crystals of a metastable reactive modification can be obtained[13]. Unfortunately, the conditions required to produce the active modification lead only to the formation of microcrystals.

One of the reasons for the large amount of work devoted to tosylate **3** is that it is relatively easy to obtain large, essentially perfect monomer crystals of high purity, and these can be converted quantitatively to polymer single crystals of comparable perfection and purity[47]. Single crystals more than 15cm long and weighing more than 10 g have been described[40]. The monomer is very sensitive to heat and light, and unless special precautions are taken a small amount of polymerization may occur during purification of the monomer, as evidenced by the development of a pink or red colour in the crystals. Procedures have been described for obtaining highly purified monomer[92]. Polymerization occurs slowly at room temperature, requiring ca. 2 months to reach completion, and has even been noted at temperatures as low as − 20°C[93]. The reaction is much faster at elevated temperatures, for example, requiring 2 hours at 90°C for completion[94]. Thermal polymerization is best carried out in the range 50–80°C; at temperatures much above 80°C, slow decomposition begins to occur. A comparison of the thermal, UV and γ-ray polymerization processes has been reported[7].

The *p*-fluorobenzenesulphonate of 2,4-hexadiyne-1,6-diol, **17**, shows behaviour comparable to the tosylate **3** although the thermal polymerization is approximately an order of magnitude slower[48,49].

Extensive studies have been carried out with various carbamate (urethane) derivatives of alkadiynediols, and representative monomers are presented in Table 2, part (f). The phenylcarbamate of 2,4-hexadiyne-1,6-diol (**18**) exists in four crystalline modifications, the most active of which is obtained by recrystallization from *p*-dioxane–water[1,8–10,95]. It contains one-half molecule of *p*-dioxane per monomer unit and polymerization, which can be accomplished with heat, ultraviolet or γ-radiation, yields a single polymer crystal in which the *p*-dioxane in incorporated at lattice sites where it forms N—H···O hydrogen bonds with two urethane groups[96].

$$RNHCO_2CH_2C{\equiv}C{-}C{\equiv}CCH_2OCONHR$$

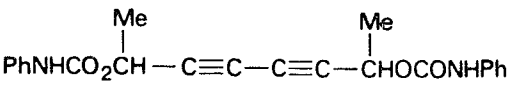
(9) R = *m*-MeC_6H_4
(18) R = Ph
(19) R = *o*-ClC_6H_4
(20) R = *o*-$MeOC_6H_4$
(21) R = *p*-ClC_6H_4

A dramatic effect is produced by the incorporation of *p*-dioxane in the *m*-tolylcarbamate (**9**) crystal[2]. Crystallization of the compound from acetone–hexane gives a moderately active 'orange' phase, while recrystallization from *p*-dioxane-water

produces a highly reactive 'blue' phase which contains one-half molecule of *p*-dioxane per monomer unit. These colours are not the true colours of the monomers, but are caused by the presence of small amounts of polymer which form during the crystallization process. The orange phase polymerizes in the presence of γ-radiation, reaching a limiting conversion of ca. 35%, whereas the blue phase polymerizes quantitatively. The orange phase is the one described previously. (Section I.B) in which adjacent diyne units are not parallel to each other in the crystal.

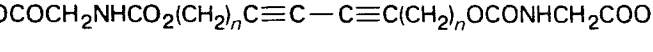
Interestingly, when crystals of the orange phase are exposed to *p*-dioxane vapour they incorporate *p*-dioxane and are converted to the blue phase. The effect of organic solvent vapours on several other inactive urethane derivatives has been studied[2]. Activation by *p*-dioxane vapour has been found for **18**, **19** and **20**, and by dimethylformamide vapour for **21**.

The phenylcarbamate of 3,5-octadiyne-2,7-diol (**22**) does not polymerize thermally at atmospheric pressure but does polymerize sluggishly at 230–270°C under 35 kbar pressure[44].



(22)

The alkoxycarbonylmethylcarbamates, **23a–d**, show negligible thermal reactivity but are readily polymerized by γ-radiation[56]. Monomer crystals frequently have a blue

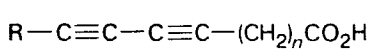


	Z	*n*		Z	*n*
23a	Et	3	**23e**	H	3
23b	Et	4	**23f**	H	4
23c	Bu	3	**23g**	K	3
23d	Bu	4	**23h**	K	4

colour indicating the presence of a small amount of polymer, presumably formed by thermal initiation at crystal defects or impurity sites. The polymers derived from these carbamates have proved to be exceedingly interesting because they are soluble in common organic solvents and undergo unusual visual conformational changes in the solid phase as well as in solution[54,55]. The polymers derived from the free acids, **23e** and **23f**, and their potassium salts, **23g** and **23h**, are soluble in water and these solutions exhibit the visual conformational changes upon variation of pH or ionic strength[97,98]. The properties of these polymers are considered in detail in Section I.F.3.a.

The unsymmetrical urethane derivatives given in Table 2, part (g), have been shown by X-ray diffraction studies to undergo head-to-tail polymerization[40].

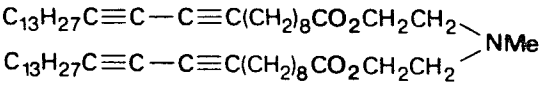
Alkadiynoic acids, **24**, given in Table 2, part (h), undergo photopolymerization in crystals, but their most interesting property is the ability to be photopolymerized in ultra-thin mono- and multi-layer structures[3,63,66,99,100,101a–d]. The acids or their salts can be spread as monolayers on the surface of water and polymerized to give extremely rigid, oriented polymer monolayers[101a]. These monolayers have significant absorption



(24)

in the visible region and can be seen as reddish-orange films on the water surface. Alternatively, monomer multilayers of known thickness can be constructed by successively dipping and withdrawing a quartz plate into and from the monolayer on the water surface, i.e. the Langmuir–Blodgett technique. As a rule of thumb, acids with 20 or more carbons and melting point above 45°C form surface states that are stable enough for multilayer formation by the Langmuir–Blodgett technique[66]. Polymerization of the multilayer structure occurs rapidly without disruption of the layer structure upon exposure to ultraviolet light. The polymer films are of considerable interest because of their potential as models for biological membranes with defined hydrophobic and hydrophilic surfaces[63].

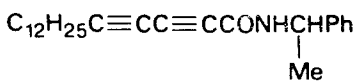
The ester and amide derivatives of 10,12-hexacosadiynoic acid listed in Table 2, part (j), which serve as phospholipid analogues, can also be spread as monolayers and polymerized[64a,b 68]. Furthermore, sonication of aqueous suspensions of **25**, or the lysolipid-type molecule **26** produces spherical multilayered liposomes which undergo photopolymerization without detectable structural change[64a,b,68].



(25)

(26)

The amides listed in Table 2, part (i), prepared from optically active *R*(+)-1-phenylethylamine by standard methods, show extreme sensitivity to ultraviolet and X-radiation, and form chiral poly(diacetylenes)[67]. Amide **27** is thermally stable but shows exceptional sensitivity to long wavelength radiation. It has photographic and lithographic applications important to microelectronic and optical device fabrication[67].



(+)−(**27**)

Examples of alkadiynedioic acids and their derivatives are given in Table 2, parts (k) and (l). Much of the information on the polymerization of these compounds is contained in the patent literature. The principal applications of the compounds are based on radiation-induced polymerization. 10,12-Docosadiynedioic acid (**28a**) and its derivatives have been investigated extensively. Applications as photosensitive materials in photographic and photocopying formulations have been described for the monomethyl ester **28b**[72,73,102,103], for the dimethyl ester **28c**[36,69,104], for the mixed amide salt **28d**[75] and the substituted diamide **28e**[74]. Additionally, **28b** can be used as a

$$ZCO(CH_2)_8C{\equiv}CC{\equiv}C(CH_2)_8COY$$

	Z	Y
28a	HO	OH
28b	MeO	OH
28c	MeO	OMe
28d	$C_6H_{13}NH$	$O^-NH_3C_6H_{13}$
28e	$MeOCH_2CH_2NH$	=Z

neutron radiographic material[61], X-ray radiographic material[70] and electrophotographic element[51,71,105–107].

Among the ethers related to 2,4-hexadiyne-1,6-diol, Table 2, part (m), the diphenyl ether **29a** exists in two crystalline forms neither of which has the proper packing for solid state polymerization[29] (See Table 1, entry 11). Interestingly, the bis(2,4-dinitrophenyl) ether **29b** polymerizes at 130°C giving lustrous green crystals[76]. The

$$ArOCH_2C{\equiv}C{-}C{\equiv}CCH_2OAr$$

(29)

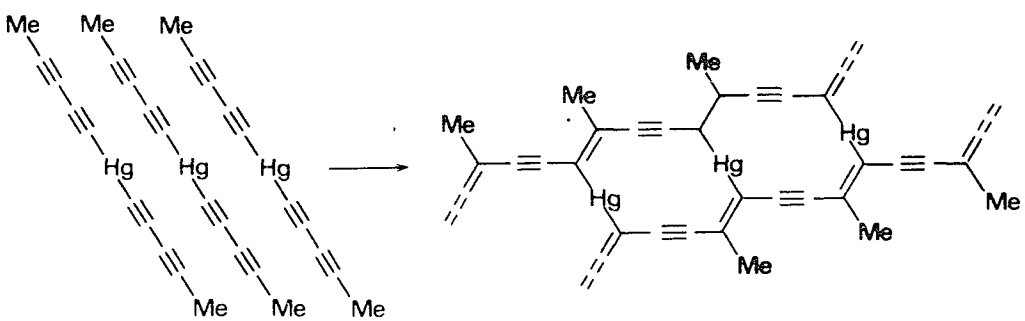
(a) Ar = Ph

(b) Ar = 2,4-$(O_2N)_2C_6H_3$

monomer undergoes an apparent ferroelectric transition at 31 K, but this anomalous behaviour is not exhibited by the polymer.

1,6-Bis(9-carbazolyl)-2,4-hexadiyne (**5**) can be polymerized quantitatively by heating at 110–240°C, or by γ-radiation to give a gold-coloured polymer with metallic lustre[78,79]. The reactivity in photopolymerization is very low, the rate being slower than that of the tosylate **3** by a factor of 10^{-4} [78]. Long-lived luminescence is observed in the monomer crystal of **5**, and it has been shown that the phosphorescing centres are the carbazolyl groups which act as traps for the excitation energy[23,108]. Measurement of the fine-structure parameters by optically detected magnetic resonance indicates that the triplet wave function is essentially localized on the carbazolyl groups, with very little delocalization to the π system of the diyne unit[108]. The low photoreactivity, then, is in part attributable to inefficient transfer of excitation energy from the carbazolyl ring, where it is initially absorbed, to the diyne system.

Bis(1,3-pentadiynyl)mercury is polymerized by ultraviolet radiation or by heating at 100–200°C to give an unusual polymer in which it is believed that adjacent polymer chains are joined through mercury atoms as shown in Scheme 5[77].



SCHEME 5

The behaviour of diarylbutadiynes was reported several years ago by Wegner[81], but relatively little has been published since then. Crystal-structure determinations for the diphenyl (**30a**)[16,30] and bis(*p*-nitrophenyl) (**30b**)[82] derivatives show that the packing arrangements in both cases are not suitable for polymerization. Examination of Table 2, part (n), reveals the interesting fact that the *para*-substituted derivatives are inactive for all cases studied, but excepting the amino-substituted derivative, the *ortho*- and *meta*-substituted derivatives do exhibit solid-state reactivity[81]. In fact, Wegner described the *o*- and *m*-acetamido derivatives, **30c** and **30d**, as being among the most reactive diynes he had encountered at that time.

$$ArC{\equiv}C-C{\equiv}CAr$$

(30)

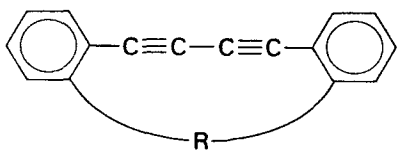
(a) Ar = Ph

(b) Ar = $(O_2N)C_6H_4$

(c) Ar = *o*-AcNH

(d) Ar = *m*-AcNH

Several diarylbutadiynes containing bridging groups between the *ortho* positions of the two rings exhibit solid-state reactivity as can be seen in Table 2 part (o). The thermal and light sensitivity of these compounds was reported by Toda and Nakagawa[83,85] several years before Wegner's paper characterizing the polymerizaion process[1], but their description of the deep colours that developed when the crystals were heated or exposed to light leaves little doubt that these compounds do undergo solid-state polymerization. In the case of the glutarate ester **31a** (n = 3), X-ray and



(31)

(a) R = $-OCO(CH_2)_nCO_2-$

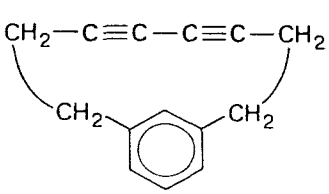
(b) R = $-O(CH_2)_nO-$

spectroscopic studies have confirmed that the polymerization, which is accomplished by ultraviolet or γ-radiation, is of the same type as found for open-chain diynes[25,84,109]. In the reactive modification the packing meets the criteria for reaction (Table 1, entry 7), but conversion to polymer is incomplete, e.g. reaching a limiting value of 35% in γ-ray polymerization, and the unchanged monomer can be extracted leaving highly disordered, almost fibre-like crystals of polymer.

The ring containing the diyne system in the glutarate derivative is under considerable strain as evidenced by the distortion of the acetylenic bond angle away from the normal 180° value to ca. 175–176°, and lengthening of the triple-bond to 1.26 Å[25]. The low reactivity of the glutarate has been attributed to restricted side-group mobility resulting from attachment of the aromatic rings directly to the diyne system[25], and also to strain in the polymer[84]. The structure of the polymer is considered in Section I.F.1.

Interestingly, the higher esters **31a** (n = 4,5,7) failed to polymerize[85]. In the case of the ether-bridged derivatives **31b**, the homologue with n = 3 is sensitive to heat, but the higher homologues with n = 4,5 or 6 are not[83].

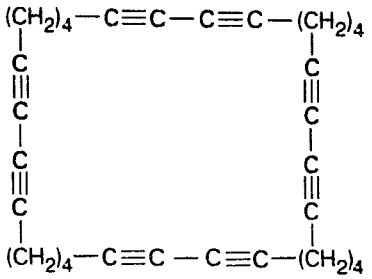
A variety of cyclic di- and higher poly-acetylenes have been studied and the results are collected in Table 2, part (p). The bicyclic derivative **32** is extremely reactive, and



(32)

polymerizes in a few seconds at room temperature, in the dark, the moment that solvent is removed from solutions of the monomer, to give a red insoluble polymer[86]. It is highly likely that the polymer formed in this case has a *cisoid* conformation as described in Section I.F.1[109].

When the cyclic octayne **33** is crystallized from chloroform, crystals are obtained which contain interstitial chloroform and which are quantitatively polymerized by

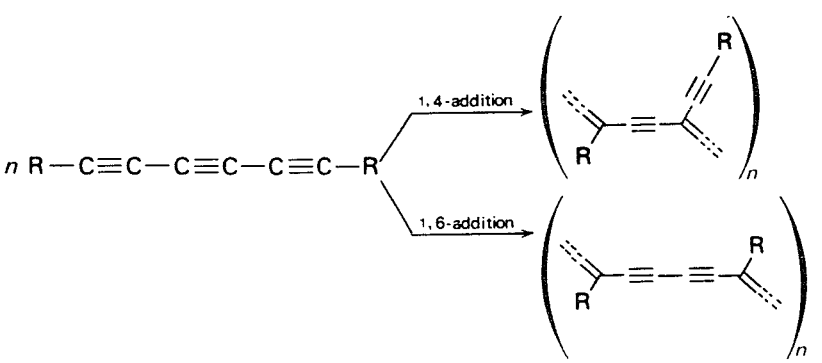


(33)

γ-radiation giving a deep-red polymer which contains one molecule of chloroform per monomer unit[87]. If the chloroform is removed from the monomer crystals by pumping, a yellow powder remains which does not polymerize. Raman and Fourier-transform infrared (FTIR) spectra show that not all of the diyne units react during polymerization, and X-ray studies reveal that although crystalline order is retained in the chain axis projection, there is loss of crystallographic register between chains[88].

The octayne **33** is obtained as one product of oxidative coupling of 1,7-octadiyne[87,89]. Along with **33** there are produced the cyclodimer and cyclotrimer. The three can be separated by chromatography and are obtained as colourless crystals. Although the cyclodimer and cyclotrimer crystals gradually turn yellow and then brown on exposure to light, they fail to develop the bright red or blue colour characteristic of the linear poly(diacetylenes).

With conjugated alkatriynes, the possibility exists for polymerization by 1,6- as well as by 1,4-addition, as shown in Scheme 6. For 2,4,6-octatriyne-1,8-diol and its deriva-



SCHEME 6

tives (Table 2, part q), the repeat distance in the polymer chain is ca. 4.9 Å, thus establishing that the polymerization is a 1,4-process[90].

Polymerization of the bis(ethylcarbamate) of 2,4,6,8-decatetrayne-1,10-diol (**34**) by γ-radiation produces a polymer in which the chains are aligned but which is otherwise

$$EtNHCO_2CH_2(C{\equiv}C)_4CH_2OCONHEt$$

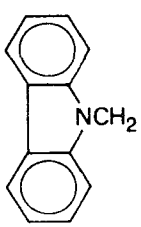
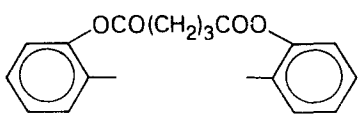
(34)

amorphous[40]. From the chain repeat distance, 4.75 Å, it is apparent that the polymerization involves diyne units, but it is not known which of the two possible diyne units is involved.

D. Abbreviations for Monomer and Polymer Names

The diacetylenes and their polymers which are frequently encountered are commonly referred to with a set of initials, usually derived from some part of the common name of the monomer. This practice will be followed here in an effort to conserve space, and for easy reference the abbreviations are collected in Table 3. The monomers will be referred to by the initials, and the polymers by prefixing poly- to the initials.

TABLE 3 Abbreviations for common diacetylene monomers, $RC{\equiv}C{-}C{\equiv}CR$

R	Abbreviation	R	Abbreviation
$HOCH_2$	HHD	$PhNHCO_2(CH_2)_3$	DDU
p-$MeC_6H_4SO_3CH_2$	PTS	$EtNHCO_2(CH_2)_3$	DDEU
p-$MeOC_6H_4SO_3CH_2$	PMBS	$PhNHCO_2(CH_2)_4$	TCDU
p-$FC_6H_4SO_3CH_2$	PFBS	$EtNHCO_2(CH_2)_4$	ETCD
p-$ClC_6H_4SO_3CH_2$	PCS	$EtOCOCH_2NHCO_2(CH_2)_3$	3 ECMU
p-$BrC_6H_4SO_3CH_2$	PBBS	$BuOCOCH_2NHCO_2(CH_2)_3$	3 BCMU
2-$C_{10}H_7SO_3CH_2$	2 NPS	$EtOCOCH_2NHCO_2(CH_2)_4$	4 ECMU
$PhNHCO_2CH_2$	HDU	$BuOCOCH_2NHCO_2(CH_2)_4$	4 BCMU
m-$(AcNH)C_6H_4$	DADD	i-$PrNHCO_2(CH_2)_4$	IPUDO
	DCHD		BPG

E. The Polymerization Reaction

Topics considered in this section include: changes observed during polymerization, kinetics and energetics, polymer chain lengths during and at the end of the reaction and reactive intermediates and mechanism.

1. *Lattice mismatch*

The polymerization process consists of polymer chains forming at random in the crystal and growing in a unique crystallographic direction. Growth continues until it is terminated by crystal strain, or by encountering a crystal defect or another growing chain. Initially the polymer exists as a solid solution of polymer in the monomer phase and changes to a solid solution of monomer in the polymer phase as the reaction progresses. As mentioned earlier, if the solutions are stable over the entire composi-

tion range, it is possible to obtain polymer single crystals. In some cases, however, the solid solutions are unstable at intermediate composition and phase separation may occur. The requirements for phase stability have been described[17]. In the case of DCHD a phase transformation at an intermediate stage makes it possible for complete polymerization to occur[22].

The repeat distance, d_2, in polymers derived from acyclic diynes is ca. 4.9 Å irrespective of side-chain structure and it can be seen in Table 1 that the stacking distance d_1 in many monomers differs significantly from 4.9 Å. For example, d_1 in PTS, 5.11 Å, is longer than the polymer repeat distance, whereas the value for DCHD, 4.55 Å, is shorter. In such cases the polymer chains are required to conform to the monomer stacking distance. With the tosylate the entire polymerization is homogeneous and as the polymer content grows the monomer lattice is compressed in the direction of chain growth as evidenced by the smooth decline in the unit cell dimension in this direction (the *b* axis) from 5.11 Å to 4.91 Å[15,110].

The lattice mismatch is even greater with DCHD, and the polymer chain must contract by approximately 8% in the monomer lattice. When the polymerization is effected by γ-radiation, the lattice parameters change smoothly at first, but at ca. 20% conversion a phase change occurs and the parameters change abruptly to values corresponding closely to those of the polymer[22,23,79,111]. The phase transition is a displacive one, but it proceeds homogeneously throughout the crystal and introduces little disorder. Polymer chains already present at the time of the transition probably prevent fragmentation of the crystal which normally would occur with such large lattice changes[22]. Quantitative thermal polymerization of DCHD is possible, but phase separation occurs causing fracture of the crystals and microcrystalline polymer is obtained.

Shifts in optical and vibrational spectra of the polymer with increasing conversion have been interpreted as resulting from changes in stress on the polymer chain[33,112–115]. For example, the resonant Raman spectra of poly(diacetylenes) contain four intense bands which are associated with backbone vibrations[116]. Of these, two modes, ν_1 and ν_2[113], correspond to triple- and double-bond stretching modes, respectively, while the remaining two are essentially bending modes. The value of ν_1 and ν_2 for crystals containing 1% and 100% polymer for poly-PTS and poly-PMBS are presented in Table 4. Shifts in the remaining two bands are substantially smaller than those observed for ν_1 and ν_2[113]. It is seen that ν_1 and ν_2 increase with increasing polymer conversion and these shifts have been attributed to the decreasing strain on the polymer chain as the reaction progresses. Support for this interpretation comes from studies of the changes in the vibrational frequencies that occur when poly(diacetylene) crystals are subjected to mechanical strain[117,118]. For example, ν_1 and

TABLE 4. Resonant Raman lines in partially and completely polymerized poly(diacetylene) crystals

	Poly-PTS[113]		Poly-PMBS[33,112]	
	1% Polymer	100% Polymer	1% Polymer	100% Polymer
ν_1 (cm^{-1})	2015	2086	1980	2084
ν_2 (cm^{-1})	1472[a]	1485[a]	1478	1482

[a]The observed values represent perturbed frequencies which arise from coupling of ν_2 with the scissor-vibrational mode of the adjacent CH_2 group. Calculated values for unperturbed ν_2 are 1460 and 1483 cm^{-1}. The unperturbed frequencies were used in deriving the frequency–strain relationship described in the text.

ν_2 for crystals of poly-PTS or poly-HDU decrease when the crystal is subjected to tensile strain in the direction of the polymer chain. Linear relationships between the frequencies and strain, as measured by the fractional increase in length of the crystal, are observed up to a certain strain; beyond this value the relationships are nonlinear and at a limiting value the crystal fractures. From the frequency–strain relationships for the pure polymer crystals, and the value of ν_1 for crystals containing a small concentration (ca. 1%) of polymer, it is calculated that the initial chains of poly-PTS are subject to approximately 3% strain. This may be compared with the value of 5% calculated from lattice parameters. Most of the elongation that occurs with applied tensile strain results from bond angle changes[113,119], and calculations indicate that the changes in vibrational frequencies result from bond anharmonicities[117,118].

The intense absorption of poly-PTS at 16,190 cm^{-1} in 100% polymer crystals is shifted to 17,500 cm^{-1} in crystals containing a small concentration of polymer, and this shift has also been attributed to polymer strain[115a]. A study of the shift in absorption energy during polymerization of microcrystalline PTS supports this interpretation[115b]. For crystals of pure polymer the absorption maximum shifts to higher frequencies with applied tensile strain, and from the derived relationship between frequency and strain it is calculated that the initial strain on poly-PTS chains is 4.6%[114]. The absorption frequency decreases linearly with applied hydrostatic pressure[120].

Chance and Sowa have criticized this interpretation of the change in the optical spectrum, and believe that the blue shift in the low conversion spectrum cannot be attributed entirely to strain[121]. Implicit in the argument above is the assumption that the polymer chains are effectively infinite in length even at low conversions. Wegner's early report of the near insolubility and very high viscosity even for polymer formed in the early stages had led to the belief that very long chains were formed from the onset[47]. Chance and Sowa argue that the initial polymer chains may be relatively short compared to those formed later and this may be partially responsible for the blue shift. They estimate that an oligomer with 24 monomer units would absorb at 17,500 cm^{-1}, the value observed for low polymer conversions. From molecular weight determinations reported recently it is estimated that the number-average degree of polymerization of PTS in the early stages is ca. 20, thus adding weight to the criticism[122].

2. *Kinetics*

Three methods that have been used most widely for monitoring kinetics are: gravimetric determination of residual polymer after the unchanged monomer has been removed by solvent extraction[7,11,13,33,47,49,123,124], differential scanning calorimetry[92,94,125–127] and diffuse reflectance spectroscopy[121]. In cases where results can be compared, the agreement among the methods is reasonably good. The extraction method is tedious and requires large samples. Solution absorption spectroscopy provides the most accurate analytical method but it is limited to those few polymers having a significant solubility[56]. A novel technique for studying the kinetics and energetics of photopolymerization involves photoacoustic photocalorimetry[128].

The polymerization of PTS is characterized by an initial 'induction period', during which the rate is very slow, followed by an 'autocatalytic period' in which the rate increases dramatically, by better than two orders of magnitude, and conversion rapidly approaches 100%. The length of the induction period ranges from ca. 600 h at 30°C, to 60 h at 50°C to 3.3 h at 80°C, but in all cases the change to the rapid regime occurs after ca. 10% conversion to polymer[7]. The ratio of rate constants in the two regimes has been estimated by various workers to be 150[94], 175[115a], 300[127] and 400[126]. In spite of the dramatic difference in rates the energy of activation is the same in both regimes, viz. 22.5 kcal mol^{-1}. Values determined by a number of groups, using the three techni-

ques described above for monitoring conversion, are within ± 0.5 kcal mol^{-1} of this value[7,94,121,124–127]. The measured value corresponds to the activation energy of the rate-determining initiation step, and we shall see below that chain growth proceeds with a very low activation energy, ca. 2 kcal mol^{-1}.

It is believed that the slow rate characterizing the induction period is a consequence of the monomer–polymer lattice mismatch described above, and a model has been derived involving crystal strain effects which gives good agreement with experimental data[129]. Slow reaction in the early stages is a consequence of strain in the polymer chain which, according to evidence cited below, limits the polymer to relatively short chain lengths. With increasing conversion the lattice mismatch decreases and effectively unstrained polymer chains can grow. The autocatalytic region is characterized by the growth of very long polymer chains, and it is this increase in chain length that is responsible for the dramatic increase in rate. The rate in the autocatalytic region varies considerably with crystal purity, suggesting that the molecular weight is controlled by chain-terminating impurities. On the other hand, in the induction period the rate is relatively insensitive to purity, in agreement with the strain-control theory[126].

Several lines of evidence support this interpretation of the induction period. The induction period decreases when hydrostatic pressure is applied to a PTS crystal, and at 60°C, it effectively disappears at pressures above 2 kbar[123]. This was taken initially to mean that the monomer lattice was compressed in the *b* direction to a value matching the polymer repeat distance, but it has been shown that the change in this parameter brought about by a pressure of 3.4 kbar is less than 10 ppm, and even at this pressure the lattice mismatch is still ca. 4.5%[120,130]. Lateral compression of the lattice is probably the major factor responsible for the acceleration[124]. Substantial changes in the *a* and *c* axes do occur during polymerization[15].

Changes in the near-IR absorption spectrum during the change from the induction to the autocatalytic regime have also been interpreted in terms of crystal strain[131]. A band is present at 4390 cm^{-1} in the monomer spectrum which is the fourth harmonic of the CH_2 wagging mode at 1362 cm^{-1} in the infrared region. The intensity of this band increases linearly with conversion until ca. 11% polymer has formed, but beyond this point the band rapidly disappears. The initial increase in intensity is attributed to increased anharmonicity of the vibration resulting from crystal strain during the induction period. As the strain decreases above 11% conversion, the anharmonicity decreases and the overtone band disappears[131].

Changes in proton spin-lattice relaxation times also support the correlation between crystal strain and the induction period[132]. This technique provides a sensitive means for monitoring polymer conversion and also for studying phase transitions in the monomer and partially polymerized material.

The autocatalytic effect is observed during γ-ray polymerization of PTS, but it is less dramatic than in the thermal reaction[7]. The optical spectrum of the polymer obtained by γ-radiation is notably different from that obtained thermally or by ultraviolet radiation, being slightly red-shifted with significant absorption extending beyond 620 nm, and with significant absorption at 615 nm at low conversions[113].

Whether or not the autocatalytic effect is present in the UV photopolymerization of PTS is difficult to ascertain and conflicting reports have appeared. Some workers have concluded that it is absent[92,133], but others have shown that the autocatalytic effect is masked unless the absorption depth is comparable to the crystal thickness, and they present strong evidence which substantiates the existence of the effect[7]. Activation energies are ca. 2 kcal mol^{-1} and 3 kcal mol^{-1} for the γ- and UV-polymerizations, respectively[7]. These are activation energies for polymer chain growth, and not the initiation event as measured in the thermal reaction.

The rate of thermal polymerization of PFBS is an order of magnitude slower than PTS, and the activation energy, 26 kcal mol^{-1}, is significantly higher[49]. An induction

period with accompanying autocatalytic behaviour is observed for both the thermal and γ-ray reactions. The *b* axis repeat distance in the monomer, 5.18 Å, changes to 4.90 Å in the polymer, corresponding to a change of 5.4%. This represents a somewhat greater mismatch than that in the tosylate and may be responsible for the longer induction period observed for PFBS[49].

The behaviour of PMBS presents a paradox: first-order kinetics are observed throughout the polymerization, the activation energy, 24.1 kcal mol^{-1}, is nearly the same as for PTS, the initial rate is approximately 100 times that of PTS, and there is no detectable induction period -- yet the evidence indicates that the initial crystal strain is greater than in PTS[33,50,112]. Lattice parameters for the monomer have not been determined, but shifts in the Raman lines during polymerization (Table 4) are somewhat greater than for PTS, and it is estimated that the lattice contraction during polymerization amounts to 5.6%[33]. However, the kinetic data are fit to Baughman's crystal strain model[129] only by assuming zero lattice strain throughout! A partial explanation for this behaviour comes from the observation that the strain in the PMBS crystal, as determined from Raman shifts, decreases much faster with conversion than it does in PTS[33,112]. For example, at 10% conversion, only 30% of the initial polymer strain remains with PMBS whereas 70% remains in PTS. It is proposed that rapid initial polymerization of PMBS carries it to an almost strain-free condition, and makes the observation of a weak autocatalytic effect difficult[33]. But the cause of the faster initial polymerization is uncertain, and it is apparent that factors other than lattice strain are important in determining the polymerization kinetics.

Recent studies with mixed crystals of arenesulphonates of 2,4-hexadiyne-1,6-diol also point up the importance of these other factors[11,13]. Thus, the induction period is greatly reduced in mixed crystals of PTS containing small amounts of 2NPS or PMBS as summarized in Table 5[11]. Whereas pure PTS polymerizes only to the extent of 7% after 6 h at 70°C, mixed crystals containing 2% or 5% 2NPS are polymerized to the extent of 13% and 89%, respectively, under the same conditions. The effect is even more dramatic for crystals containing PMBS where, for example, 98% conversion occurs for a crystal containing 2% PMBS. Results of X-ray structure studies of these mixed crystals should prove interesting.

Mixed crystals of PTS and PCS containing less than 5% of the latter show shorter induction times than pure PTS, but for levels higher than this the reverse is found[13]. The only change in lattice parameters in the mixed crystals is a monotonic decrease in the stacking distance d_1 with increasing concentration of PCS, e.g. from 5.11 Å in pure PTS to 5.05 Å in a mixed crystal containing 15% PCS. The other lattice parameters do not change detectably. Mixed crystals of PTS and PBBS show a gradual increase in induction period with increasing concentration of PBBS[13].

TABLE 5. Conversion to polymer after 6 h at 70°C for pure PTS, and mixed crystals of PTS with 2NPS, and with PMBS[11]

Monomer composition			
PTS (%)	2NPS (%)	PMBS (%)	Conversion (%)
100	—	—	7
99	1	—	4
98	2	—	13
95	5	—	89
99	—	1	86
98	—	2	98

An autocatalytic effect is observed in the thermal polymerization of DCHD, but it is not comparable in magnitude to that of PTS; for γ-ray-induced polymerization, however, the effect is more dramatic and approaches that of the tosylate[79]. In this case the onset of the autocatalytic region coincides with a phase transition, which was referred to earlier. As the radiation-induced polymerization progresses the *b* axis of the unit cell increases smoothly from its value of 4.55 Å in the monomer to ca. 4.65 Å at 25% conversion[22]. At this point the phase transition occurs and the *b* axis changes abruptly to 4.91 Å, corresponding to the value for the polymer unit cell. The reaction rate increases markedly during and after this transition.

Thermal polymerization of DCHD occurs in the range 110–240°C; it is very slow at the low end of the range, requiring two weeks for complete reaction[22,79]. The activation energy has been reported as 24.1[78] and 25 kcal mol^{-1} [79]. Polymerization starts from crystal edges and other visible defects, and it has been found that more nearly perfect monomer crystals require longer reaction times than defect-rich ones. When a monomer crystal is cooled, it undergoes a phase transition at −131°C to a structure in which the stacking distance is 4.20 Å[25], and a small amount of polymerization occurs when the crystal passes through the phase change[111]. This is surprising not only because it is more than 200°C below that where thermal polymerization ordinarily occurs, but also because the stacking distance in the new phase that forms below the transition temperature is even less favourable for polymerization than that in the higher temperature phase. It has been proposed that the deformation of the lattice at the boundary between the two phases at the transition temperature is such that optimal packing for polymerization is approached[111]. It has also been found that the polymer content increases when crystals which have been cycled through the phase transition are allowed to stand at room temperature. Crystal defects produced during the phase change are believed responsible for initiating polymerization in this case[111].

There is no evidence for the autocatalytic effect in the γ-ray polymerization of 4BCMU and 3BCMU, suggesting the absence of mismatch between monomer and polymer lattices[56]. The reactivity of 4BCMU is significantly greater than that of 3BCMU; e.g. after 5 Mrad of γ-radiation, 4BCMU polymerized to the extent of 66% while after a 50 Mrad dose, only 60% polymerization of 3BCMU was found[56,134]. The greater reactivity of 4BCMU has been rationalized on the basis of least-motion arguments.

Extremely large secondary kinetic isotope effects have been reported for the polymerization of labelled PTS and HDU[135]. For example, the relative rates of polymerization of **3**, **3**-d_9, and **3**-d_2 after the induction period are 1:0.62:0.31. The activation energy, 20.2 kcal mol^{-1}, is the same for all three and the different rates result from differences in the preexponential terms. An inverse isotope effect is observed during the induction period, with relative rates being in the order **3**-d_9 > **3**-d_2 > **3**. Even the ^{13}C-labelled derivative, **3**-^{13}C exhibits a kinetic isotope effect of ca. 0.6! The origin of these isotope effects is unclear.

$$R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

(**3**) R = *p*-$CH_3C_6H_4SO_3CH_2$
(**3**-d_9) R = *p*-$CD_3C_6D_4SO_3CD_2$
(**3**-d_2) R = *p*-$CH_3C_6D_4SO_3CD_2$
(**3**-^{13}C) R = *p*-$CH_3C_6H_4SO_3^{13}CH_2$

Kinetic studies of photopolymerization of PTS are considered in Section I.E.4.b in conjuction with mechanistic considerations.

3. Polymer chain lengths

Although early evidence has been interpreted as indicating that poly-PTS chains are effectively infinite in length even at low conversions[47,115a], more recent studies by Patel have shown that this is not the case[122]. Patel found that the polymer formed at less than 12% conversion, i.e. during the induction period, is completely soluble in dimethylformamide, whereas that formed beyond this point is entirely insoluble indicating a very high molecular weight. Molecular weight determination on the low-conversion polymer by gel-permeation chromatography has shown the material to have a very broad molecular weight distribution. Furthermore, there is no change in the distribution during the entire induction period, signifying that increasing conversion in this range results from the generation of new chains rather than the propagation of existing chains. The number-average degree of polymerization in the induction period is calculated to ca. 20[122]. A large fraction of the polymer chains have very low degrees of polymerization, but there is also present a very small fraction with chains having 100–200 monomer units and which slowly precipitates on standing.

If the increase in rate in the autocatalytic region is entirely due to increased chain length, then from the rate ratios presented earlier, the average chain length for poly-PTS formed in the autocatalytic region is in the range 3000–8000 monomer units. Measurements by scanning electron microscopy have shown the average chain length in the autocatalytic region to be ca 4 μm, equivalent to ca. 8000 monomer units per chain[4b]. This is somewhat higher than the value of 1000 determined for poly-3BCMU by gel-permeation chromatography[57]. In this case intermediate weight oligomers are not formed; instead, from the onset, polymerization leads to very long chains. There is no appreciable increase in molecular weight with conversion, and the molecular weight distribution is very broad at all stages.

The presence of oligomers has been reported in the polymer from 2,4-heptadecadiynoic acid[62].

Because of the large differences in elastic constants between monomer and polymer crystals and because the elastic constant in the polymer chain direction is strongly affected by the chain length, chain lengths during polymerization can be determined by Brillouin spectroscopy. Results with PTS indicate an initial degree of polymerization of ca. 5, which increases steadily during polymerization, reaching a value of ca. 500 at 90% conversion[15,136]. Studies with DCHD indicate the presence of only oligomers at low conversions, but polymers with chain lengths of 1000 or more at high conversions[22].

4. Mechanism of polymerization

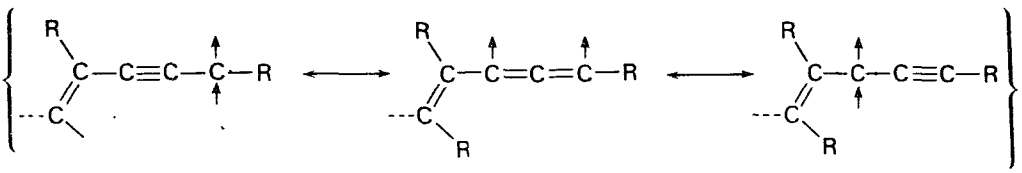
a. Thermal initiation. Evidence from ESR studies provides support for the existence of triplet carbenes as reactive intermediates in the thermal polymerization of PTS[137–139]. Two sets of extra lines, besides the usual line at $g = 2$, are observed during polymerization at 60°C[137]. Both sets are characteristic of triplet species and first appear after 20 hours, just at the onset of rapid polymerization. The set at high field initially grows in intensity, then diminishes and finally disappears at the end of the rapid regime, suggesting that these lines belong to the reactive intermediate associated with the growing chain*. The lower field set of lines persists after the rapid reaction period, and can be observed even after 80 hours of heating. It disappears only when

*There are in fact high-field lines for two triplet species which show different angle dependences. These arise because there are two kinds of polymer chain in the unit cell which differ in the conformation of the side-groups (see Section I.F.3). The different lines correspond to triplet states on these different types of chains.

polymerization is complete (100 h), and is believed to be associated with distorted polymer chains or trapped chain ends which rearrange slowly to non-paramagnetic structures.

However, these same sets of ESR signals are observed when a PTS crystal is heated until it is in the autocatalytic region and then cooled to room temperature, where the rate of polymerization is negligible[138]. This signifies that the high-field signal is also associated with a nonpropagating chain-end.

The fine structure parameters, which provide an indication of the electron density distribution, are $D/hc = 0.2731\ cm^{-1}$ and $E/hc = -0.0049\ cm^{-1}$ [139]. The zero-field parameter, D, which depends on the mean separation between the unpaired electrons, is about twice the maximum value for two spins on adjacent carbons, and hence there must be a contribution from two unpaired spins on the same carbon. A mesomeric triplet carbene with contributing structures, shown in **35**, has been proposed for this



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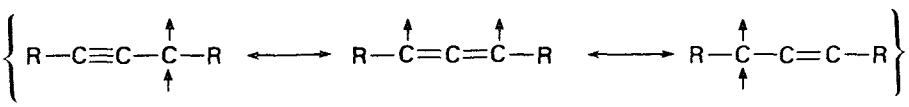
intermediate[138]. However, the value of D is only about one-half that found for simple propargylenes[140], **36**, and since the delocalization in **36** corresponds to that shown

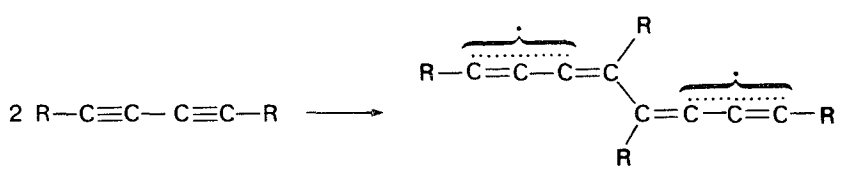


(36)

in **35**, it would seem that even more extensive delocalization exists in the polymerization intermediate. One of the unpaired electrons in **35** is in a π orbital which is extensively delocalized along the polymer backbone, and this spin would be expected to be delocalized beyond just one repeat unit.

When partially polymerized PTS crystals are cooled to 4.2 K and irradiated with 440–480 nm light, they exhibit fluorescence and it has been suggested that the fluorescing centre could be a trapped ground-state triplet carbene at the end of a polymer chain[141].

Thermochemical arguments support a bimolecular process leading to a diradical **37**



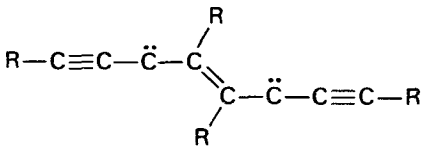
(1)

(37)

as the rate-determining initiation step (equation 1) in the thermal polymerization[125,127]. From the heat of polymerization, −36.4 kcal mol^{-1}, and $C(sp^2)—C(sp^2)$ σ bond energy, 94.5 kcal mol^{-1}, the enthalpy change for the formation of **37** is calculated to be 21 kcal mol^{-1}, in good agreement with the experimental activation energy, 22.5 kcal mol^{-1}. Others have proposed a biscarbene as the intermediate formed in the initiation step, but it is estimated that the formation of a biscarbene dimer would have a much greater energy requirement, ca. 58 kcal mol^{-1} [127].

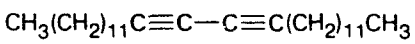
The frequency factor for polymerization of PTS, $10^7\ s^{-1}$, is surprisingly low, and this has been attributed to the formation of **37** in a triplet configuration[7]. This would be the lowest energy configuration of the diradical, but its formation from singlet precursors would be spin-forbidden and expected to display a low frequency factor.

It should be pointed out that the observation of a carbene species at a nonpropagating chain-end does not preclude an initiation step or propagation steps involving diradicals. In fact, the distinction between diradicals and carbenes becomes hazy for these molecules. For example, **38** and three other 'biscarbene' structures are contributing structures, although minor, for the 'diradical' **37**.



(38)

b. Photochemical initiation. Absorption of radiation by the diyne unit, by a chromophore in the side-chain or by sensitizers contained in mixed crystals can initiate photopolymerization. Thus the photoaction spectrum of **39** shows a maximum rate for 265 nm light, and a maximum in the absorption spectrum appears in this same region[37]. Similarly, the photoaction spectrum of **40** in a multilayer assembly exhibits



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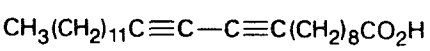
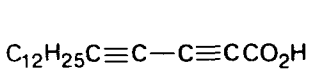


(40)

maxima at 256 and 242 nm, corresponding to maxima observed in the absorption spectrum[66]. On the other hand, the rate of polymerization of HDU reaches a maximum at ca. 290 nm, corresponding to absorption by the phenylcarbamoyl group[37]. Usually, diacetylenes with chromophore besides the diyne unit are photo-active over the whole range of absorption irrespective of the location of the chromophore relative to the diyne, and the photoaction curves are distorted versions of the absorption curves[99].

Mixed crystals of **41** and phenazine (**42**) undergo sensitized photopolymerization upon irradiation at 420 nm, corresponding to phenazine excitation, even though **41** itself is not polymerized by light with wave-lengths longer than 300 nm[142,143]. Similarly, sensitized polymerization occurs when mixed crystals of **41** and the cyanine dye **43** are irradiated at 600 nm[65].



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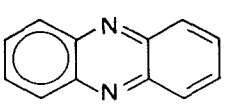

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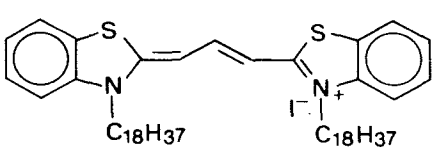


(43)

The lowest excited electronic state of diynes, the triplet state, lies ca. 72 kcal mol^{-1} above the ground state[144a], whereas the activation energy for thermal polymerization of diacetylenes is only 22.5 kcal mol^{-1}. Consequently, initiation in the photo and thermal polymerizations either occurs by different pathways, involving an electronically excited monomer for the former and a vibrationally excited state for the latter, or

there is a common vibrationally excited monomer precursor which can be populated by thermal excitation or by radiationless decay of an electronically excited monomer. Comparison of the solution and solid-state ultraviolet spectra of various diynes indicates that a coupling of electronic excitation and crystal vibrations is of basic importance in the solid state polymerization[38].

The results of the sensitized photopolymerization of mixed crystals described above seem to provide support for a vibrationally excited intermediate provided, of course, that the sensitized and nonsensitized reactions involve the same precursor state. Thus, the excited states of **42** and **43** lie well below the lowest excited state of the diyne, and electronic excitation of the diyne by energy transfer from excited sensitizer is unlikely. It has been proposed, however, that the sensitized and nonsensitized processes do proceed by different mechanisms[143]. The proposal is based on slightly different activation energies found for the two processes. Thus, for 420 nm light the activation energy for polymerization in mixed crystals of **41** and **42** is 4.8 kcal mol^{-1}, whereas it is 3.9 kcal mol^{-1} for 280 nm light. The difference, 0.9 kcal mol^{-1}, is somewhat larger than the experimental error, and is associated with the formation of a chain-initiating species for the sensitized reaction; it has been suggested that this may involve proton transfer from the acid to phenazine[143].

The rate of polymerization of mixed crystals of **41** and **42** remains constant up to ca. 10% conversion for both 280 and 420 nm radiation, indicating that deactivation of the primary excited states by polymer molecules is very inefficient[143]. The quantum efficiency, i.e. the number of monomer units added per photon absorbed, is 0.5 for 280 and 0.1 for 420 nm radiation. Calculations indicate a very short intrinsic lifetime for the electronically excited state, suggesting a singlet for both monomer and sensitizer excitation[143].

Results for the photopolymerization of PTS, however, have been interpreted as involving a triplet diradical state as the principal chain-initiation species[7,58]. The preferred scheme, corresponding to excitation of the side-chain chromophore (R), is summarized in Scheme 7[58]. The singlet-excited state of the side-group (S_R) is expected

$$S_0 + h\nu \longrightarrow S_R \xrightarrow[\text{transfer}]{\text{energy}} S_D \xrightarrow[\text{crossing}]{\text{intersystem}} T_D \longrightarrow \text{polymer}$$

SCHEME 7

to correspond roughly in energy to that of toluene, 4.3 eV (99 kcal mol^{-1}), which is higher than that of the lowest excited singlet of the diyne unit in the *trans*–bent configuration (S_D), 3.7 eV (85 kcal mol^{-1})[114b,c]. Consequently, energy transfer from the side chain to the diyne unit is possible. The triplet state of the diyne (T_D) at 3.1 eV (72 kcal mol^{-1}), formed from the singlet by intersystem crossing, is the initiator of polymerization[58].

Photopolymerization of DCHD is much slower than that of PTS[78], and it has been pointed out in an earlier section that this may be a consequence of the fact that the triplet state of the carbazolyl group, at 3.0 eV, lies below that of the diyne, and that the interaction between the carbazolyl and diyne π systems is negligible[23,138].

The kinetics of photopolymerization of PTS have been studied using flash photochemical techniques[58]. Thus, crystals of PTS were irradiated with 3 ns pulses of 337 nm light from a nitrogen laser, and the formation of polymer was monitored by measuring the reflectance at 575 nm. The first change in reflectivity, announcing formation of polymer, was noted ca. 300 ns after the laser pulse. Polymer formation then proceeded with slowly decreasing rate and ceased after a few milliseconds. The 300 ns delay represents the time necessary to build up polymer chains of sufficient

length to reflect significantly in the region where the long chain polymer does, i.e. ca, 10 monomer units.

Low-temperature photopolymerization studies have provided a great deal of information about reactive intermediates in the reaction. Photoinitiation occurs at temperatures in the range 4–77 K, but chain-growth ceases at an early stage, yielding short-chain oligomeric species with reactive chain-ends. Information about these species has been obtained by ESR[21,145–148] and absorption spectroscopy[58,149–151] of crystals in which small concentrations have been trapped. Evidence that these are truly intermediates in the growth of the polymer chain is provided by the fact that they disappear and polymer chains simultaneously appear when the crystals are allowed to warm up.

When PTS is irradiated with UV at 4.2 K, a low concentration of oligomers arises as evidenced by continuously increasing absorption in the region between monomer and polymer maxima, but polymer formation does not occur[149]. Two intense long-wavelength maxima appear at 664 and 714 nm, along with weak maxima at 425 and 510 nm. When the crystal is allowed to warm up, the 510 nm peak disappears at ca. 50 K and the 425 nm peak at ca. 90 K; the 664 and 714 nm peaks begin to deform at 100 K and disappear at 105 K—absorption attributable to the polymer increases up to 150 K[149]. Studies of the transient behaviour of the 425 and 510 absorptions have been carried out by irradiating a PTS crystal with 15 ns laser pulses of wavelength 308 nm, and monitoring the absorption at 425 and 510 nm[150]. If the crystal is irradiated at 77 K, absorption rises sharply within ca. 50 ns after the laser pulse and then remains stable as long as the temperature is not raised. At room temperature, however, absorption at 425 nm reaches a maximum and then decays quickly; onset of absorption at 510 nm occurs 370 ns after the laser pulse, reaches a maximum and decays with approximately the same time constant as the 425 nm peak. Polymer formation occurs slowly after the transient absorptions disappear. It has been concluded that the species absorbing at 510 nm is formed from the one which absorbs at 425 nm by a bimolecular process with an activation energy of ca. 4.6 kcal mol^{-1} [150]. Evidence presented below suggests that the species under study here may be diamagnetic trimers and tetramers, possibly diradicals.

When a PTS crystal at 4 K is irradiated with 312 nm light, a set of ESR lines is observed which have been attributed to triplet carbenes, F—J (see Figure 1)[145]. The

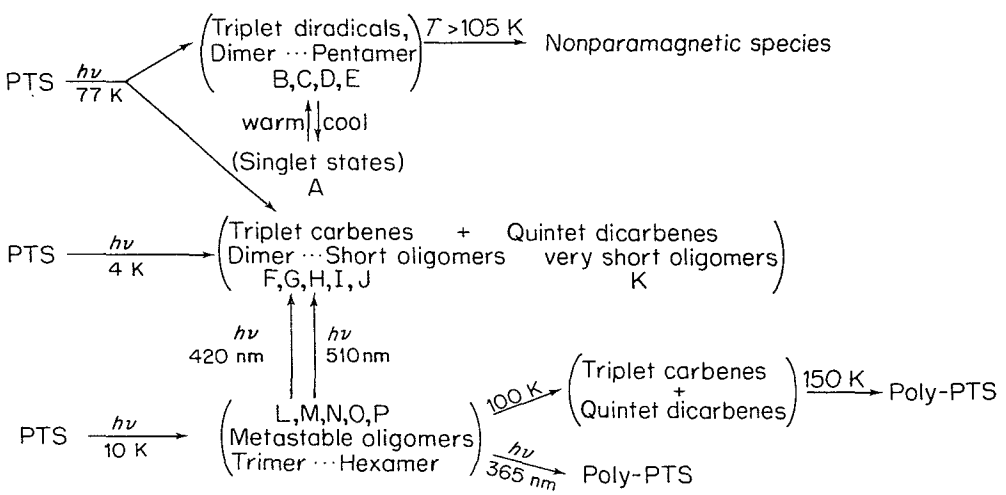
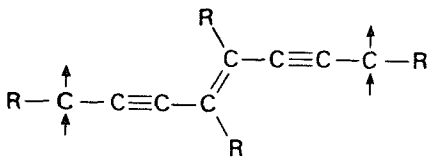


FIGURE 1. ESR and optical intermediates in low-temperature photopolymerization of PTS.

lines occur in pairs as a consequence of the two different orientations of monomer stacks that exist in the low-temperature phase, but only one member of each pair is considered here since the two sets show the same behaviour. The ESR spectra are related to that of the triplet carbene **35** observed during thermal polymerization, but fine-structure splittings are larger for the photo intermediates. For example, D/hc ranges from 0.2746 to 0.3675 cm^{-1}, and this is interpreted to mean that the carbenes are associated with short oligomer chains, instead of the polymer-length chain of the thermal intermediate. Differences in fine-structure splitting among the photo intermediates are attributed principally to differences in oligomer lengths, the largest D value assigned to the shortest chains and vice-versa. Evidence presented below suggests that F is a dimer, G a trimer, etc.

As with the thermal intermediate, the structure of one terminal unit is represented as a hybrid of the three resonance structures **35**. All of the signals show hyperfine splitting which arises from hyperconjugative coupling with the methylene unit of the $TsOCH_2$ group, and the magnitude of the coupling leads to a calculated spin density of 0.4 on the terminal sp carbon[145].

The chain lengths could not be ascertained from the ESR data, nor could the nature of the active species on the other end of the oligomer, except that the splitting pattern showed no evidence for a quintet state ($S = 2$). On this basis, quintet dicarbenes, illustrated for the dimer in **44**, were ruled out, but triplet dicarbenes such as **45** were



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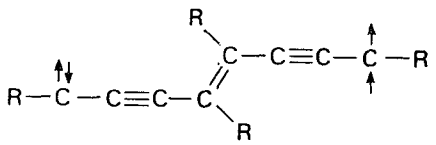
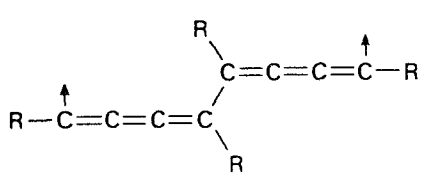


(45)

considered as likely structures[145]. In more recent studies, quintet states have been detected among the photo products from PTS at 4.2 K, and have been assigned as dicarbenes on very short oligomers, as in **44**[147a,b]. ESR signals of these states disappear irreversibly within a few minutes above 110 K.

When the irradiation of PTS is carried out at 77 K, signals for the triplet carbenes, F—J, appear, but in addition there are signals for three new paramagnetic species, B, C and E[146,148]. These have much smaller fine-structure splittings, viz. D/hc = 0.0306, 0.0393 and 0.0538 cm^{-1}, respectively, and show hyperfine coupling to four protons of two CH_2 groups. The spin density at each of the terminal sp carbons has been esimated to be 0.5. From these results, it has been concluded that the triplet electrons are localized symmetrically at both ends of extremely short oligomers. Agreement with observed splittings is obtained by assuming a major contribution (ca. 95%) by the diradical-type structure **46** and only a minor contribution (5%) by the triplet carbene structure, **47**. Trimers and higher oligomers C—E would have structures analogous to **46** with spins concentrated on the terminal carbons.



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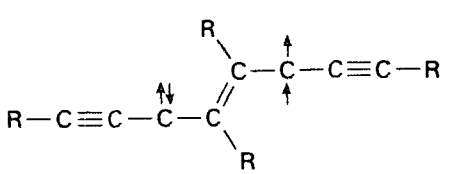


(47)

The signals for these triplet diradicals are temperature-dependent[146,148]. Below 90 K they disappear and reappear reversibly when the crystal is cooled or warmed. This behaviour signifies that the triplet diradicals are thermally excited states of the singlet ground states, A (see Figure 1), which is estimated to lie ca. 0.2 kcal mol^{-1} below the triplets.

Above 100 K the ESR signal of B begins to decrease and at the same time that of C initially increases, then decreases, and finally disappears above 105 K[146,148]. There is evidence that B is the only triplet diradical formed initially. The rate of formation of B is proportional to the square of the light intensity, indicating a bimolecular process, and consequently B is believed to be a dimer. The remaining diradicals, C—E, are believed to be trimers, tetramers and pentamers formed by successive addition of monomer units. Fine-structure splittings for the presumed tetramer D have not been observed, but it is included in the scheme to obtain agreement with the splittings that have been observed and with the decay kinetics[146,148].

Optical absorption spectroscopy has provided evidence for a group of five diamagnetic metastable oligomers, L—P (Figure 1), which are formed when PTS is irradiated with 315 nm radiation at 10 K [151]. The intermediates are generated sequentially in the order listed, i.e. L is the first to appear and P the last, and L appears to be formed directly from monomer. After the steady-state concentration of intermediates is established, if the 315 nm source is replaced by a 365 nm source, the generation process ceases and the intermediates disappear sequentially in the same order as their generation. After ca. 10 minutes, all the intermediates disappear and polymer molecules are produced.

The intermediates are converted to triplet carbenes by light of the same wavelength as their individual absorption maxima[151]. Thus L, which shows maximum absorption at 420 nm, is converted to the triplet carbene trimer G by 420 nm radiation. Similarly, M is converted to H by 510 nm light. The intermediates are thermally unstable and at 90–100 K they disappear, in the same order as their generation, and are converted to triplet carbenes and quintet dicarbenes. They have not been characterized completely, but apparently these paramagnetic species are different from F—K. Finally, at 130–150 K the paramagnetic intermediates disappear and poly-PTS is formed[151].

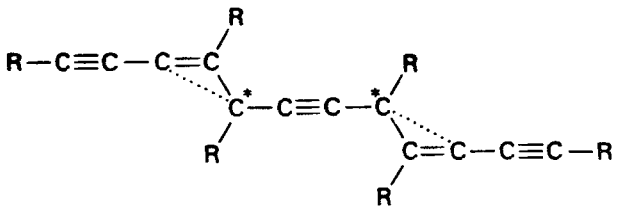
The absorption maxima of these diamagnetic intermediates are at considerably longer wavelengths than would be expected for short-chain oligomers. Thus for L, believed to be a trimer, the maximum is at 420 nm, whereas the expected value for a trimer, i.e. a system with six conjugated multiple bonds, is ca. 365 nm[152]. For P, presumably a heptamer, the observed and calculated values are 710 and 470 nm.

Highly unusual structures have been proposed for these intermediates involving a 'distorted pseudo-cyclopropene with one extended weak σ bond'[151]. For example, **48** is the structure proposed for the trimer.

Higher oligomers have the same types of terminal units, separated by additional monomer units. Contributions from structures involving charge separation were proposed to account for the red shift in the absorptions of these species.

A major problem with the proposed structures, which makes them highly unlikely, arises from the enforced planarity of the system, which requires that all four bonds from the starred carbons in **48** be coplanar!

A more reasonable possibility is that the diamagnetic oligomers are singlet diradicals, comparable to the dimer diradical **37** proposed for the thermal reaction, and illustrated in **49** for the trimer L. Arrows designating electron spins are included to emphasize the distinction from the triplet diradical **46** and the biscarbene contributor is included to emphasize that this is the same species as a so-called 'singlet dicarbene'. There is support in the litererature for this interpretation. Several years ago Bergman and coworkers were able to demonstrate that the benzene-1,4-diyl **50** is an intermedi-



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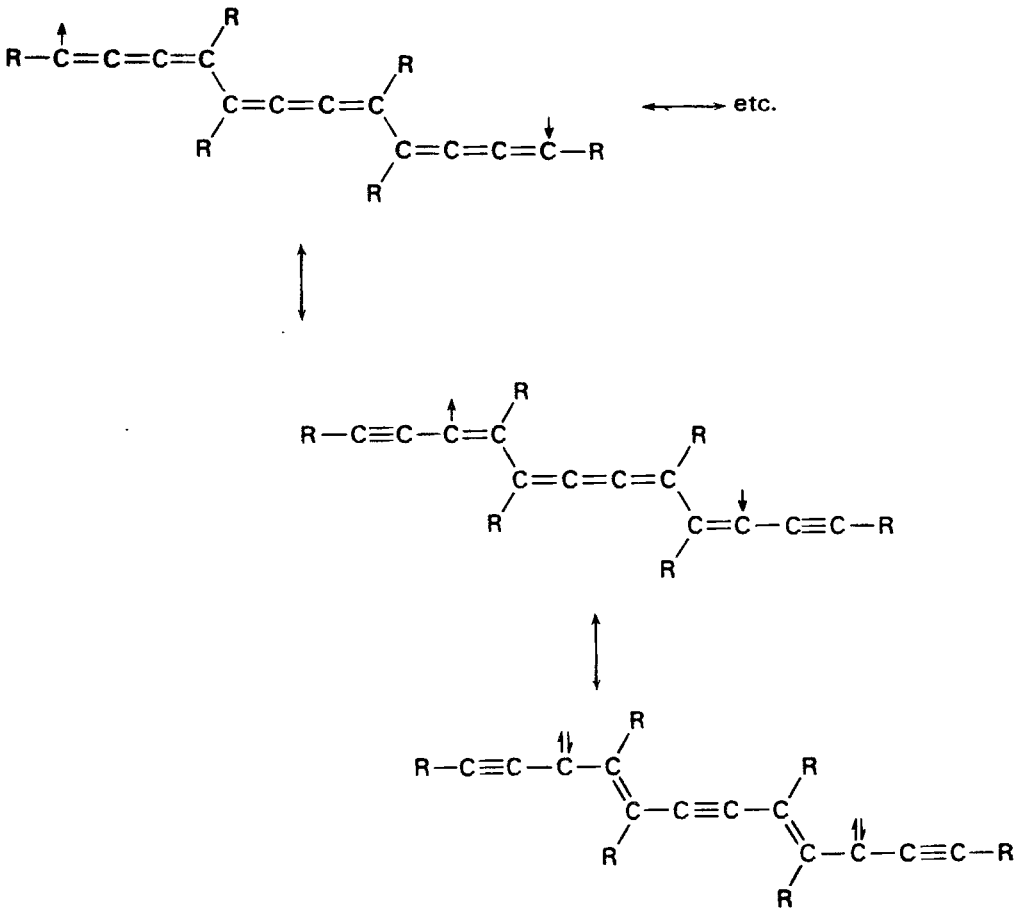

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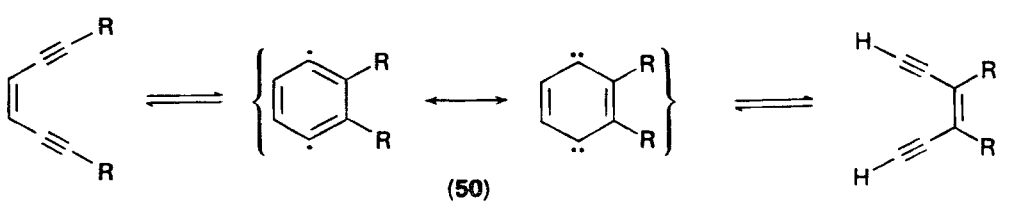
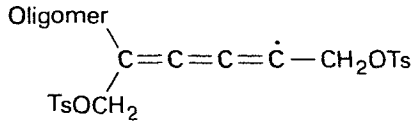


(50)

ate in the thermal rearrangement of 3-hexen-1,5-diynes[153]. That it is a true intermediate, and not a transition state, was demonstrated by trapping experiments in which **50** reacted with solvent, e.g. by hydrogen abstraction to give benzene. The formation of **50** is simply the intramolecular counterpart of the bimolecular process proposed as the initial step in both the thermal and photopolymerization reactions.

Although X-irradiation of PTS at 77 K at low dosages resulted in the formation of radicals ($S = \frac{1}{2}$), for which structure **51** was proposed[154], later studies have shown that



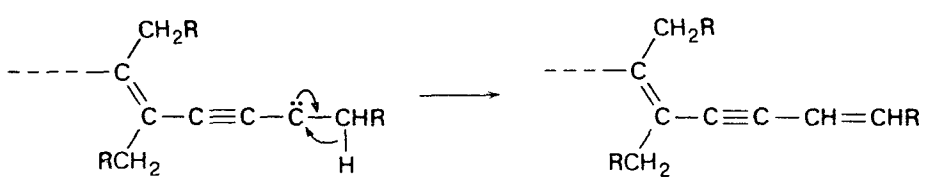
(51)

triplet diradicals are the principal intermediates along with a small concentration of $S = \frac{1}{2}$ radicals when TCDU is treated similarly[155]. The dimer diradical **46** was proposed as the initiator, with chain-growth involving consecutive addition of monomer units to the ends of the diradical.

The photopolymerization of TCDU at 4.2 K has also been studied[21]. Four triplet centres, Q—T, were resolved in the ESR spectrum with D/hc values of 0.2982, 0.2932, 0.2894 and 0.2871 cm^{-1} respectively. Signals appear in succession for Q—T, and when the temperature is raised, they disappear in the same order. Centre Q simply decays at ca. 100 K, but the others initially increase in intensity and then decrease at successively higher temperatures. The total concentration of triplet radicals remains essentially constant up to ca. 200 K where the last centre T begins to decay. Long oligomers with triplet diradical–carbene chain-ends have been proposed as structures for these centres[21]. From the zero-field splitting parameters, it has been deduced that the oligomers contain 7–10 monomer units, i.e. they are somewhat longer than the PTS oligomers F—J formed under the same conditions. The increase in activation energy for each monomer unit added is approximately constant and equal to 2 kcal, probably reflecting increasing crystal strain with increasing chain length.

When BPG crystals are irradiated with UV light at 4.2 K, ESR signals appear which correspond to ground-state triplet carbene diradicals located at the ends of short polymer chains; the hyperfine parameters are $D/hc = 0.2630$ cm^{-1} and $E/hc = -0.0079$ cm^{-1} [156]. In addition, three metastable excited state triplets, which appear only while the sample is being irradiated, have been shown to arise from triplet excitation of the monomer.

c. Termination. There has been only limited speculation concerning the termination step of the polymerization. Alkylcarbenes are known to undergo rapid rearrangement by hydrogen migration to give alkenes[157], and one attractive possibility for the termination step based on this type of rearrangment is illustrated in equation (2).

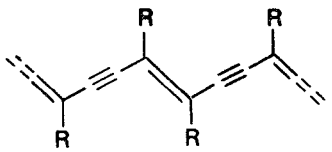


(2)

F. Properties of the Poly(diacetylenes)

1. Structure

As pointed out in Section I.B, the polymers derived from acyclic diynes are found to have repeat distances of 4.9 ± 0.1 Å, with angles of 12–13° between the backbone carbons and the polymer chain direction. The *transoid* conformation **52** has been found in all cases examined; no examples of backbones with the *cisoid* conformation **53** have been established, although it seems likely that it is present in the polymer



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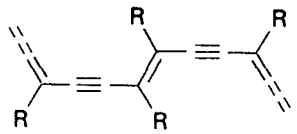
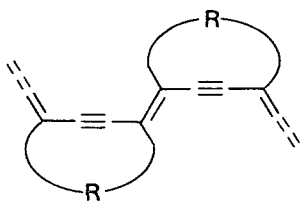


(53)

derived from the bicyclic diyne **32**[139], as illustrated in **54a**. It might be expected that ring-strain would force the poly-BPG backbone into the *cisoid* conformation, **54b**, but X-ray studies have established the customary transoid arrangement with the bridging groups alternating above and below the backbone plane in a spiral-type arrangement as depicted in **55**[25]. In this case, of course, the repeat distance is twice the customary value.



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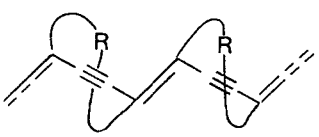
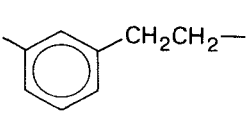
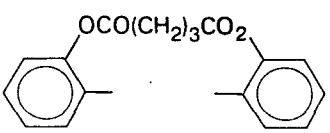
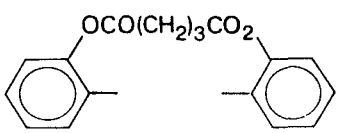


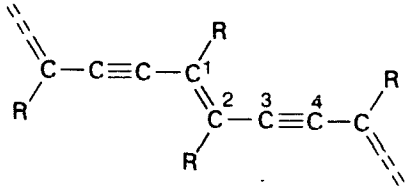
(a) R = 

(55) R = 

(b) R = 

a. Bond lengths. Determination of the bonding scheme in the poly(diacetylene) backbone has been the object of extensive investigations. As mentioned previously, there are two principal contributing structures, **56** and **57**, commonly referred to as the 'acetylene' and 'butatriene' structures. Efforts have been directed toward determination of which of these pairing schemes best represents the backbone structure, and whether or not the structure varies when the side-chain R is varied.

Significant differences in carbon–carbon bond lengths would be expected for the two extremes, **56** and **57**, and experimental determination of bond lengths in poly(diacetylenes) by X-ray diffraction provides the most reliable evidence for bonding



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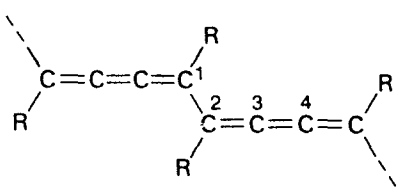


(57)

patterns. The values expected for the limiting structures, as well as experimental values for five polymers are summarized in Table 6. It is seen that the experimental values for poly-PTS, HDU and DCHD are very similar and correspond closely to those expected for structure **56**, but the values for poly-TCDU and poly-BPG are significantly different. In poly-TCDU the 1–2 bond length corresponds to that anticipated for the butatriene structure **57**, while the 2–3 bond falls between the two extremes, and the 3–4 bond is even shorter than expected for the triple-bond length in **56**. In poly-BPG the 3–4 bond corresponds closely to the theoretical value for the butatriene structure, but the other two fall between the extremes.

TABLE 6. Bond lengths in poly(diacetylenes)

	Bond length (Å)						
	Expected for		Found for polymer of				
Bond	**56**[20]	**57**[20]	PTS[158]	HDU[96]	DCHD[159]	TCDU[20]	BPG[84]
1–2	1.34	1.46	1.36	1.36	1.33	1.46	1.42
2–3	1.43	1.32	1.43	1.41	1.44	1.38	1.38
3–4	1.21	1.28	1.21	1.21	1.21	1.17	1.29

These results, along with others obtained from spectroscopic studies summarized below, have been interpreted to mean that the butatriene structure makes a significant contribution[20,84,160–162a]; in fact, some workers have proposed that poly-TCDU is an example of a poly(diacetylene) possessing the butatriene structure, **57**[161,162a]. However, the only part of the side-chain in poly-TCDU, $PhNHCO_2(CH_2)_4$, that would be expected to interact significantly with the π system of the backbone, i.e. the phenylcarbamoyloxy group is insulated from the backbone by a chain of four methylene units. Consequently, there is no reason to expect that electronic interactions with the side-chain would cause the butatriene structure to become more stable than the acetylenic structure in this polymer. Instead, there is evidence that hydrogen bonding between the phenylcarbamoyl groups of adjacent side-chain introduces strain in the polymer chain, and this is probably the factor than causes deviation of the bond lengths[53]. It is possible, of course, that the butatriene pairing scheme is the more stable one in the strained chain. The ^{13}C-NMR spectra of solutions of poly-3BCMU and -4BCMU show that the polymer backbone has the acetylenic structure[162b].

In poly-BPG the π system of the backbone is conjugated with the aromatic rings constituting the side-chains, and electronic interactions could conceivably stabilize the butatriene structure. However, there is severe strain in this polymer also[25], and this seems a more likely cause for distortion of the bond lengths.

b. Theoretical calculations. Calculations of the backbone electronic structure of poly(diacetylenes) by a variety of methods, including Hückel and extended Hückel[163–167] and SCF[168–175] indicate the acetylenic structure **56** to be more stable

than the butatriene structure. The energy difference between the two structures has been calculated as 11[174] and 16.6 kcal mol^{-1} [167]. Interestingly, the orbital correlation diagram indicates the polymerization of diacetylenes to be thermally forbidden and photochemically allowed[167].

Poly(diacetylenes) have been classified into two groups on the basis of the lowest energy transition in their optical spectra: the band appears in the range 15,000–16,000 cm^{-1} in one group and at 18,000–19,000 cm^{-1} in the second. Poly-PTS and poly-DCHD are typical examples of the first group while poly-TCDU and poly-ETCD fall in the second category. The absorption involves excitation of the backbone π system, and it has been assumed that absorption in the low-energy range is characteristic of polymers with an acetylenic backbone, whereas the higher energy transition corresponds to a butatriene skeleton[60,161,162,176]. However, all theoretical calculations indicate that the polymer with the butatriene backbone should exhibit the *higher* energy transition. In line with the discussion above, it seems likely that the differences in absorption spectra are the result of strain on the backbone rather than a fundamental difference in electronic structure[45,53a,134]. This is discussed more fully in Section I.F.3.

2. *Photoelectron spectroscopy*

The highest valence band in poly(diacetylenes) derives from the backbone π electrons and has an ionization potential of ca. 6–7 eV[177–180]. This value can be compared with the theoretical values calculated by a variety of methods which are summarized in Table 7. The best agreement is with the $SCFX_\alpha$ calculation. The width of this π band is estimated to be about 5 eV for poly-PTS, indicating that the discrete highest filled π states of the monomer are replaced by a wide π band in the polymer as is to be expected when a conjugated carbon skeleton of effectively infinite length is formed[179].

Unfortunately, the information which can be derived from photoelectron spectra regarding deeper valence bands of the backbone is meagre because the energy range of interest is dominated by spectral features originating in the side-groups[179,180]. This is particularly true for poly-PTS and poly-DDU[180]. The spectrum of poly(2,4-hexadiyne-1,6-diol), HD, in which less side-group interference might be expected, is, unfortunately, relatively free of structure[180]. One common low-lying peak at ca 17.5 eV is observed in the spectra of poly-PTS, poly-DDU and poly-HD, and is attributed to a backbone σ orbital.

Stevens, Bloor and Williams report that the width of the valence band in poly-DDU, poly-PTS and poly-HD is 17.5, 16.9 and 17.5 eV, respectively[180]. Comparison with values derived from theoretical calculations given in Table 7 shows that again the best agreement is with the $SCFX_\alpha$ calculated value[180]. It should be noted, however, that Knecht and Bässler have reported a deep-lying σ state, binding energy 42 eV, for poly-PTS which implies a much greater total valence band-width than obtained in any of the calculations[179].

TABLE 7. Calculated ionization potentials and valence band-widths for poly(diacetylenes)

Calculation method	Ionization potential (eV)	Valence band-width	References
$SCFX_\alpha$	6.8	15.8	169
Extended Hückel	10.8	19	164
Extended Hückel[a]	11.9	16.8	173
Ab initio	10	24	172

[a]Calculated for polymer with CH_2OH side-chain.

3. *Electronic spectroscopy*

Poly(diacetylene) crystals exhibit an intense electronic transition around 17,000 cm^{-1}, the 2 eV band, which is responsible for the deep colours of the crystals. The locations of the maxima for several polymers are presented in Table 8. The transition involves excitation of the π system of the backbone and is strongly polarized in the chain direction. As a consequence, the crystals are strongly dichroic and birefringent, Light polarized in the chain direction is very strongly absorbed while the spectrum for light polarized in a perpendicular direction is either without structure in the 2 eV region, e.g. poly-TCDU[161], or very weak as in poly-PTS[181]

Because of the very large absorption coefficients for light polarized in the chain direction, typically greater than 10^5 cm^{-1}, it is very difficult to prepare crystalline samples thin enough for transmission spectroscopy. It is possible to obtain absorption spectra from reflectance measurements, but this involves a Kramers–Kronig transformation of the data, which is tedious and introduces approximations[93,116,184].

With poly-4BCMU the absorption spectrum by transmission can be measured by using thin polymer crystals and light polarized perpendicular to the chain direction[183a]. Absorption occurs in this case because the transition moment does not coincide exactly with the chain direction. The peak absorption coefficient, $k_\perp$, is ca. 1000 cm^{-1}, and form the dichroic ratio, $k_\parallel/k_\perp = 200$, measured on partially polymerized samples, it is estimated that the absorption coefficient in the chain direction is 2×10^5 cm^{-1} [183a].

Polymer absorption spectra can be measured in thin sections of monomer crystals containing very small concentrations of polymer chains[115a]. Because the polymer absorbs at much longer wavelengths than the monomer, it is possible to measure the polymer spectrum without interference from monomer absorption. However, strain on the polymer chains in the partially polymerized crystal may cause distortion of the spectrum from that observed for the fully polymerized material[115a]. The presence of polymer with substantially shorter chains in the early stages of polymerization in some cases may also lead to spectra substantially different from that of the final polymer[121,122]. The colour of partially polymerized diacetylene crystals can be correlated with the number of methylene groups in the side chain[183b].

The 2 eV electronic transition is accompanied by progressions of weaker side-bands on the high-frequency side. Comparison with Raman spectra shows that the shifts in

TABLE 8. Absorption maxima in the electronic spectra of crystalline poly(diacetylenes)

Polymer	E_0 (cm^{-1})[a]	References
Poly-PTS	16,200[b]	182
Poly-DDU	15,800	53a
Poly-3BCMU	15,700	183a
Poly-ETCD	15,750; 18,500 (120°C)	59
Poly-4BCMU	15,800; 18,900 (110°C)	183a
Poly-IPUDO	15,750; 18,500 (116°C)	60
Poly-TCDU	15,500; 18,800[c]	160, 162a

[a]Some polymers undergo phase transitions which lead to large shifts in absorption maxima. In these cases, the value below the transition temperature is cited first, followed by the value above, and the transition temperature given in parentheses.

[b]Poly-PTS undergoes a phase transition at ca. −100°C but no sharp change in absorption maximum occurs. Instead, the absorption is split into two components below this temperature (see text).

[c]Sluggish and incomplete phase transition occurs below −170°C[160]. Complete conversion can be accomplished under pressure[162a].

these side-bands correspond to vibrational modes of the polymer backbone[182]. The vibrational structure is greatly enhanced for crystals with maximum absorption in the 15,000–16,000 cm^{-1} range compared to those with maxima in the 18,000–19,000 cm^{-1} range[176].

The question of whether the 2 eV transition is a band-to-band or an excitonic transition is considered in Section I.F.5.

a. Conformational and side-group packing effects. (i) Low-temperature splitting of poly-PTS bands. The absorption maximum for poly-PTS which appears at 16,200 cm^{-1} in the room-temperature spectrum shifts toward the red and splits into two bands at low temperatures[182]. The splitting, which is first detectable at ca. 200 K and is observed with both fully and partially polymerized crystals, increases as the temperature is lowered and amounts to 260 cm^{-1} at 4 K for fully, and 500 cm^{-1} for partially polymerized crystals[182,185–189]. The piezo-modulated reflectance spectrum indicates that weak splitting persists even at 300 K, but it is not detected in ordinary reflection spectra because of thermal broadening of the bands[188]. Studies of the effect of pressure on the splitting, however, indicate that the weak splitting at 300 K has a different origin than the low-temperature splitting[106].

A number of explanations were proposed originally to account for the low-temperature splitting[189,190,191], but the actual cause was not identified until X-ray studies revealed the occurrence of a second-order phase transition at ca. 200 K in both polymer and monomer crystals[15,110,192–194]. The phase change for the polymer is caused by a change in conformation of the side-groups belonging to polymer chains situated on every second (102) cleavage plane. This leads to a doubling of the unit cell in the *a* direction, and the presence in the unit cell of two pairs of nonequivalent chains. The presence of these two kinds of chains is believed to be responsible for the splitting in the polymer crystal, even though careful X-ray studies have failed to reveal any structural differences between the backbones of the two types of polymer chains[186]. The transition, which occurs over a wide temperature range, is complex, and spectroscopic studies indicate that it has some two-dimensional character[186].

The monomer crystal also undergoes the same type of phase transition around 200 K as the polymer[110,193,194], and this is believed responsible for the splitting in monomer crystals containing small concentrations of polymer[187,195].

Studies of the low-temperature spectra of other poly(diacetylenes) have failed to reveal similar splittings[48].

(ii) Solvent—nonsolvent-induced changes. Polymers with alkoxycarbonylmethylcarbamate side-chains, $ROCOCH_2NH(CH_2)_m$, have provided a key link in our understanding of the poly(diacetylenes)[54,55,196]. These polymers are quite soluble in polar solvents such as chloroform, THF and DMF in spite of their high molecular weights, e.g. 1000–2000 repeat units. The high solubility in chloroform is attributed to long flexible side-chains and the presence of the ester and urethane functions, for which chloroform shows a special affinity[4,57]. Dissolving, then, is a consequence of solvation of the side-chains. The discussion that follows will be concerned with chloroform solutions unless specified otherwise.

Solutions of 4BCMU and 3BCMU are yellow with absorption maxima occurring at ca. 21,500 cm^{-1}, substantially blue-shifted from the maxima at ca. 16,000 cm^{-1} (Table 8) observed for the crystals at room temperature[53]. Conjugation length, l_c, the length of polymer backbone over which planarity is maintained without interruption, and not the polymer chain length itself, determines the location of absorption maxima. Rotation by 90° about a 'single' bond in the polymer backbone interrupts the conjugation and determines the end of a conjugation length. It is estimated that the rotation is endothermic but this is more than compensated for by the increased entropy of the side-chain, and by the increased solvation of the side-chains made possible by the rotation[4,196]. From the location of the absorption maxima, it is estimated that the

average conjugation lengths in poly-3BCMU and poly-4BCMU yellow solutions are 6–7 repeat units. There is probably a statistical distribution of 90° rotations about the single bonds along the backbone. Absorption maxima of ca. 16,000 cm^{-1} for the crystalline polymers corresponds to an effectively infinite conjugation length[4].

Dramatic colour changes occur when a polymer 'nonsolvent' which is miscible with chloroform is added to solutions of poly-ACMUs in chloroform, e.g. solutions of poly-3BCMU turn blue and those of poly-4BCMU turn red when hexane is added until the mole fraction of chloroform, X_c, in the solvent is reduced to ca. 0.7 and 0.5, respectively[4,55,196]. Additional hexane leads to precipitation of polymer, but the original solutions are true solutions. The colour changes are sharp, are independent of polymer concentration, and therefore are purely single-chain phenomena. They are attributed to conformational changes resulting in a planar chain, with large increases in conjugation length. For solutions of poly-3BCMU, addition of hexane shifts the absorption maximum to 15,900 cm^{-1}, a value corresponding to an effectively infinite conjugation length, and it is believed that the actual conjugation length is at least 30 repeat units.

The ordering of the polymer chains in the blue solutions is the result of *intramolecular* hydrogen bonding between the carbamate functionalities of adjacent side-chains, as illustrated in Figure 2. Infrared spectroscopic studies summarized in Table 9 pro-

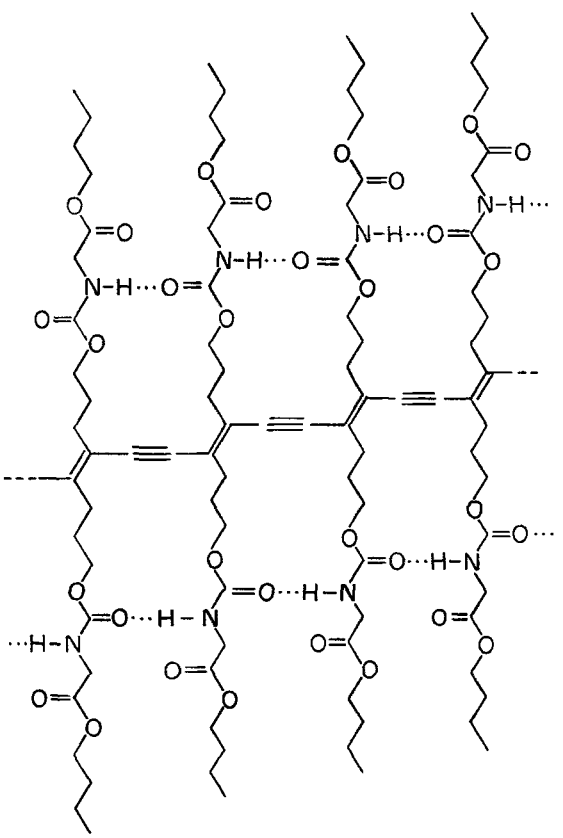


FIGURE 2. Segment of poly-3BCMU chain in the planar conformation, illustrating the hydrogen bonding between carbamate functions on adjacent side-chains.

TABLE 9. Infrared absorptions for 3BCMU and poly-3BCMU solutions[4]

	E_0 (cm^{-1})		
	3BCMU	Poly-3BCMU	
	$X_c = 1$	Yellow soln., $X_c = 1$	Blue soln., $X_c = 0.66$
ν_1 (ester C=O)	1745	1750	1750
ν_2 (urethane C=O)	1725	1715	1695
ν_3 (amide II)	1520	1530	1545
ν_4 (N—H str.)	3445	3340, 3445	3320

vide support for this interpretation[4]. Pertinent bands for the monomer, given in the second column, correspond well with the free, nonhydrogen-bonded values, and are virtually unaffected by X_c variations. The ester carbonyl frequency, ν_1, is virtually unchanged in the polymer, and does not change with solvent composition, thus demonstrating that the ester function does not participate in hydrogen bonding. The values for the carbamate absorptions, however, show that this function is involved in hydrogen bonding to varying extents, dependent on solvent composition. The locations and shapes of the band for the blue solution, as well as the enhanced intensity of ν_4, correspond to a strongly hydrogen-bonded structure, e.g. as in Figure 2. It is estimated that the hydrogen bonds contribute 14–20 kcal mol^{-1} toward the stablilization of the planar structure. On the other hand, the spectrum of the the yellow solution shows the presence of both free and hydrogen-bonded functions. From the intensities of the two N—H absorptions, it is estimated that one out of four N—H groups is not involved in hydrogen bonding. This suggests an average conjugation length of ca. 4 repeat units for the polymer in the yellow solution, in reasonable agreement with the value of 6–7 repeat units deduced from the optical spectra[4].

When a nonsolvent is added to a solution of a *flexible* polymer, the molecular coil contracts, and the reduced viscosity decreases with increasing amounts of non-solvent. With solutions of poly-3BCMU, however, there is no change in reduced viscosity upon addition of a nonsolvent, signifying that the extended-chain conformation present in the blue solutions is present in the yellow solutions as well[57].

Addition of very small amounts of trifluoroacetic acid ($X_{TFA} = 0.005$), a very powerful hydrogen-bonding donor, to a blue solution of poly-3BCMU or a red solution of poly-4BCMU converts it completely to the yellow solution[4]. This provides a dramatic demonstration of the role of hydrogen bonding in the conformational transitions of these polymers. The FTIR spectra of the solutions show that the dominant interaction of trifluoroacetic acid involves hydrogen bonding with the carbonyl groups of the ester and urethane functions.

It has been found that solutions of poly(diacetylenes) with simple carbamate functions in the side-chain, e.g. poly-DDU and poly-TCDU, show the same kind of chromic behaviour as poly-3- and 4-BCMU[53a]. These polymers are slightly soluble in DMF, and solutions with concentrations in the range of 10^{-1} mol l^{-1} can be prepared. (In describing polymer concentrations, the term mole refers to moles of repeat units.) It is likely that the soluble polymers are at the low end of the molecular-weight range. The solutions are yellow, with an absorption maximum at 21,100 cm^{-1}. Upon the adition of a nonsolvent (chloroform or methanol) the maximum shifts to 17,100 cm^{-1} for poly-DDU and 19,400 cm^{-1} for poly-TCDU, and it is clear that the planar–nonplanar transition also occurs with these polymers.

(iii) Effect of pH and electrolyte concentration. Poly(diacetylenes) with carboxylate groups in the side-chain, as in **58–61**, are quite soluble in water, and their aqueous

$KO_2CCH_2NHCO_2(CH_2)_nC{\equiv}C{-}C{\equiv}C(CH_2)_nOCONHCH_2CO_2K$ $KO_2C(CH_2)_mC{\equiv}C{-}C{\equiv}C(CH_2)_mCO_2K$

(58) $n = 3$ **(60)** $m = 2$

(59) $n = 4$ **(61)** $m = 3$

solutions undergo visual conformational transitions which are analogous to the helix–coil transformation of polypeptides[97,98]. The nonplanar–planar (or twisted) conformational transitions are of the same type as described above for poly-3BCMU and -4BCMU, and are effected for the aqueous solutions by varying the pH or electrolyte concentration.

Solutions of **58** are yellow, and remain yellow at pH > 7. When the pH is lowered below 7, however, the colour changes abruptly to red, and then gradually to deep purple at pH ≅ 2. Precipitation of polymer as a blue-black solid occurs if the pH is lowered below 2. The absorption maximum shifts from 21,600 cm^{-1} at pH = 9.5 to 18,700 cm^{-1} at pH = 3, with an additional peak at 17,400 cm^{-1} also appearing in the low-pH range. When KCl, NaCl or LiCl is added to a solution of **58** with pH = 9.9, a new absorption band appears at 19,400 cm^{-1} and the solution turns red.

At high pH values the carboxyl groups will exist entirely as carboxylate ions, $-COO^-$, and electrostatic repulsion between these charged groups prevents close approach of the side-chains and hence forces the polymer backbone into the nonplanar conformation[97]. As the pH is lowered, the charged groups are progressively converted to uncharged carboxyl groups, facilitating the transition to the planar conformation. Reduction of intergroup repulsion through ion pairing is believed responsible for the analogous conformational change that occurs when the concentration of electrolyte is increased.

(iv) Abrupt dissolution. In contrast to the 'good' solvents for the poly-nACMUs, there is another group of 'poor' solvents, including xylene, *o*-dichlorobenzene, methyl ethyl ketone, ethyl acetate and acetic acid, in which the polymers are completely insoluble at room temperature, but dissolve almost instantaneously at higher temperatures[197]. Dissolution occurs abruptly over a narrow temperature range (ca. 3°C), and is accompanied by a colour change. This is believed to be the first report of a dramatic increase in the solvent power of liquids on varying the temperature. For example, when poly-4BCMU is heated in *o*-dichlorobenzene, a metallic-to-red transition occurs at 49°C, and red fibrous particles are formed. If this mixture is stirred, and heated slowly between 49 and 55°C over a period of half an hour, a red solution is formed, but if it is heated rapidly, a yellow solution arises abruptly (<½ min) at 58°C, accompanied by a dramatic increase in viscosity. The temperature at which the thermochromic transitions occur is dependent on the polymer and the solvent. The heat of dissolution of poly-4BCMU in *o*-dichlorobenzene, measured by differential scanning calorimetry, is 8.4 kcal mol^{-1} [197].

It is proposed that the metallic-to-red transition is due to intermolecular dissolution in which the solvent diffuses into the polymer crystal[197]. The red-to-yellow transition involves intramolecular dissolution of the individual polymer chains in which the intramolecular hydrogen bonds are broken. Breaking of the intramolecular hydrogen bonds is believed to be a cooperative process, i.e. once the planarity of the backbone is interrupted by the breaking of a few hydrogen bonds due to solvent–side-chain interactions, the whole molecule becomes nonplanar very rapidly by a sequential breaking of the adjacent hydrogen bonds.

(v) Effects of strain. The shift in the absorption maximum during the polymerization of PTS, attributed in part to strain caused by lattice mismatch, as well as the shifts produced by applying mechanical stress to poly-PTS crystals has been described in

Section I.E.1. Shifts in absorption maxima may also result from interactions between side-chain groups which, in turn, introduce strain on the backbone. It is these interactions that will be considered in this section.

For polymers containing a carbamate function in the side-chain, $RNHCO_2(CH_2)_m^-$, the value of m seems to be the major factor in determining side-chain interactions, and the nature of R has little effect[4]. For those with $m = 3$, models indicate that the optimal arrangement for hydrogen bonding between adjacent chains can be achieved without the introduction of strain, in agreement with the results found for poly-3BCMU. For $m = 4$ on the other hand, the formation of hydrogen bonds requires distortion of the tetramethylene chain, as well as possible distortion of the polymer backbone itself[4]. This is the factor believed to be responsible for the differences in the optical properties of solutions of poly-3- and 4-BCMU in their planar form. Maximum absorption for the planar form of poly-3BCMU is at 15,900 cm^{-1}, corresponding to an effectively infinite conjugation length, whereas it is at 18,900 cm^{-1} for poly-4BCMU, corresponding to a conjugation length of ca. 15 repeat units. The shortened planar segments are probably a consequence of the strain involved in forming the hydrogen bonds required to maintain the planar conformation.

In poly-TCDU the carbamate function is also separated from the polymer backbone by a four-carbon chain, and in line with the ideas presented above, it is not surprising to find that visible and Raman spectra for poly-TCDU crystals and solutions of poly-4BCMU in the planar form are virtually identical[4]. Furthermore, X-ray diffraction spectra of poly-TCDU clearly show the intramolecular hydrogen bonding between the urethane groups, and gross distortions in the tetramethylene chain.

The initial polymer formed by UV irradiation of multilayer assemblies of 10,12-pentacosadiynoic acid and related compounds is blue, with absorption maxima at ca. 15,700 and 17,000 cm^{-1} [64a,65,66,99]. A change to red-coloured polymer, with absorption maxima at ca. 18,700 and 20,000 cm^{-1}, occurs when the samples are irradiated for longer periods or are heated at 90°C. Changes in backbone strain, brought about by changes in side-group packing, are believed to be responsible for the spectral shift[53a].

Large spectral shifts are frequently observed when monomer is removed from partially polymerized samples by extraction with a suitable solvent. With the initial blue polymer of 10,12-pentacosadiynoic acid described above, for example, removal of monomer leads to an immediate colour change to red with concomitant shift in absorption maxima to 18,700 and 20,000 cm^{-1} [66]. Similar behaviour is observed for the blue phase of the polymer derived from the bis(*m*-tolylcarbamate) of 2,4-hexadiyne-1,6-diol[2]. The shifts are believed to be due to the release of strain from the backbone, as well as some twisting made possible by removal of the monomer matrix.

(vi) Thermochromism. Many poly(diacetylenes) exhibit thermochromic properties, and the factors responsible are the same as those responsible for the spectral shifts which have been described in the preceding sections, i.e. planar–nonplanar transitions, backbone strain and the interplay of inter- and intra-molecular hydrogen bonding.

When yellow solutions of poly-3- or 4-BCMU in *o*-dichlorobenzene at 115–120°C with polymer concentrations less than 0.1% are cooled to room temperature, deeply coloured, viscous solutions are formed[198]. The poly-3BCMU solutions are blue, with maximum absorption at 15,750 cm^{-1}, and the poly-4BCMU solutions are red, with maximum absorption at 18,350 cm^{-1}. Plots of the poly-3-BCMU spectra measured at various temperatures show the presence of an isosbestic point. FTIR spectra of the blue and red solutions show ester and carbamate frequencies that are virtually identical with those given in Table 9 for solutions of poly-3BCMU in chloroform-hexane, and correspond to hydrogen-bonded carbamate frequencies. Spectra of the high-temperature yellow solutions show free N—H and free C=O bands, and correspond to those for poly-3BCMU in pure chloroform. Thus, the thermal behaviour of these

solutions can also be accounted for in terms of planar–nonplanar transitions. The presence of an isosbestic point both with varying temperature as well as with varying solvent–nonsolvent ratios, means that the planar and nonplanar forms exist in equilibrium with each other[198].

When hot *o*-dichlorobenzene solutions containing more than 0.1% poly-3- or 4-BMCU are cooled, brightly coloured blue or red gels form[198]. The process is reversible, and the gels redissolve with heating. The gels are amorphous by X-ray studies, and are interchain complexes associated at widely separated points. Differential scanning calorimetry shows endothermic transitions when the gels are heated. These transitions are attributed to the breaking of intramolecular hydrogen bonds, and the enthalpy change for the planar–nonplanar transition is found to be ca. 7 kcal mol^{-1} of repeat units. From this it is concluded that all of the intramolecular hydrogen bonds are broken in the transition to the yellow, nonplanar form[198].

Films of poly-3 and 4-BCMU are formed by slow evaporation of chloroform solutions[183a]. Poly-3BCMU films are blue, and poly-4BCMU films are red, signifying the presence of planar forms. At room temperature, poly-3BCMU films show maximum absorption at 15,800 cm^{-1}, and poly-4BCMU films at 18,700 cm^{-1}, values which correspond closely to those of solutions of the planar forms. When the temperature is raised the films turn yellow and the absorption maxima shift to 21,000 cm^{-1} and 22,000 cm^{-1} respectively. Changes in the FTIR spectra of the films with increasing temperature correspond to a change from a hydrogen-bonded to a free structure, in a manner totally analogous to the solution behaviour[183a].

Crystals of many poly(diacetylenes), particularly those with a carbamate function separated from the polymer backbone by a four-carbon chain, undergo thermochromic phase transitions[54,59,60,152,160,162,183a,199,200]. Most of these exhibit maxima in the 15,000–16,000 cm^{-1} range below the transition temperature, and the crystals have a reddish-gold colour. (see Table 8). Above the transition temperature the maxima shift to 18,000–19,000 cm^{-1}, and the crystals take on a greenish metallic sheen.

The degree of reversibility of the transition varies from one polymer to another. For example, when a poly-IPUDO crystal is cooled from the transition temperature to 25°C, the spectrum resembles closely the original room-temperature spectrum[61]. On the other hand, when a poly-TCDU crystal is cooled to 77 K, some parts of the crystal show a golden lustre, while others continue to exhibit the original green metallic sheen, and these same domains continue to coexist in the crystal after it is warmed back to room temperature[162].

Some workers have proposed that the thermochromic transition involves a change from the acetylenic backbone structure at lower temperatures to the butatriene structure at higher temperatures[61,160,162]. However, there is mounting experimental evidence that the thermochromism is a consequence of backbone distortion caused by changes in side-group packing on going from the low-temperature phase (I) to the high-temperature phase (II)[53a,54,147,183a,199,200]. Hydrogen bonding plays a major role in the side-chain interactions. The optical properties of phase II correspond closely to those of polymer films and solutions (planar form) in which the chains are reasonably free of intermolecular constraints. It follows, then, that phase I is stabilized by intermolecular effects on side-chain packing, and intermolecular hydrogen bonding is likely to be a major factor here. On this basis, it has been proposed that thermochromism involves a change from inter- to intra-molecular hydrogen bonding[53a]. If, as seems likely, intramolecular hydrogen bonding is retained in phase I, it is suggested that either the geometry of the hydrogen bonding is altered from the near optimal arrangement of phase II, or the strain caused by the hydrogen bonding is taken up by other bonds in the side-group and is not transmitted to the backbone.

When crystalline poly-3BCMU is heated it undergoes two thermochromic transitions, metallic to red and red to yellow, and differential scanning calorimetry shows corresponding endotherms at 420 and 450 K[199,200]. The low-temperature endotherm and the corresponding metallic-to-red colour change are not observed in the amorphous polymer, and this transition is attributed to intermolecular melting. Intramolecular hydrogen bonds still persist, and maintain one-dimensional order in the polymer. The endotherm at 450 K corresponds to rupture of the intramolecular hydrogen bonds. This interpretation is supported by FTIR studies[199].

Monomeric DCHD crystals, but not the fully converted polymer, undergo a phase transition at 142 K which has been described in Section I.E.1[22,111]. When monomer crystals containing a small concentration of polymer are cooled through the transition temperature, the colour of the polymer changes reversibly from blue to red, and the absorption maximum shifts from 15,100 to 18,640 cm^{-1} [111]. This is the largest shift yet observed for a poly(diacetylene) and it is opposite in sense from those described above for polymers with urethane functions in the side-groups. Relatively small shifts in the backbone stretching frequencies are noted in the Raman spectrum, in spite of the large change in lattice parameters, showing that the major change must be in bond angles. The large change in the absorption frequency is attributed to the deformation of the polymer structure at the phase transition[111].

b. Optical nonlinearities. Two-photon absorption. Crystalline poly-PTS and poly-TCDU exhibit very large values for the third-order susceptibility which are comparable to those of inorganic semiconductors[201,202]. This behaviour can be attributed to the one-dimensional electron delocalization along the conjugated backbone of the polymer[203]. Third-order mixing in solutions of poly-4BCMU has also been observed[204,205].

The large third-order susceptibility of poly(diacetylene) crystals coupled with their stability at high optical intensities, up to 50 CW/cm^2 with picosecond pulses, suggest that they might find important applications in devices such as parametric amplifiers, ultrafast light shutters and optical pulse sharpeners[201,206]. However, the usefulness of the polymers in these applications has been found to be limited by a strong two-photon absorption[202,207]. The two-photon process was ascribed initially to the presence of defects in the crystals[202,207], but later workers have shown that strong two-photon absorption is a fundamental property of the poly(diacetylene) backbone[204,205]. The energy and band-width, as well as symmetry assignment and oscillator strength for the two-photon transition in solutions of poly-4BCMU have been determined[205].

4. Vibrational spectroscopy

Infrared spectra of poly(diacetylenes) are complex and are generally dominated by side-group vibrations[90,131]. The use of IR spectroscopy for studying side-group interactions involving hydrogen bonding has been described in Section I.F.3.a. Near-IR spectroscopy has provided useful information about strain in partially polymerized PTS crystals[131], and far-IR spectroscopy has been used for studying the low-temperature phase transitions of PTS and poly-PTS[186,208].

Resonant Raman spectroscopy provides the capability of studying the backbone vibrations of poly(diacetylenes) without significant interference from side-group vibrations, and consequently it has proved to be a powerful tool for studying these polymers[116]. Resonant Raman scattering occurs when the frequency of the exciting radiation is close to that of the $\pi \rightarrow \pi^*$ transition of the conjugated chain, and the Raman spectrum is dominated by those vibrations that couple strongly with the electronic states of the backbone. The great majority of the normal modes of the

TABLE 10. Higher frequency Raman lines for poly(diacetylenes)

Polymer[a]	Raman lines (cm^{-1}) 1	2	Others	References
Poly-PTS	2086	1485	1203, 953	113, 116
Poly-PMBS	2084	1482	1202, 954	112
Poly-HHD[b]	2120	1518	1262, 1198, 963, 937	211
Poly-DUDD	2072	1460	1345, 1215, 1050, 700	116
Poly-DADD[b]	2098	1450	1398, 1287, 1199, 1050	211
Poly-DDEU	2078	1458	[c]	160
Poly-HDU	2110	1504	[c]	39
Poly-TCDU, phase II[d]	2088	1488	1216	160
Poly-TCDU, phase I[d]	2077	1444	1204	160
Poly-DCHD, phase II[b,d]	2124	1470	1243, 672	111
Poly-DCHD, phase I[b,d]	2144	1508	1248, 982	111

[a]Values are for completely polymerized samples unless noted otherwise.
[b]Spectra measured on monomer crystals containing a few percent polymer.
[c]No values reported.
[d]Phase I and phase II refer to low- and high-temperature phases, respectively.

polymer are associated with side-group motions which interact only weakly with the backbone electrons. Consequently, the resonant Raman spectra are much simpler than nonresonant spectra, and contain from four to ten intense lines between 600 and 2200 cm^{-1} [91,116,152,209,210]. The applications of resonant Raman spectroscopy to poly(diacetylenes) have been reviewed[116].

Raman lines that have been reported for a selection of representative poly(diacetylenes) are presented in Table 10. The two highest frequency vibrations, ν_1 and ν_2, corresponding to triple-bond and double-bond stretching modes respectively, are the fingerprint frequencies for these polymers[116], and are listed separately from the others in the second and third columns. While ν_1 and ν_2 are reasonably independent of the side-chain, the lower frequencies, which involve side-group motions to a greater extent, show greater dependence on the nature of the side-group[211]. The calculated frequencies based on a model with simple point masses and harmonic force constants are in excellent agreement with those observed experimentally for four poly(diacetylenes) with greatly different side-chains[211].

For a series of 19 different poly(diacetylenes), ν_1 was found to range between 2067 and 2133 cm^{-1}, with an average value of 2108 cm^{-1}; similarly, ν_2 fell in the range 1455–1533 cm^{-1}, with an average value of 1501 cm^{-1} [39]. A linear correlation was found between ν_2 and ν_1, and this was cited as evidence for significant contribution from the butatriene backbone structure.

Raman spectra do not provide an unequivocal answer to the question of the extent of butatriene contribution. Poly-PTS is recognised from X-ray data to have a predominantly acetylenic backbone, and if the values of ν_1 and ν_2 for poly-PTS are characteristic of the acetylenic backbone, then it would seem that the majority of the other polymers in Table 10 possess essentially the same type of backbone. For a series of crystalline, monomeric tetraarylbutatrienes, $Ar^1Ar^2C{=}C{=}C{=}CAr^3Ar^4$, Raman lines appear at 2030, 1580 and 1220 cm^{-1} [160], and it is seen that only small differences exist between butatriene and 'acetylenic' frequencies.

Different frequencies are observed for poly-TCDU in the low- and high-temperature phases. Originally these were attributed to an acetylenic backbone for the polymer in the low- and a butatriene structure in the high-temperature phase[160], but it

is likely that the different frequencies result from differences in side-group interactions as described in Section I.F.3.a.

The absorption spectrum of poly-ETCD contains three broad bands at 15,900, 18,500 and 21,700 cm^{-1}, and this has been interpreted in terms of a distribution of conjugation lengths, peaked at the three lengths corresponding to these excitation frequencies[152]. The resonant Raman lines of the polymer vary somewhat in location and intensity when the excitation wave-length is changed. It has been proposed that these changes correspond to excitation of polymer with different average conjugation lengths. This polymer undergoes a thermochromic phase transition, green to red, at ca. 135°C, and the changes observed in the Raman spectrum of the high-temperature phase are interpreted to mean a difference in the distribution of the polymer chains in the three conjugation length domains[152].

Small shifts are observed in the Raman lines of poly-DCHD present in low concentration in monomer crystals when the monomer undergoes a phase transition at 142 K, as shown in Table 10, and these shifts are also attributed to changes in strain on the polymer brought about by the phase change[111].

The Raman frequencies of several poly(diacetylenes) shift when tensile stress is applied to the polymer crystal, and this forms the basis of a method described recently for obtaining frequency-modulated visible light[212,213]. In the method a periodic stress is applied to a poly(diacetylene) fibre, e.g. poly-HDU, and the frequency of the Raman light scattered from the fibre is modulated at the frequency of the applied stress. The method promises to have applications in information transfer systems.

5. *Electrical properties*

The distinct metallic lustre of poly(diacetylene) crystals might lead to the naive expectation that they will exhibit high electrical conductivity. Such is far from their actual behaviour. They are insulators, or at best, wide gap semiconductors. It has been pointed out that all it takes to reconcile metallic lustre with low electrical conductivity is the presence of a strong absorption band in the visible range in which the excited electrons are not very mobile, e.g. an exciton band[214].

a. Conductivity. Careful studies with poly-PTS have given dark-conductivity values of 2.2×10^{-11} ohm^{-1} m^{-1} in the chain direction and 2.4×10^{-14} and 1.3×10^{-14} ohm^{-1} m^{-1} in directions perpendicular to the chain[101,192]. Thus the charge carrier mobility along the polymer chain is 10^3 times that perpendicular to the chain. The ohmic conductivity for the samples studied was caused by impurities creating a carrier concentration of ca. 3×10^{16} m^{-3}, which corresponds to one carrier per 30 m on a single chain! Others have also concluded that the dark conductivity of poly-PTS must be attributed to impurities, and they estimate that the true intrinsic dark conductivity of the polymer should be around 10^{-15} ohm^{-1} m^{-1} at 300 K[215].

From the temperature dependence of conductivity it was deduced that a level exists 0.8 eV below the band edge (ca. 2.4 eV) which dominates the current by containing most of the carriers, and which is present at a concentration of ca. 10^{17} m^{-1}. The level can be due either to an impurity or a chain-end[216].

It has been concluded from these results that poly-PTS can be classified as a one-dimensional semiconductor which can be obtained with a purity and electronic perfection comparable to conventional inorganic semiconductors[216].

b. Photoconductivity. Poly(diacetylenes) exhibit photoconductivity, and numerous studies have been devoted to attempts to unravel the details of charge-carrier generation and the mechanism of charge transport. Some early workers suggested that the intense 2 eV absorption of these polymers represented a valence band-to-conduction band transition, and hence the onset of photoconduction[163,217]. From an

analysis of the line-shapes for poly-PTS and poly-BPG, for example, it was concluded that the transition is a band-to-band transition of a one-dimensional semiconductor[217]. Others proposed, however, that the transition is a more localized, excitonic type transition, i.e. one in which bound electron-hole pairs are created, and which is not a conducting state. Excitation to a conducting state requires higher energy radiation. Subsequent experiments have confirmed that the transition is excitonic, and some of the pertinent evidence is summarized here.

The profusion of vibrational side-bands in the electronic transition, and resonant Raman scattering, as observed with these polymers, are normally observed with excitonic rather than band transitions[182]. The distinction is not clear-cut, however, since valence and conduction bands in organic crystals can also be subject to vibronic splitting[218].

The photocurrent action spectra of poly(diacetylenes) exhibit a minimum at the main peak of the crystal absorption spectrum, confirming that the dominant crystal transition is photoelectrically inactive and thus cannot be a band gap transition[34,43,161,206,215,219–223].

A transition between valence and conduction bands, constituted by highest filled and lowest vacant π states, does occur, and it is responsible for the photoconductivity that is observed at photon energies above the 2 eV peak[222]. However, the oscillator strength of this transition is much smaller than that of the exciton transition, and it is buried under the accompanying vibronic side-bands. Because of this the determination of the band gap energies for these polymers has proved very difficult, and in spite of the fact that several reports of measured values have appeared, some workers believe that there is not yet a reliable value[43,224]. Values of the band-gap energy determined from photoaction spectra at room temperature include: 17,000 cm^{-1} (2 eV) for poly-PTS; 21,000 cm^{-1} (2.6 eV) for poly-TCDU and 17,700 cm^{-1} (2.2 eV) for poly-DCHD[222]. Comparison of these values with the energies of the optical transitions of these polymers (Table 8) shows that the band-gap lies ca. 1000–2000 cm^{-1} above the excitonic transition. The band-gap for poly-PTS at 2 K, as determined from the electroreflectance spectrum is 19,700 cm^{-1} (2.44 eV)[225].

Part of the difficulty encountered in determining the band-gap for poly(diacetylene) crystals can be overcome by using multilayer assemblies containing only a few layers of polymer molecules[222]. In this manner, the band-gap of poly(10,12-tricosadiynoic acid) was found to be 20,000 cm^{-1} (2.5 eV) for the blue polymer and 21,000 cm^{-1} (2.6 eV) for the red polymer; the corresponding absorption maxima were at 15,600 and 18,700 cm^{-1}.

Studies with poly-PTS show that light polarized in the chain direction is at least ten times more effective in photoionization than light polarized perpendicular to the chain[218]. Similarly, the quantum yield for photoelectric charge generation is higher by a factor of 10^2 when the electric field is parallel to the chain[226]. Charge-carrier mobilities have been measured by several groups[43,218,221,226]. The mobility in the chain direction is 800 times that perpendicular to the chain, further demonstrating the one-dimensional nature of the photoconduction[226,227]. There is disagreement, however, about the magnitude of the mobility along the chain. One group concludes that poly-PTS is a high-mobility semiconductor in which the carriers travel a constant distance on the order of 1 mm in less than 1 μs, independent of the field, before being trapped[221]. Another group concludes that the mobility is near the lower limit for band-like transport, and they classify poly-PTS as a low mobility, band-like semiconductor[43].

It was mentioned above that the dark conductivity of poly-PTS is dominated by a localized energy level 6500 cm^{-1} (0.8 eV) below the band-edge. A steep photoconductive edge is also found at 6500 cm^{-1}, which is in agreement with the existence of such a localized level[43,215].

c. Doping experiments. Treatment of poly(acetylene) films with substances such as AsF_5, iodine or bromine yields materials with high room-temperature electrical conductivity[5]. Attempts to induce similar behaviour in poly(diacetylenes) have not been successful[6]. Upon exposure of a multilayer assembly of the polymer derived from 10,12-pentacosadiynoic acid to iodine vapour, an increase in conductivity occurred which was comparable to that reported for poly(acetylene), but the sample still remained an insulator because the initial resistance of the film ($> 10^{13}$ohm) was so high. The effect was only transient, however, and when the iodine was removed the conductivity dropped to a value only ca. 30 times its initial value.

6. Defect properties

Defects in poly(diacetylene) crystals give rise to shifts in electronic excitation energies and to states in the forbidden gap of the perfect chain[182]. These lead to continuous optical absorption and ESR centres with complex thermal behaviour.

Partially polymerized PTS as single crystals or polycrystals exhibit fluorescence with frequencies significantly higher than the absorption edge of perfect polymer chains[141,228]. Thus, excitation at 4.2 K yields two emission bands at 20,468 and 20,802 cm^{-1}, accompanied by vibrational side-bands. The fluorescence intensity depends on the location of the excitation laser spot on the crystal surface, the strongest emission being observed in polycrystalline samples when the boundaries between crystallites are irradiated. The fluorescence is attributed to localized defects connected to a polymer chain, possibly trapped active chain-ends[141].

Intense laser pulses of picosecond duration induce tailing in the absorption curve of poly-PTS[202]. The tailing has been attributed to defects created by breaks in conjugation.

Possible modes of defect formation in poly(diacetylenes) have been examined[229]. One plausible mode, orbital flipping, involves rotation by 90° of the p orbitals on two adjacent sp^2 carbons so that they become parallel to the in-plane p orbitals of the adjacent sp carbons, and leads to interruption of conjugation in the out-of-plane π system. A comparison of the possible intrinsic conformational defect states has been presented[230].

7. Other properties

The mechanical properties—Young's modulus, ultimate tensile strength and deformation processes—have been determined for crystals of poly-HDU and poly-PTS[118,231]. The ultimate tensile strengths, 1.7×10^9 and 2.0×10^9 N m^{-2}, respectively, indicate crystals of a very high degree of perfection. The per-chain modulus for each polymer is nearly as high as that of diamond.

Poly-HDU crystals exhibit negative thermal expansion coefficients in the chain direction[95,119], and a patent has been issued for the formulation of polymers with near-zero uniaxial thermal expansion coefficients[232]. For poly-PTS the coefficient is positive at room temperature, but changes sign below 70 K[130]. The origin of the negative coefficients has been discussed[95,119,130,209].

The heat capacities of monomeric and poly-PTS single crystals have been measured from 3 to 300 K[233]. The heat capacity for the polymer crystal, which serves as a model for quasi-one-dimensional solids, is strongly influenced by the lattice vibrations of the polymer chains. Small peaks in the heat-capacity curves appear at 161 K for the monomer and 198 K for the polymer, corresponding to the phase transitions described previously.

Poly-PTS exhibits a higher dielectric constant parallel to the polymer chain than that of the monomer, as a result of the greater π delocalization[234]. Measurements

have been carried out at 10.0 MHz, 9.04 GHz and at optical frequencies[165,189,234].

The pyroelectric effect in poly-PTS has been studied over the range 76–300 K[235]. A change in sign occurs between 170 and 210 K, which is related to the phase change that occurs in this range.

Some of the unusual features of the optical spectra of poly(diacetylenes) can be accounted for in terms of a strong phonon–electron coupling which gives rise to Fano-type interference[236]. Exciton surface polaritons have been detected in poly-PTS crystals at room temperature by attenuated total reflection spectroscopy[214].

Studies of the morphology, mechanism of deformation and twinning of poly-PTS crystals have been reported[237–242].

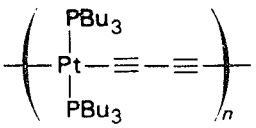
G. Uses

In addition to the uses that have been described in preceding sections, these applications of the polymers and the polymerization reaction may be cited: as cumulative time–temperature indicators and radiation dosimeters[41,80,188,234,244], for recording latent fingerprints[245], and for accelerating cross-linking in other polymers[246,247].

Crystalline poly-BCMU is quite resistant to radiation, but the amorphous polymer undergoes cross-linking between side-groups and is converted to a gel[248].

II. POLYYNE POLYMERS CONTAINING TRANSITION-METAL ATOMS IN THE MAIN CHAIN

An interesting class of polymers containing conjugated acetylenic groups and σ-bonded transition-metal atoms in the backbone has been described recently[249]. The transition metals that have been included in the chain are platinum, palladium and nickel as illustrated in **62–64**. In addition, polymers have been prepared in which two



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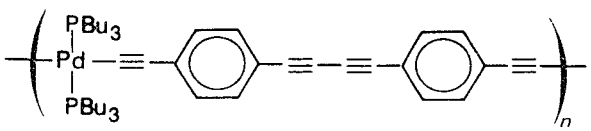

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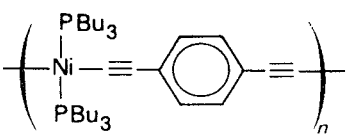


(64)

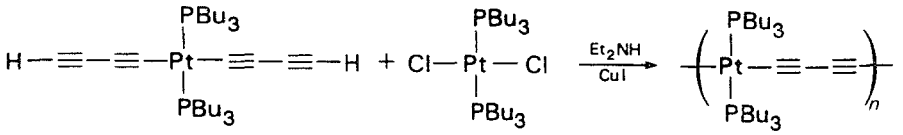
different metals appear at alternating positions in the chain. The groups are arranged in a *trans* configuration about the square-planar metal atom, and the polymers have an extended rod shape. In all of the polymers the metal is complexed with *trans*-trialkylphosphine ligands. Besides the usual stabilization of the metal in the + 2 oxidation state, these groups may stabilize the polymers by preventing close approach of polymer chains to each other.

A. Preparation of the Polymers

Three methods have been used for preparing the polymers: (1) Condensation of dialkynylmetal complexes with metal halides in amine solutions, catalysed by cop-

per(I) halides, (2) oxidative coupling of dialkynylmetal complexes and (3) alkynyl ligand exchange reactions. All three methods serve for the preparation of platinum- and palladium-containing polymers, but, because of side-reactions in the first two methods, only the third one has been found successful for nickel derivatives[250].

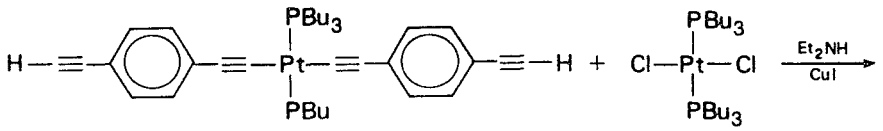
Condensation of the bis(butadiynyl)platinum complex **65** with **66** in diethylamine containing a catalytic amount of a copper (I) halide gives the polymer **62** as a yellow-



(3)

(65) (66) (62)

coloured powder in 96% yield (equation 3)[249,251]. Similarly, use of **67** as the alkynyl component provides polymer **68** with *p*-diethynylbenzene repeat units (equation 4).



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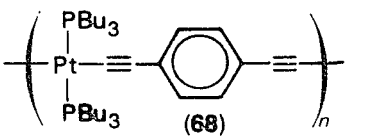
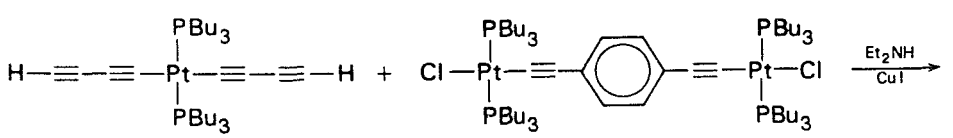


(4)

(68)

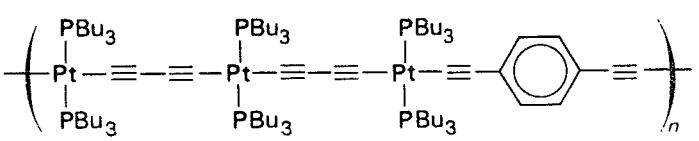
Diethylamine serves as solvent and acid scavenger, and is also believed to serve as a ligand for copper(I) intermediates[252]. Polymerization does not occur in the absence of the copper(I) salt. The reaction is carried out in an inert gas atmosphere to prevent oxidative coupling of the alkynyl component[251]. The reaction occurs slowly at room temperature, e.g. **62**, with weight-average molecular weight ($\overline{M}_w$) 70,000, is formed from **65** and **66** after one month at room temperature, but the reaction is considerably faster when it is carried out in refluxing diethylamine, **62** with $\overline{M}_w$ = 70,000 being formed after 24 h under these conditions.

Polymer **70**, with both butadiynyl- and *p*-diethynylbenzene units in the chain, has been prepared by condenstaion of **65** and **69** (equation 5)[253]. In this case the reaction



(5)

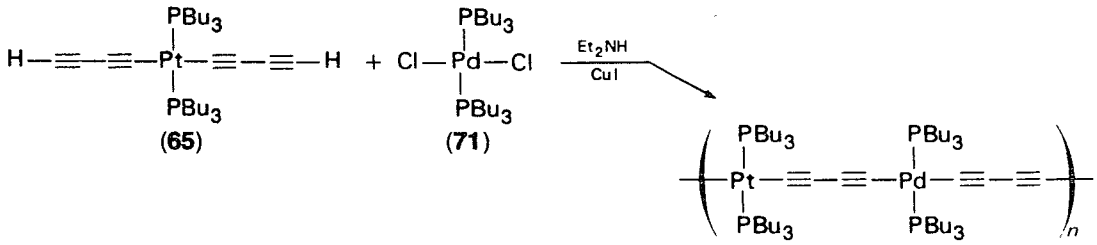
(65) (69)



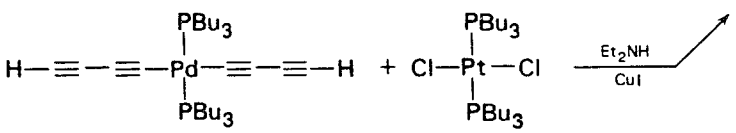
(70)

temperature has an effect on the regularity of the repeat units in the polymer chain. When the reaction is carried out at room temperature for 12 days, polymer with $\overline{M}_w$ = 34,000 and with a high degree of regularity is obtained. When the reaction is carried out in boiling diethylamine for 20 h, however, polymer with comparable molecular weight is obtained, but in this case there is significant irregularity in the structure.

Polymers such as **72**, with alternating platinum and palladium atoms, have been prepared by condensation of **65** with **71**, and also **73** with **66** (equation 6)[254]. The



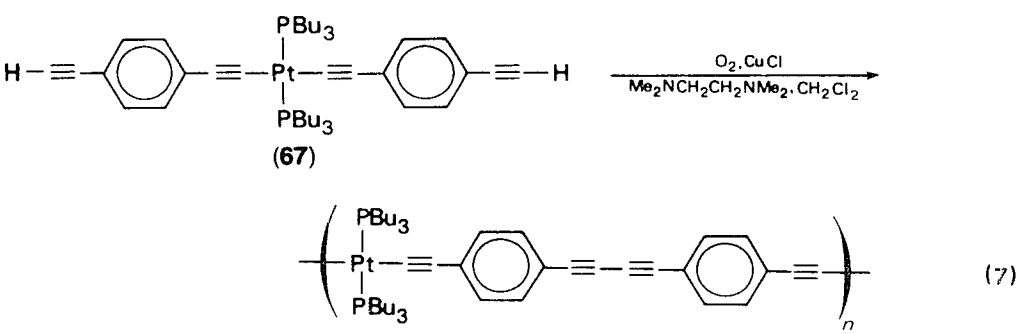
(65) **(71)** **(72)** (6)



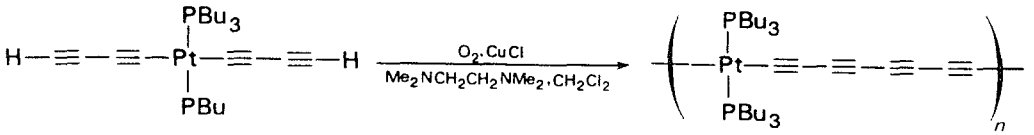
(73) **(66)**

polymers obtained by the two routes are almost indistinguishable, but the broadening of the bands in the ultraviolet spectrum of the polymer prepared by the second route, as well as the results of depolymerization studies, indicate some disorder in the chain, compared to that prepared by the first route.

The second route to these polymers, oxidative coupling of bis(acetylide) complexes of transition metals, is illustrated by the preparation of **74** from **67**, and of **75** from **65** (equations 7 and 8)[255]. The palladium analogue of **74** can be obtained by the same route. The value of $\overline{M}_w$ for **74** was 95,000, but the molecular weight of **75** could not be determined because of its insolubility. The solvent for the oxidative coupling polymerization should be one in which the polymer as well as the reactants are soluble,



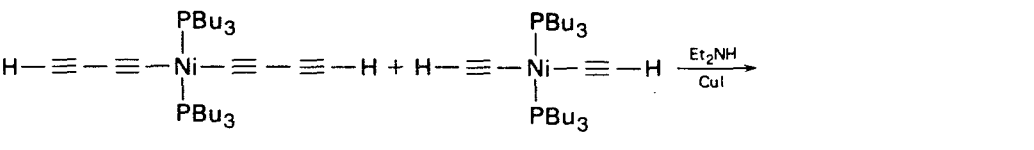
(67) **(74)** (7)



(65) (75) (8)

otherwise, precipitation of product at intermediate stages will lead to low-molecular-weight polymer. Methylene chloride has been found to be a good solvent, both for the reactants and for the polymeric products.

Polymers containing nickel atoms in the backbone are not obtained by either of the two preceding methods, because of side-reactions of dihalonickel complexes with amines or of dialkynylnickel complexes under oxidative coupling conditions[250]. They can be obtained, however, by alkynyl ligand exchange in the presence of copper(I) halides. Thus, the nickel-containing polymer **78**, with $\overline{M}_w$ = 13,000, is obtained from the reaction of **76** with **77** (equation 9). Mixed nickel-platinum polymers **79** have been



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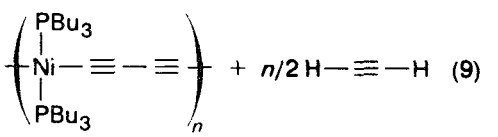
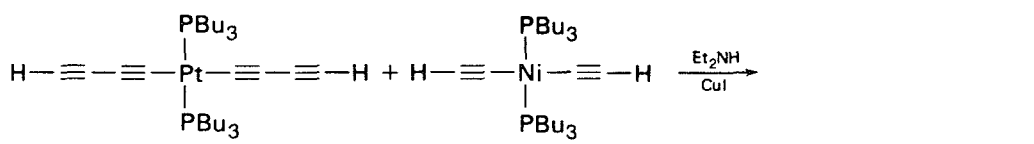
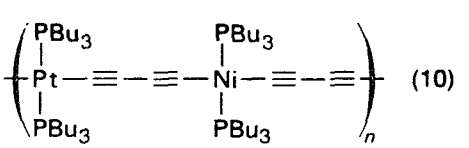


(78)

prepared by the reaction of **77** with the butadiynylplatinum derivative **65** (equation 10).



(65) (77)

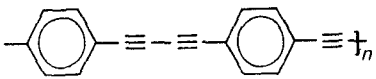


(79)

B. Properties of the Polymers

The polymers are obtained as yellow or brownish-yellow powders which are generally soluble in diethylamine, dichloromethane, THF, benzene and toluene but insoluble in methanol. They are air-stable and can be purified by chromatography over alumina.

TABLE 11. Properties of polyyne polymers with transition metals in the main chain

Polymer[a]	$\bar{M}_w$[b]	Decomp. temp. (°C)[c]	UV[e] λ_{max} (log ε)	IR $\nu_{C\equiv C}$ (cm^{-1})	^{31}P-NMR[f] δ (ppm)	References
$+Pt(L)_2-\equiv-\equiv+_n$	70,000	270[d]	384(4.5)	2000	−4.2	251
$+Pd(L)_2-\equiv-\equiv+_n$	35,000	196	342(4.3)	1978 2240	−10.74	54
$+Ni(L)_2-\equiv-\equiv+_n$	13,000	150	414(4.1)	2120 1980	−12.69	250
$+Pt(L)_2-\equiv-\equiv-Pd(L)_2-\equiv-\equiv+_n$	26,000	251	364(4.4)	1985 2110	−11.04 (P on Pd) −4.38 (P on Pt)	254
$+Pt(L)_2-\equiv-\equiv-\equiv-\equiv+_n$	—	210	501(2.7)	2135 2005	−5.2	255
$+Ni(L)_2-\equiv-\equiv-Pt(L)_2-\equiv-\equiv+_n$	10,000	159	383(4.5)	2100 2085 1950	−13.4 (P on Ni) −2.91 (P on Pt)	250
	170,000	295	403(5.1)	2090	−3.5	255

[a] L = Bu_3P.
[b] Weight-average molecular weights.
[c] Determined in nitrogen atmosphere except as noted.
[d] In air.
[e] Only the longest wavelength absorption is cited.
[f] 85% H_3PO_4 reference.

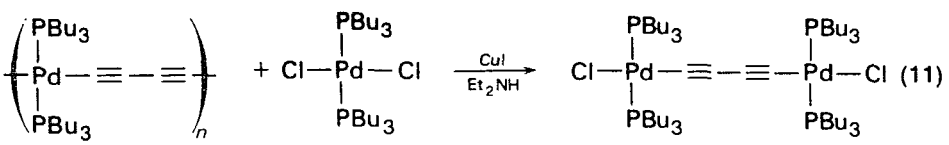
Properties of representative examples are summarized in Table 11. Molecular weights, given in the second column, are seen to range from 10,000 to 170,000. Decomposition temperatures are listed in the third column, and it is seen by comparing the first three entries that thermal stability decreases in the order Pt, Pd and Ni. Decomposition temperatures are generally higher when the sample is heated in a nitrogen atmosphere than when it is heated in air.

The lowest-energy electronic transitions, listed in the fourth column, have been assigned as metal-to-ligand charge-transfer transitions[250]. Comparison of the wavelengths for the simple polyyne polymers listed as the first three entries shows that the transition moves to lower energies in the sequence Pd, Pt, Ni, reflecting increasing metal-to-alkynyl charge-transfer interaction[250].

The polymers exhibit one or more IR absorptions in the carbon–carbon triple-bond stretching region, as can be seen in column 5. The intensities of the bands vary greatly from polymer to polymer.

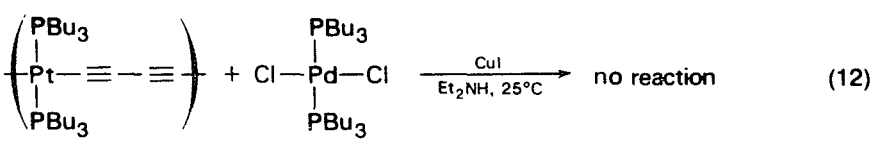
^{31}P-NMR spectroscopy has proved to be extremely useful for assigning configuration around the transition metal in these polymers. For example, studies with model compounds of known configuration have shown that the chemical shift of ^{31}P in *trans*-dialkynylbis(tributylphosphine)platinum(II) derivatives is in the range −3.0 to − 4.5 ppm (with respect to 85% H_3PO_4), whereas that of the *cis* isomers is upfield from the reference and falls in the range +2.6 to +3.6 ppm[255]. The chemical shifts cited in the sixth column of Table 11 correspond entirely to the *trans* configuration. No evidence for the *cis* isomer has been noted for any of the polymers.

Depolymerization studies have been very useful in determining polymer structures. The palladium–carbon bond, weakened by the *trans* alkynyl group, is cleaved when palladium-containing polymers are treated with platinum or palladium halides and a catalytic amount of copper(I) iodide in diethylamine at 25°C[254,255]. For example, **80** is cleaved smoothly to **81** under these conditions (equation 11). Platinum–alkynyl bonds



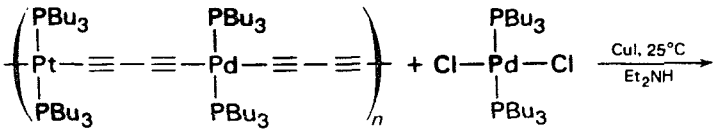
(80) (81) (11)

are not cleaved under these conditions; polymer **62**, for example, fails to react at room temperature (equation 12), and reacts only very slowly in boiling diethylamine.

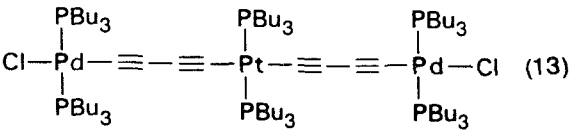


(62) (12)

Advantage is taken of this difference in metal–carbon bond strengths in determining the regularity of structure in mixed metal polymer. Mixed metal polymer **72**, prepared by condensation of **65** and **71**, gives the trinuclear complex **82** exclusively (equation 13) as shown by gel-permeation chromatography, and demonstrating complete regularity in the polymer backbone[254]. The polymer which was obtained by condensation of **73** and **66**, on the other hand, gave a mixture of oligomers under the same conditions, and it was concluded that there is significant disorder in the chain.



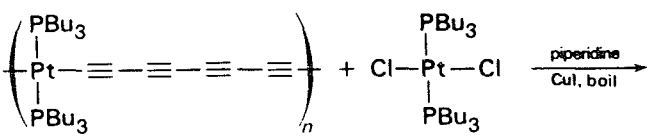
(72)



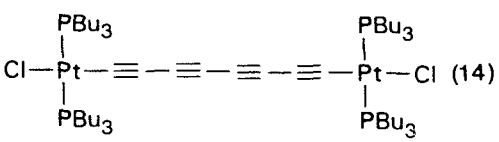
(13)

(82)

Platinum–alkynyl bonds can be cleaved under more drastic conditions[253,255]. Thus, **75** undergoes depolymerization slowly in boiling piperidine in the present of CuI and **66** to give the tetraynyl derivative **83** (equation 14).



(75) (66)



(14)

(83)

The formation of a liquid crystalline phase has been observed in concentrated solutions of these polymers[256]. For example, concentrated solutions of **62** in trichloroethylene appear turbid even though there is no undissolved material. The solutions appear opalescent on gentle stirring, but this fades rapidly when stirring is stopped. The viscosity behaviour is typical of liquid crystalline materials.

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CHAPTER **23**

Cyclodimerization of alkynes and reactivity of aluminium halide σ complexes of cyclobutadienes

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I. INTRODUCTION

The thermal oligomerization of alkynes has been known for more than a century[1,48]; the temperatures required are as high as 400°C for the uncatalysed reactions. The cyclization of acetylene to benzene, cyclooctatetraene and styrene under the influence of Ni(II) catalyst occurs at much lower temperatures (60–70°C)[53]. Since Reppe's discovery, a large number of publications have appeared concerning catalytic and stoichiometric reactions of transition metals with triple bonds. Some of the more recent reviews include the following: the synthesis and use of alkyne–transition-metal complexes in general[47], the synthesis of pyridines from alkynes and nitriles with organocobalt catalysts[2], the synthesis of rhodium complexes from diynes and their reaction with a number of substrates to give benzenes and aromatic heterocycles[46] and the synthesis of transition-metal cyclobutadiene complexes from, for example, alkynes[18]. In addition, Vollhardt[64] has demonstrated the applicability of specific cycloaddition reactions of properly substituted alkynes to afford polycyclic compounds using organocobalt catalysts.

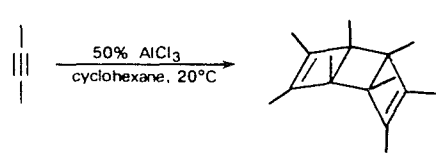
Cyclodimerization of alkynes at or below room temperature has been mainly achieved by Lewis acids such as $AlCl_3$ and $AlBr_3$: the aluminium halide σ complexes of the corresponding cyclobutadienes show a variety of chemical reactions leading to 4-, 5- and 6-membered ring compounds.

In the present review the synthesis of aluminium halide σ complexes of substituted cyclobutadienes from alkynes and their chemical reactivity will be dealt with and a comparison will be made with similar reactions of alkynes under the influence of transition-metal complexes.

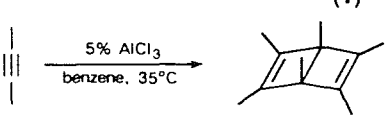
II. CYCLODIMERIZATION OF ALKYNES

A. Cyclodimerization of Alkynes to Aluminium Halide σ Complexes of Cyclobutadienes

More than a decade ago the $AlCl_3$-induced tetramerization and trimerization of 2-butyne were reported: 2-butyne and $AlCl_3$ in cyclohexane[54] afford octamethyl *syn*-tricyclo[4.2.0.$0^{2,5}$]-octadiene (**1**) (equation 1)* and 2-butyne and (a catalytic amount of) $AlCl_3$ in benzene[55,56] yields hexamethyl(Dewar)benzene (**2**) (equation 2). Some years later it was found that 2-butyne cyclodimerizes with $AlCl_3$ to an $AlCl_3$ σ complex of tetramethylcyclobutadiene (**3**) (equation 3) in methylene chloride using 2-butyne and $AlCl_3$ in a 2:1 molar ratio[41]. Reactions (1) and (2) are likely to proceed via complex **3**: when complex **3** is decomposed with DMSO in the presence of 2-butyne both compounds **1** and **2** are observed together with some hexamethylbenzene (equation 4)[35].



(1) (1)



(2) (2)

*In this review the methyl group will be represented by a line, as in terpene chemistry.

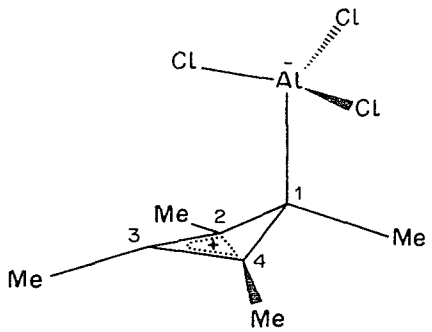
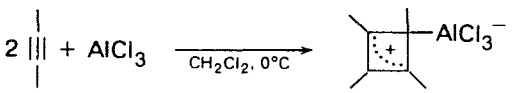
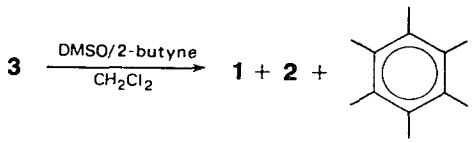


FIGURE 1. Representation of the spatial structure of complex **3**.



(3)

(3)

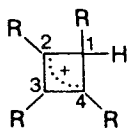


(4)

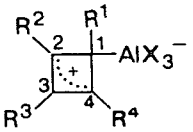
The structure of complex **3** has been determined by X-ray diffraction (Figure 1)[42], clearly showing the nonplanarity of the four-membered ring (dihedral angle 30°) and a relatively short C(2)—C(4) distance of 1.775 Å. These features are probably due to a C(2)—C(4) homoaromatic interaction, which has also been recognized on the basis of ^{13}C-NMR chemical shift values. In cyclobutenyl cations **4** there is a large effect of the nature of the substituents on the ^{13}C-NMR chemical shift values of C(2,4) and C(3) (Table 1)[50]. It has been concluded that ion **4a** possesses allylic, and ion **4b** homocyclopropenium character, ion **4c** representing an intermediate case. From the ^{13}C-NMR chemical shift values of complex **3** (Table 1) and its molecular structure in the crystalline phase, it has been inferred that complex **3** exhibits homoaromatic interaction as well[13]. The same is thought to be true for complexes **15** and **17**. For reasons of simplicity however, we shall denote the σ complexes in this review by the allylic structure.

TABLE 1. ^{13}C-NMR chemical shift values (ppm) of C(2,4) and C(3) of **3**, **4**, **15** and **17**

	C(2,4)	C(3)
3	162.0	164.3
4a	190.0	152.3
4b	133.5	187.6
4c	171.3	171.3
15	184.0	152.3
17	162.8	165.4



(4)

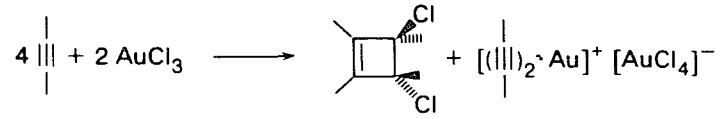


(a) R = Ph (3) $R^1 = R^2 = R^3 = R^4$ = Me, X = Cl

(b) R = H (15) $R^1 = R^3$ = H, $R^2 = R^4$ = Me, X = Br

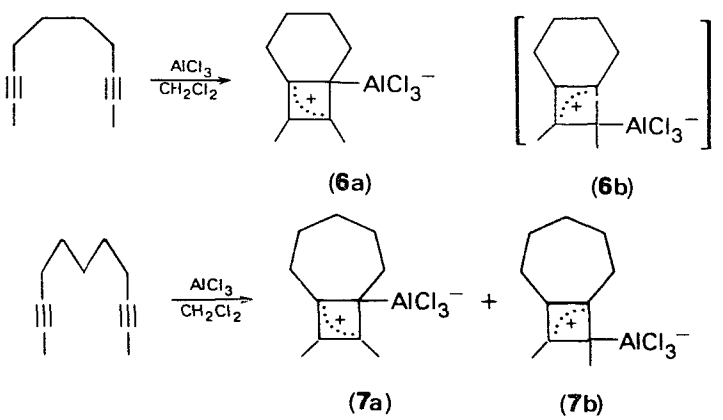
(c) R = Me (17) R^1 = H, $R^2 = R^3 = R^4$ = Me, X = Br

Besides the use of $AlCl_3$, other Lewis acids induce a similar cyclodimerization of 2-butyne. Complexes analogous to complex **3** have been obtained using $AlBr_3$ [14], BCl_3 [22] and $GaCl_3$ [3]. In some cases the chemistry of these complexes differs from that of complex **3**, which will be exemplified in Section III.A. Reaction of 2-butyne with $AuCl_3$ does not afford a $AuCl_3$ σ complex of tetramethylcyclobutadiene; instead *trans*-3,4-dichloro-1,2,3,4-tetramethylcyclobutene (**5**) is isolated (equation 5)[39]. With diphenylacetylene analogous results are obtained.



(5) (5)

Inspired by the convenient preparation of complex **3** from 2-butyne and $AlCl_3$, a number of alkynes have been subjected to Lewis acids, and found to give similar cyclodimerizations. 2,8-Decadiyne and 2,9-undecadiyne react with $AlCl_3$ in methylene chloride to afford complexes **6a** and **7a** and **b**, respectively. The exclusive formation of **6a** (**6b** has not been detected by NMR spectroscopy), if compared to the 1:1 ratio of complexes **7a** and **7b**, is remarkable. Inspection of Dreiding models has

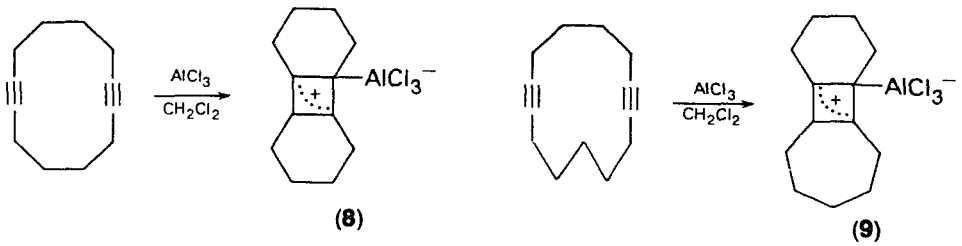


(6a) (6b)

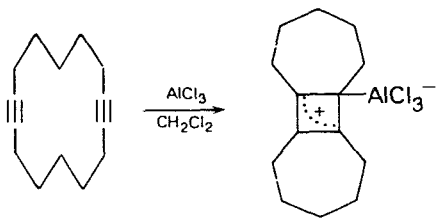
(7a) (7b)

shown that compound **6b** cannot be formed without severe disturbance of the cyclobutenyl ring skeleton[15], whereas the model study does not indicate a preference for either **7a** or **7b**. Attempts to cyclodimerize 2,7-nonadiyne failed, as expected from inspection of Dreiding models[33].

With the cyclic diynes 1,7-cyclododecadiyne, 1,7-cyclotridecadiyne and 1,8-cyclotetradecadiyne, intramolecular cyclodimerizations have been performed that



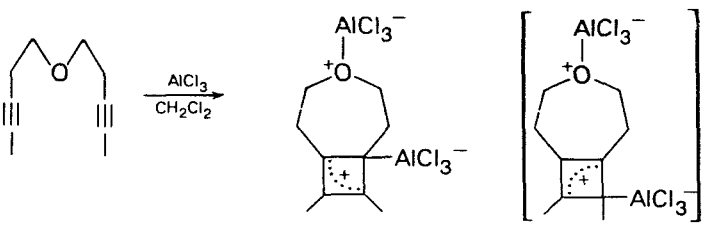
(8) (9)



(10)

result in complexes **8**, **9** and **10**, respectively[14,25]. The assignment of the structure of complex **9** is based on the similarity with complex **6a**.

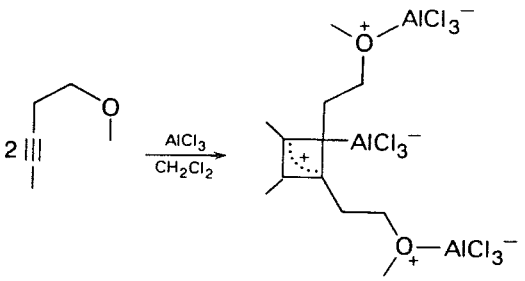
Besides dialkyl-substituted alkynes, alkynes containing a heteroatom have also been used in the cyclodimerization. 6-Oxa-2,9-undecadiyne cyclodimerizes intramolecularly to complex **11a**, when treated with $AlCl_3$ in a 1:2 molar ratio. This ratio is necessary



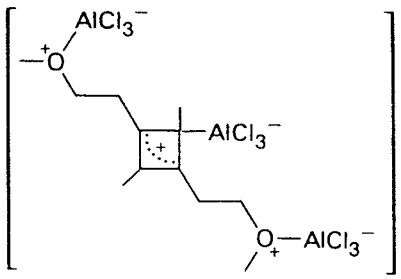
(11a) (11b)

because of the complexation of $AlCl_3$ to the oxygen atom[19]. Of the two theoretically possible structural isomers only **11a** is observed, which contrasts with the 1:1 occurrence of the all-carbon 7-membered ring complexes **7a** and **7b**. This is possibly caused by an electronic effect of the oxonium ion, as suggested by the observation that cyclodimerization of 1-methoxy-3-pentyne affords only two of the four possible isomers **12a–d**: complexes **12a** and **12b** (observed in a 7:3 ratio) contain only one β-oxonium-ion-substituted ethyl group on the positively charged allylic cation moiety. Attempts to perform a similar reaction with 1-methoxy-2-butyne have been unsuccessful, as is the case with 5-oxa-2,7-nonadiyne and 7-oxa-2,11-tridecadiyne[19]. Analogous to the reaction of 6-oxa-2,9-undecadiyne, 6-isopropyl-6-aza-2,9-undecadiyne undergoes an intramolecular cyclodimerization to yield complex **13**[34]. The structure of **13** has not been established by ^1H- and ^{13}C-NMR spectroscopic measurements due to insolubility, but has been deduced from a subsequent reaction with ethyl cyanoformate (Section III.A).

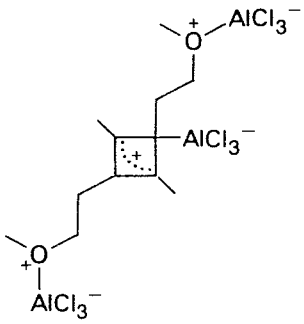
* Intramolecular cyclization of 5-oxa-1,8-cyclotetradecadiyne with $AlBr_3$ results in a mixture of isomers, presumably **14a** and **14b**[19].



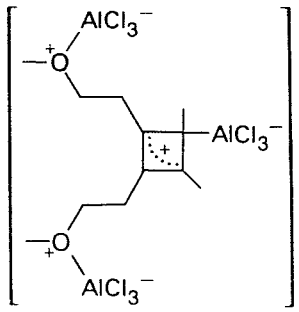
(12a)



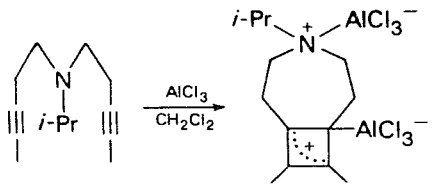
(12c)



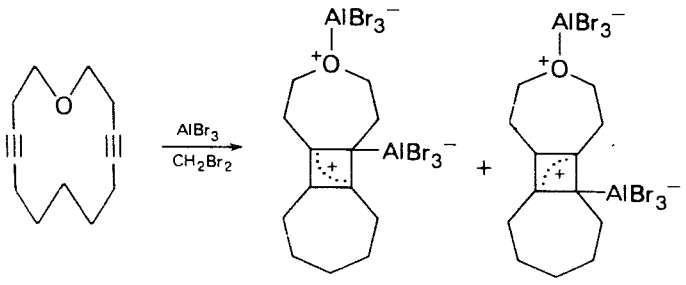
(12b)



(12d)



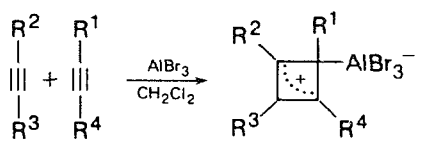
(13)



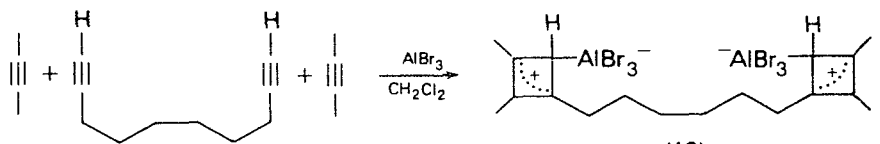
(14a) (14b)

Monoalkyl-substituted alkynes have also been used in the cyclodimerization. At −85°C propyne cyclodimerizes with $AlBr_3$ in a regioselective way yielding complex **15**[32]. A similar cyclodimerization is observed with *t*-butylacetylene producing complex **16**. The use of $AlBr_3$ instead of $AlCl_3$ is crucial. for $AlCl_3$ induces only polymerization of the terminal alkyne, which might be due to the low solubility of $AlCl_3$. Moreover, a low temperature (−85°C) is beneficial for complex formation: complex **15** is formed in 70% yield at −85°C and in 35% yield at −40°C.

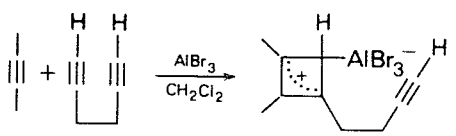
Quite interesting is the strong preference for cocyclodimerization of 2-butyne and propyne to yield complex **17**; complex **3** ($AlBr_3$) or **15** are not observed in the ^{1}H-NMR spectrum of the reaction mixture[32]. When 2-butyne and phenylacetylene are used in a 1:1.2 molar ratio, complex **18** is obtained. Phenylacetylene itself decomposes under the influence of $AlBr_3$ and no cyclodimerization of it has been observed. On using 1,9-decadiyne and 2-butyne in a 1:2 molar ratio a cocyclodimerization affording complex **19** is observed. A similar reaction with 1,5-hexadiyne results in complex **20**; the addition of a second molecule of 2-butyne does not occur[31].



(15) $R^1 = R^3 = H$, $R^2 = R^4 = Me$
(16) $R^1 = R^3 = H$, $R^2 = R^4 = t\text{-Bu}$
(17) $R^1 = H$, $R^2 = R^3 = R^4 = Me$
(18) $R^1 = H$, $R^2 = R^3 = CH_3$, $R^4 = Ph$



(19)



(20)

Preliminary results with acetylene and $AlCl_3$ or $AlBr_3$ indicate that, probably due to polymerization of acetylene, no cyclodimerization occurs[22].

Finally, it is worth mentioning that the reaction of 2-butyne with chlorine in the presence of BF_3 affords *trans*-3,4-dichloro-1,2,3,4-tetramethylcyclobutene[7,8]. The latter reaction is, however, limited to 2-butyne only[8].

Furthermore, Lewis acids were shown to be useful in the cycloaddition of alkynes with olefins to yield cyclobutene derivatives[6,21,44,60].

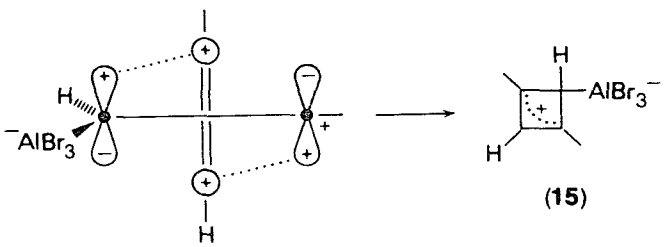
B. Mechanism of the Cyclodimerization of Alkynes by Aluminium Halides

The interaction of Lewis acids with alkynes leads to alkyne–Lewis acid π complexes. IR measurements at −100°C have shown such an interaction between dialkyl-substituted alkynes and $AlBr_3$, whereas in the case of monoalkyl-substituted alkynes only polymerization has been detected[52]. With 2-butyne and diphenyl-

acetylene AuCl and Au_2Cl_4 π complexes have been observed by means of ^{1}H-NMR measurements[39]. In addition, ^{1}H- and ^{13}C-NMR spectroscopic measurements at −100°C of solutions of 2-butyne and $AlBr_3$ have shown the presence of a π complex[32]. Line-broadening measurements reveal the presence of a degenerate exchange process (Scheme 1). The transition state or intermediate of this bimolecular exchange may involve a pentacoordinated aluminium atom.

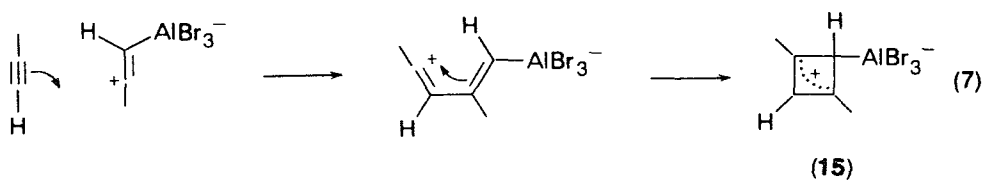
SCHEME 1. Dynamic process of 2-butyne with $AlBr_3$.

The cyclodimerization of alkynes to aluminium halide σ complexes of cyclobutadienes may proceed via a complex, having two alkynes coordinated to the aluminium atom, although a comparison with the cyclodimerization with proton acids (Section II.C) makes a concerted $_\pi2_s + {}_\pi2_a$[70] or a stepwise cationic mechanism as exemplified for propyne in equations (6) and (7) respectively, more likely.



(6)

(15)



(7)

(15)

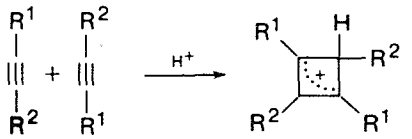
C. Comparison of the Cyclodimerization of Alkynes by Proton Acids, Organotransition-metal Complexes and Aluminium Halides

Besides Lewis acids, proton acids and organotransition metal complexes can also cyclodimerize alkynes. The dimerizations of alkynes with transition-metal derivatives and the chemical behaviour of the resulting dimeric organotransition-metal complexes have been extensively investigated and reviewed as mentioned in the introduction. In order to compare these reactions a few aspects of the cyclodimerization of alkynes as effected by proton acids, organotransition-metal complexes and aluminium halides, will be dealt with.

1. Proton acids

Strong proton acids, e.g. CF_3COOH, FSO_3H and HBF_4 have been used for the cyclodimerization of disubstituted alkynes to cyclobutenyl cations, which have a structure similar to the aluminium halide σ complexes of cyclobutadienes (Section II.A, Figure 1). For example, diphenylacetylene[43,49], 3,3-dimethyl-1-phenylbutyne[61],

1-phenylpropyne[49] and 3,3-dimethyl-1-butynyldimethylamine[63] cyclodimerize to **21**, **22**, **23** and **24**, respectively. In the reaction of 2-butyne with FSO_3H, the tetramethylcyclobutenyl cation **25** has been observed as a minor product[50]. As opposed to the cyclo-



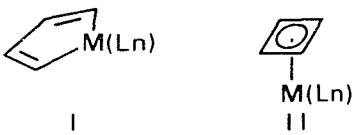
(**21**) $R^1 = R^2 = Ph$
(**22**) $R^1 = Ph$, $R^2 = t\text{-Bu}$
(**23**) $R^1 = Ph$, $R^2 = Me$
(**24**) $R^1 = NMe_2$, $R^2 = t\text{-Bu}$
(**25**) $R^1 = R^2 = Me$

dimerization by aluminium halides (Section II.A), cyclodimerization of mono-substituted alkynes, e.g. *t*-butylacetylene[51] and phenylacetylene[49] has not been accomplished.

With weaker acids, e.g. HCl and HBr, the cyclodimerization of mono- and di-alkyl-substituted alkynes leads to mixtures of products, including the chlorinated and brominated cyclobutanes, respectively[27,57].

2. *Organotransition-metal complexes*

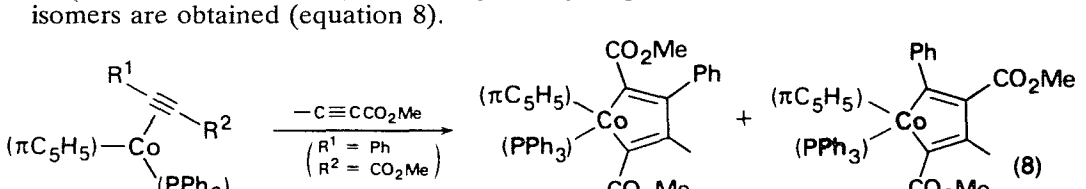
In general, two types of complexes have been prepared from alkynes and transition-metal derivatives, namely type I complexes, which contain a 5-membered ring with the metal atom being part of the ring (metallocyclopentadienes) and type II complexes in which the cyclobutadiene moiety is π-bonded to the metal atom.



I II

Although the aluminium halides σ complexes of cyclobutadienes have so far been mainly prepared from (di)*alkyl*-substituted alkynes, the synthesis of complexes of type I have been frequently performed with *phenyl*-substituted alkynes. For example, complexes of type I have been synthesized from 1,6-, 1,7- and 1,8-phenylsubstituted diynes and $M(PPh_3)_3Cl$ (M = Rh or Ir)[46]. In addition, diphenylacetylene and in some cases dimethyl acetylenedicarboxylate has been used to synthesize complexes of type I with the metal being Pd[40,45], Ir[5], Pt[45], Ti[65], Co[67,72], Fe[38] or Ru[58].

As pointed out in Section II.A, in the few cases investigated, the cyclodimerization of a mixture of two alkynes by Lewis acids affords exclusively the mixed aluminium halide σ complex of a cyclobutadiene. Similar mixed cyclodimerizations have been performed using an organotransition metal: e.g. preformed π alkyne complexes of structure **26** react with either phenylacetylene, methyl phenylacetylenecarboxylate, methyl methylpropiolate, *p*-tolylacetylene or 1,4-dimethoxy-2-butyne[66,67] to afford metallocyclopentadienes containing two different alkynes. In the reaction of complex **26** ($R^1 = Ph$, $R^2 = CO_2Me$) with methyl methylpropiolate only two of the four possible isomers are obtained (equation 8).



(**26**) (8)

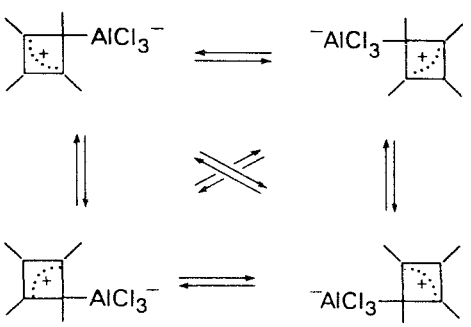
The complexes of type II, prepared from alkynes and transition-metal complexes have been recently reviewed by Efraty[18]. In most examples phenyl-substituted alkynes have been used, although a number of other alkynes, such as acetylene, 2-butyne and 3-hexyne and a few diynes have also been reported. In addition the cooligomerization of α,ω-diynes with (bis)trimethylsilylacetylene and di-*t*-butylacetylene using $CpCo(CO)_2$ as a catalyst has been shown to afford mixed cyclobutadiene cobalt sandwich complexes[28].

III. CHEMICAL REACTIVITY OF THE CYCLODIMERIC COMPLEXES OF ALKYNES

A. Aluminium Halide σ Complexes of Cyclobutadienes

In this section the chemical reactivity of the aluminium halide σ complexes of cyclobutadienes will be presented. With regard to the chemical reactivity the weakness of the carbon–aluminium bond of these complexes is probably the most important feature: the loss of the aluminium halide group leaves formally a cyclobutadiene moiety, which can undergo reactions with a variety of substrates. Whether or not a free cyclobutadiene moiety is actually generated as an intermediate is uncertain; in some reactions its presence becomes very improbable.

The weakness of the carbon–aluminium bond has been demonstrated by NMR spectroscopy[15]. At room temperature a solution of complex **3** in methylene chloride shows line-broadening of the ^{1}H-NMR signals. The process responsible for this phenomenon has been shown to involve a 1,2-migration of the $AlCl_3$ group (Scheme 2), the 1,3-migration being effectively absent. ^{13}C-NMR measurements reveal a

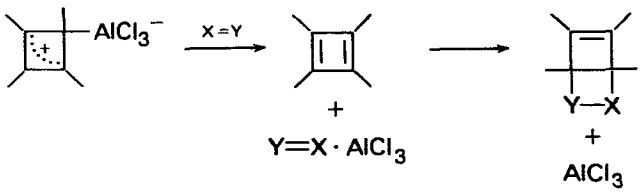


SCHEME 2. Degenerate isomerizations in complex **3** by means of migration of the $AlCl_3$ group.

temperature-dependent line-broadening of the signals of both the methyl groups and the cyclobutenyl ring-atoms, thereby excluding a migration process involving the methyl groups. In contrast to the dynamic behaviour of complex **3**, the Al_2Cl_6 complex **3a**, prepared by using a 100% excess of $AlCl_3$, exhibits no line-broadening up to 75°C, indicating that migration of the Al_2Cl_6 group should be a factor of at least 2500 smaller[15]. Similar to the behaviour of complex **3** the signals of **6a** and **7a,b** show line-broadening on raising the temperature. In complex **6a**, the rate of the 1,2-shifts has been determined to be about 2100 times smaller than that of complex **3**. Due to the complexity of the ^{1}H-NMR spectrum of complexes **7a,b** the line-broadening process has not been analysed in detail, but the rate constants have the same order of

magnitude as that of complex **3**[15]. Recently, the susceptibility of the carbon–aluminium bond to irradiation has been demonstrated by ESR spectroscopy. Irradiation of a solution of complexes **3** or **3a** with UV light at −85°C results in homolysis of the carbon–aluminium bond and the ESR spectrum of the tetramethylcyclobutadiene radical cation has been detected[4].

In principle, the aluminium halide σ complexes of cyclobutadienes can react by at least three different pathways. The first one (equation 9) involves liberation of a cyclobutadiene by loss of the aluminium halide to a species which possesses a π bond or a lone pair of electrons, followed by a cycloaddition of that species to the



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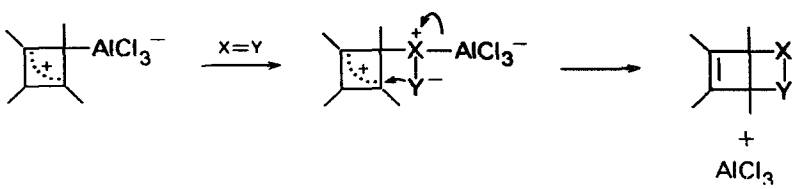

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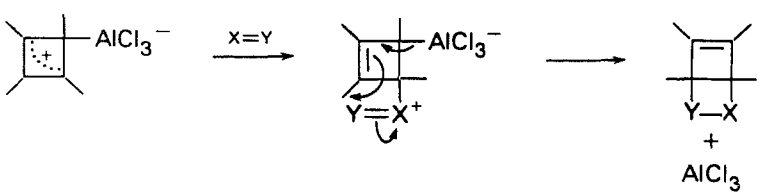


(11)

cyclobutadiene. The second one (equation 10) implies an insertion of a reactive substrate into the labile carbon–aluminium bond followed by a cyclization. In the third (equation 11), the reaction starts with an electrophilic addition of the allylic cation moiety to an electronegative centre, followed by cyclization. In some reactions evidence has been obtained for the occurrence of one of these reaction types; this evidence, which is mainly derived from the substitution pattern in the obtained products, will be dealt with at the appropriate places in this chapter. In the following section a variety of reactions of complexes **3** and **6–20** will be presented.

1. Reactions with carbon–carbon triple bonds

Complex **3** reacts with carbon–carbon triple bonds yielding (Dewar)benzene derivatives. Reaction of complex **3** with dimethyl acetylenedicarboxylate results in 1,4,5,6-tetramethylbicyclo[2.2.0]hexa-2,5-diene (**27**)[41]. The same reaction, employing complexes **6–11**, produces (Dewar)benzene diesters **28–33** in yields varying from 44% to 73% (Table 2)[13,14,19]. In some cases two experimentally different methods have been employed for the synthesis of the (Dewar)benzenes. The first procedure involves direct reaction of dimethyl acetylenedicarboxylate with the aluminium halide σ complex of tetramethylcyclobutadiene[41], whereas in the second procedure dimethyl

TABLE 2. Reactions of aluminium halide σ complexes of cyclobutadienes with carbon–carbon triple bonds

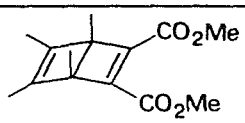
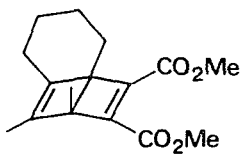
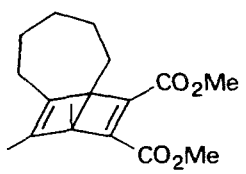
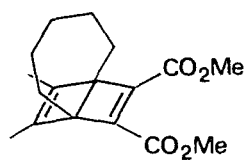
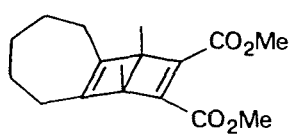
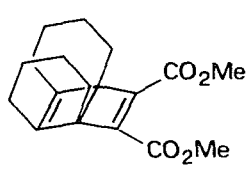
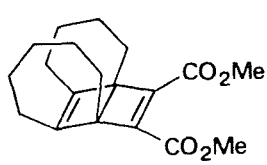
Complex	Alkyne	Product(s)	Yield (%)[a]
3	$MeO_2CC{\equiv}CCO_2Me$	 **(27)**	27[b]
6a	$MeO_2CC{\equiv}CCO_2Me$	 **(28)**	73[b]
7a,b	$MeO_2CC{\equiv}CCO_2Me$	 **(29a)**  **(29b)**	63[b] **a/b/c** = 2/1/1
		 **(29c)**	
8	$MeO_2CC{\equiv}CCO_2Me$	 **(30)**	49[b]
9	$MeO_2CC{\equiv}CCO_2Me$	 **(31)**	44[b]

TABLE 2. *continued*

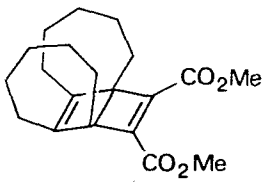
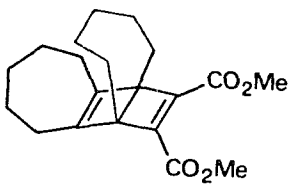
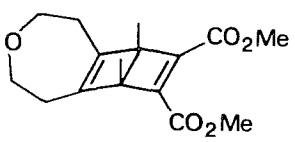
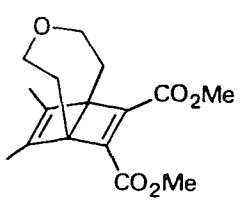
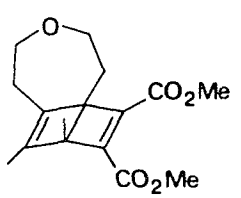
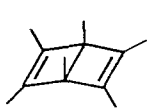
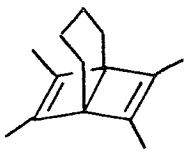
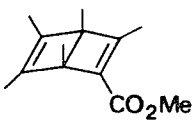
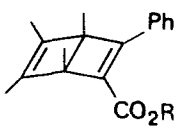
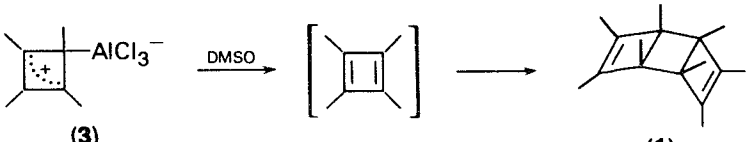
Complex	Alkyne	Product(s)	Yield (%)[a]
10	$MeO_2CC{\equiv}CCO_2Me$	 (**32a**)	45[b] **a/b** = 2/3
		 (**32b**)	
11a	$MeO_2CC{\equiv}CCO_2Me$	 (**33a**)	67[b] **a/b/c** = 1/1/3
		 (**33b**)	
		 (**33c**)	
3	$-C{\equiv}C-$	 (**2**)	40

TABLE 2. *continued*

Complex	Alkyne	Product(s)	Yield (%)[a]
6a	—C≡C—	 **(34)**	22
3	—C≡CCO$_2$Me	 **(35)**	90[b]
3	PhC≡CCO$_2$R	 **(36)** (a) R = methyl (b) R = menthyl (c) R = bornyl (d) R = *s*-octyl	75 60 – –

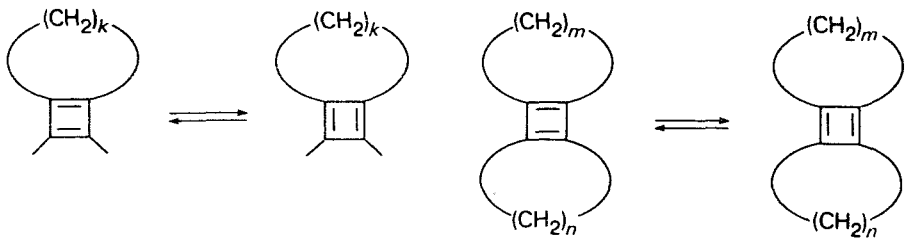
[a]Yields are based on the amount of alkyne used.
[b]Isolated and characterized as the (di)acid(s), obtained by alkaline hydrolysis of the esters.

acetylenedicarboxylate has been added to aluminium halide σ complexes at −50°C (at which temperature no reaction occurs), followed by addition of dimethyl sulphoxide (DMSO) thereby inducing the cycloaddition with dimethyl acetylenedicarboxylate[13,14]. In the absence of dimethyl acetylenedicarboxylate, complex **3** reacts at −40°C with DMSO to the *syn* dimer of tetramethylcyclobutadiene (**1**) in 79% yield (equation 12)[35]; it is therefore believed that DMSO liberates the



(3) **(1)** (12)

tetramethylcyclobutadiene at this temperature. In the case the reaction of the aluminium halide σ complexes of cyclobutadienes with dimethyl acetylenedicarboxylate would proceed via intermediate cyclobutadienes, the product distribution might reflect the equilibrium of the valence isomers of the cyclobutadienes. Recently, convincing chemical evidence has been reported for the existence of such an equilibrium in the parent cyclobutadiene[69]. On this basis the equilibria as depicted in Scheme 3 should occur, showing in the case of a six-membered ring a preference for an endocyclic double bond, whereas such a preference does not exist with the seven-membered ring species[13].



			$m = n = 4$	> 90%
$k = 4$	> 90%		$m = 4, n = 5$	> 90%
$k = 5$	50%	50%	$m = n = 5$	40%
				60%

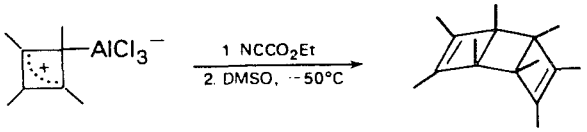
SCHEME 3. Equilibria of the valence isomers of cyclobutadienes on the basis of product formation (Table 2).

When complex **3** is treated with methyl methylpropiolate in the presence of DMSO at −50°C, it results in the formation of compound **1** only. However, it has been found that the (Dewar)benzene derivative **35** is obtained if the reaction is performed at 0°C without the use of DMSO[15]. At the same temperature, methyl and the optically active menthyl, bornyl and *s*-octyl phenylpropiolates afford compounds **36a, b, c** and **d**, respectively[10–12], with optical yields of the hydrolysed products of 21%, 6.5% and 6.9% in the latter three cases.

Finally, complex **3** and **6a** have been found to react with 2-butyne affording the (Dewar)benzene derivatives **2**[35] and **34**[13] respectively. As mentioned before hexamethyl(Dewar)benzene has also been prepared in the $AlCl_3$-catalysed trimerization of 2-butyne in benzene (Section II.A, equation 2)[55,56].

2. *Reactions with carbon–nitrogen triple bonds*

Besides the reactions of the aluminium halide σ complexes of cyclobutadienes with carbon–carbon triple bonds carbon–nitrogen triple bonds (nitriles) have also been found to react, yielding pyridines; e.g. with ethyl cyanoformate complex **3** gives 1-carboethoxy-2,3,4,5-tetramethylpyridine (**37**) in 60% yield (Table 3). On using this nitrile, complexes **6–11** and **13–20** afford the substituted pyridines **38** to **51** in yields varying from 18% to 59% (Table 3)[15,16,19,31,34]. In the case of complex **15** it has been observed that the yield of pyridine is very sensitive to the amount of $AlBr_3$. Reaction of **15** yields only 12% of a mixture of isomeric pyridines **46a** and **46b**, whereas on using **15**·(Al_2Br_6) the yield increases to 54%[31]. The difference in yield is due to a faster and therefore cleaner reaction of **15**·(Al_2Br_6). On adding ethyl cyanoformate to complex **3** at −50°C, no reaction occurs and addition of DMSO results in the dimerization of tetramethylcyclobutadiene affording **1** (equation 13). Apparently the cycloaddition of ethyl cyanoformate with complex **3** has to be initiated by the ethyl cyanoformate itself[13]. The results with complexes **15–20** show that the major (or exclusive) pyridine



(13)

(3) **(1)**

TABLE 3. Reactions of aluminium halide σ complexes of cyclobutadienes with nitriles

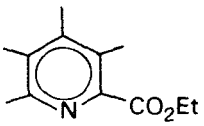
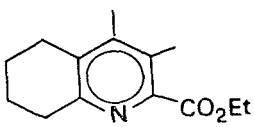
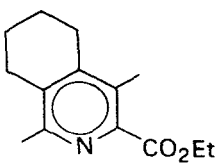
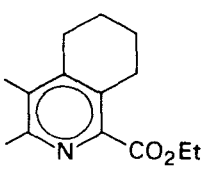
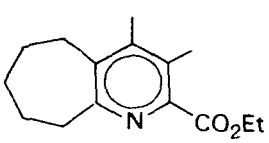
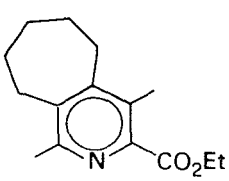
Complex	Nitrile	Product(s)	Yield (%)[a]
3	$N{\equiv}CCO_2Et$	 **(37)**	60
6a	$N{\equiv}CCO_2Et$	 **(38a)**  **(38b)**  **(38c)**	53 **a/b** or **c** = 6/1
7a,b	$N{\equiv}CCO_2Et$	 **(39a)**  **(39b)**	50 **a/b** or **c** = 3/4

TABLE 3. *continued*

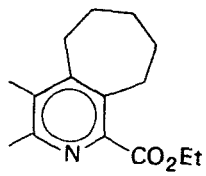
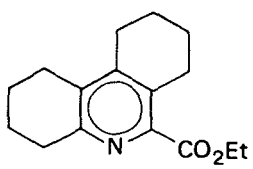
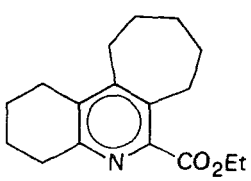
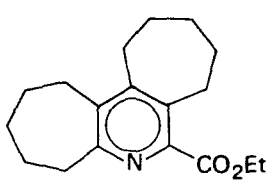
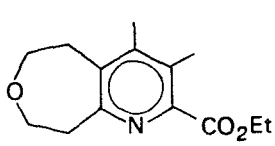
Complex	Nitrile	Product(s)	Yield (%)[a]
		 **(39c)**	
8	$N{\equiv}CCO_2Et$	 **(40)**	41
9	$N{\equiv}CCO_2Et$	 **(41)**	40
10	$N{\equiv}CCO_2Et$	 **(42)**	43
11a	$N{\equiv}CCO_2Et$	 **(43a)**	53 **a**/**b** or **c** = 6/1

TABLE 3. *continued*

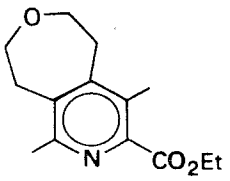
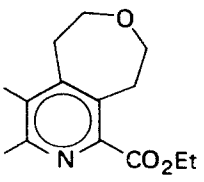
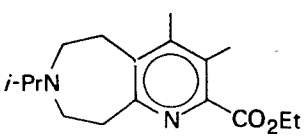
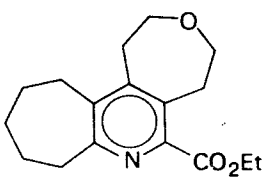
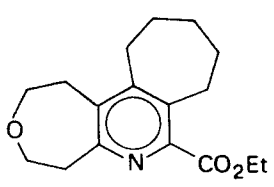
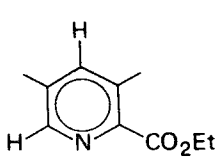
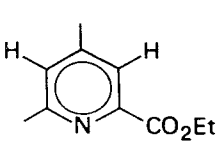
Complex	Nitrile	Product(s)	Yield (%)[a]
		 **(43b)**	
		 **(43c)**	
13	$N{\equiv}CCO_2Et$	 **(44)**	18
14	$N{\equiv}CCO_2Et$	 **(45a)**	26 **a/b** = 2/5
		 **(45b)**	
15·(Al_2Br_6)[b]	$N{\equiv}CCO_2Et$	 **(46a)**  **(46b)**	54 **a/b** = 6/1

TABLE 3. *continued*

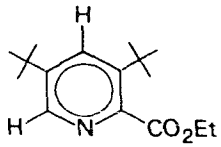
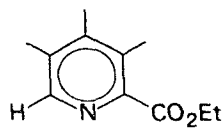
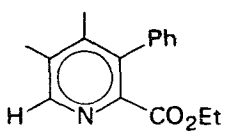
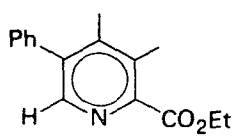
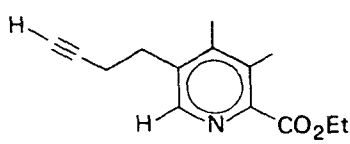
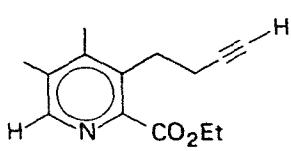
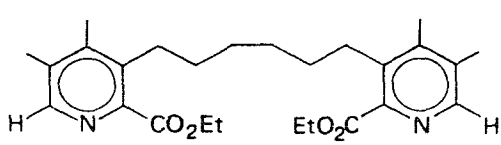
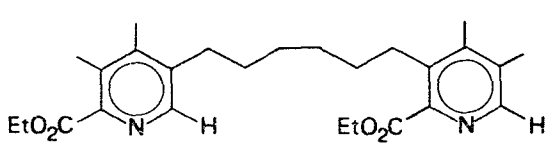
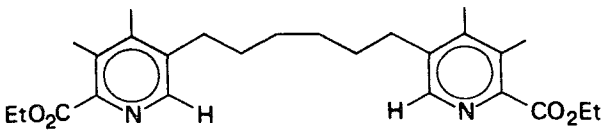
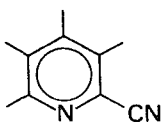
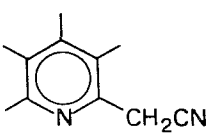
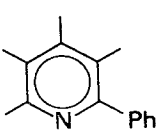
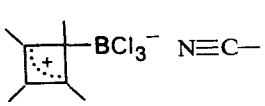
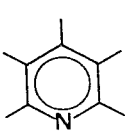
Complex	Nitrile	Product(s)	Yield (%)[a]
16·$(Al_2Br_6)^b$	$N{\equiv}CCO_2Et$	 **(47)**	38
17·$(Al_2Br_6)^b$	$N{\equiv}CCO_2Et$	 **(48)**	58
18·$(Al_2Br_6)^b$	$N{\equiv}CCO_2Et$	 **(49a)**  **(49b)**	40 **a/b** = 1/6
20·$(Al_2Br_6)^b$	$N{\equiv}CCO_2Et$	 **(50a)**  **(50b)**	45 **a/b** = 1/1
19·$(Al_2Br_6)^b$	$N{\equiv}CCO_2Et$	 **(51a)**  **(51b)**	59 **a/b/c** = 1/3/2

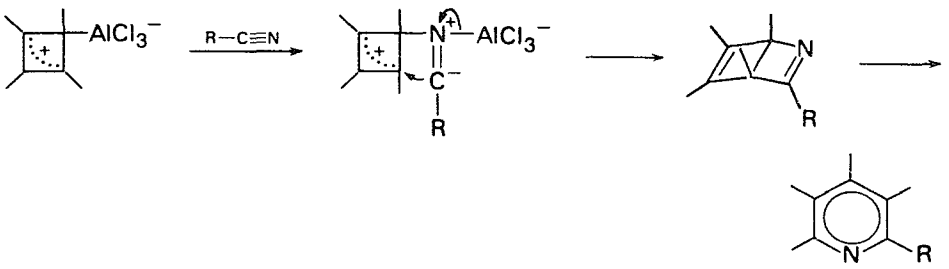
TABLE 3. *continued*

Complex	Nitrile	Product(s)	Yield (%)[a]
		 **(51c)**	
3a	N≡CCN	 **(52)**	65
3a	$N{\equiv}CCH_2CN$	 **(53)**	22
3a	N≡CPh	 **(54)**	18
		 **(55)**	22

[a]Yields are based on the amount of alkyne used; **a**/**b** or **c** indicates that the spectroscopic data of the second compound cannot distinguish between structures **b** and **c**.
[b]In these complexes the $AlBr_3$ group has been replaced by Al_2Br_6.

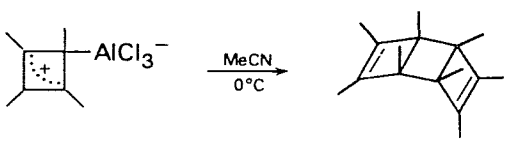
isomer obtained has the hydrogen atom attached to the α carbon atom. This means a preferential attack of the nitrile nitrogen atom on the carbon atom bearing the aluminium bromide group. The structure of the pyridines **38**, **41** and **43** obtained from complexes **6**, **9**, and **11**, respectively, is in agreement with this hypothesis. The mechanism of the reaction probably involves an insertion of the nitrile in the carbon–aluminium bond followed by ring-closure, as exemplified for complex **3** in equation (14). The failure to detect a (Dewar)pyridine is probably due to its instability, especially in the presence of a Lewis acid, which can act as a catalyst in the aromatization. It should be pointed out that this mechanism does not allow for the formation of minor quantities of isomeric pyridines in some of the reactions (Table 3).

Other nitriles have also been used in the reaction of complex **3** (Table 3) and the



(14)

results indicate that the pyridine formation depends on the electron-withdrawing character of the group attached to the nitrile. With cyanogen (CN being a powerful electron-withdrawing group) a 65% yield of **52** is observed, while malononitrile and benzonitrile give yields of 22% (**53**) and 18% (**54**) respectively[30]. With acetonitrile no pyridine is formed; instead the dimer of tetramethylcyclobutadiene (**1**) is obtained (equation 15)[16]. However, on using the BCl_3 σ complex of tetramethylcyclobutadiene, pentamethylpyridine (**55**) has been isolated in 22% yield[22].

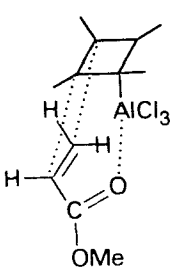


(15)

(3) **(1)**

3. *Reactions with carbon–carbon double bonds*

It has been found that complex **3** also reacts with carbon–carbon double bonds: the formed bicyclo[2.2.0]hexenes **56–65** together with the alkenes used are listed in Table 4[25,62,71]. From the structure of products **56–65** it is deduced that the cycloaddition follows the *endo* rule for Diels–Alder reactions and that no isomerization occurs at the carbon–carbon double bond of the alkene during the cycloaddition. It is believed that the abstraction of the $AlCl_3$ group and the cycloaddition are simultaneous and possibly proceed via structure **66**[62].



(66)

4. *Reactions with heterocumulenes*

The aluminium halide σ complexes of cyclobutadienes have been found to react with heterocumulenes such as isocyanates, methyl isothiocyanate, carbodiimides and sulphinylaniline.

Complex **3** reacts at room temperature with methyl, phenyl and cyclohexyl isocyanate to give the substituted 3-oxo-2-aza-bicyclo[2.2.0]hex-5-enes ('Dewar

TABLE 4. Reactions of complex **3** with alkenes

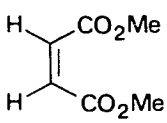
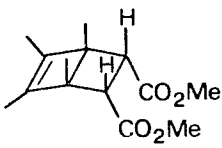
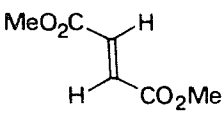
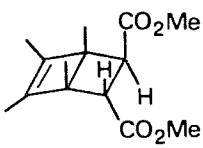
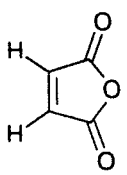
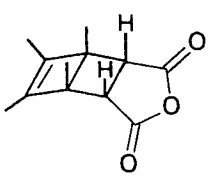
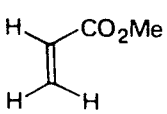
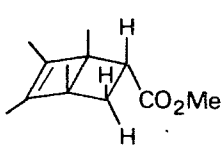
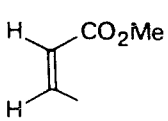
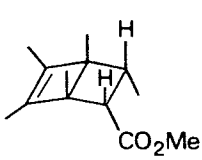
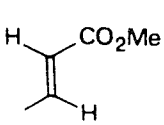
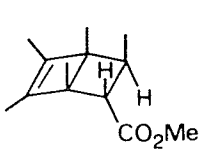
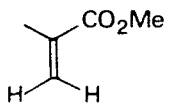
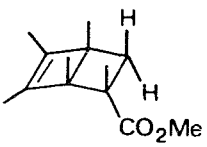
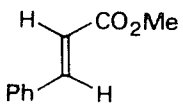
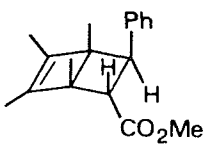
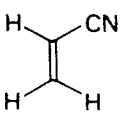
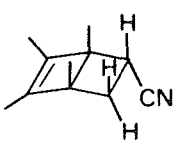
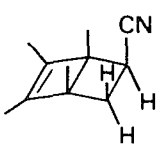
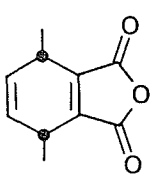
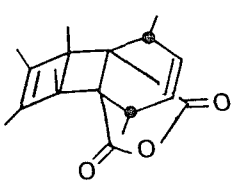
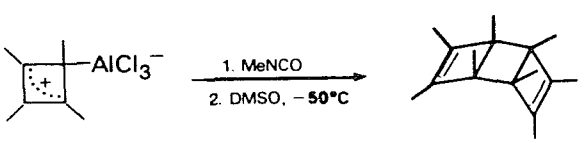
Alkene	Product(s)	Yield (%)[a]
	 **(56)**	35
	 **(57)**	30
	 **(58)**	52
	 **(59)**	21
	 **(60)**	40
	 **(61)**	39

TABLE 4. *continued*

Alkene	Product(s)	Yield (%)[a]
	 **(62)**	39
	 **(63)**	34
	 **(64a)**  **(64b)**	65(55)[b] **a**/**b** or **b**/**a** = 4/1
	 **(65)**	64

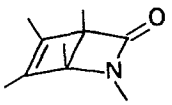
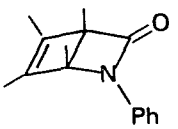
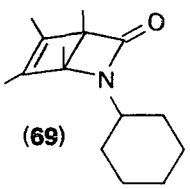
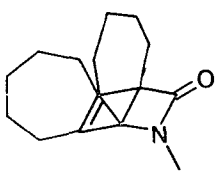
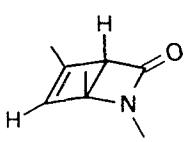
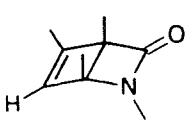
[a] Yields are based on the amount of alkyne used.
[b] This yield has been obtained by van Rantwijk and coworkers[62] for one of the isomers.

pyridones') **67**, **68** and **69** respectively (Table 5)[31]. The addition of methyl isocyanate to complexes **10**, **15**·(Al_2Br_6) and **17**·(Al_2Br_6) shows a remarkable regioselectivity in the formation of (Dewar)pyridones **70**, **71** and **72** respectively. Furthermore, when DMSO is added to a solution of complex **3** and methyl isocyanate at −50°C, at which temperature the latter two compounds do not react, formation of compound **1** is observed (equation 16). Therefore it is concluded that reaction of these complexes



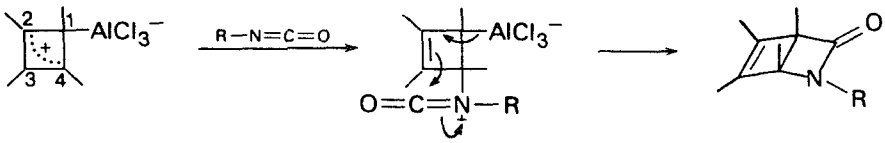
(3) **(1)** (16)

TABLE 5. Reaction of aluminium halide σ complexes of cyclobutadienes with isocyanates, R—N=C=O

Complex	R	Product	Yield (%)[a]
3	Me	 **(67)**	85
3	Ph	 **(68)**	46
3	C-Hex	 **(69)**	57
10	Me	 **(70)**	62
15·(Al_2Br_6)[b]	Me	 **(71)**	69
17·(Al_2Br_6)[b]	Me	 **(72)**	85

[a] Yields are based on the amount of alkyne used.
[b] In these complexes the $AlBr_3$ group has been replaced by Al_2Br_6.

with isocyanates proceeds via a nucleophilic attack of the isocyanate nitrogen atom at the 2(4) carbon atom of the allylic cation, followed by a cyclization on the 3-position (equation 17).



(17)

On using di-*t*-butyl- and diphenyl-carbodiimide as heterocumulenes in the reaction with complex **3**, the substituted 2-aza-3-imino-bicyclo[2.2.0]hex-5-enes **73** and **74** are observed respectively (Table 6)[31].

Reaction of complexes **3** and **17**·(Al_2Br_6) with methyl isothiocyanate leads to compounds **75** and **76** in 66% and 70% yield, respectively (Table 6). A remarkable difference is apparent in these products: product **75** contains a carbon–nitrogen double bond and product **76** a carbon–sulphur double bond. The synthesis of **76** is carried out below −30°C and that of compound **75** under identical conditions at 0°C or higher. It

TABLE 6. Reactions of aluminium halide σ complexes of cyclobutadienes with carbodiimides, methyl isothiocyanate and sulphinylaniline

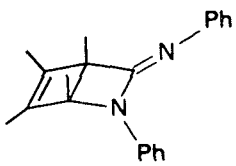
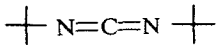
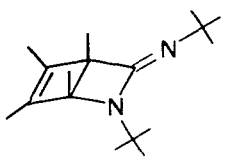
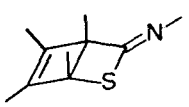
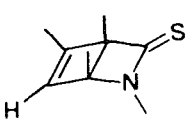
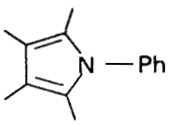
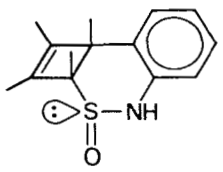
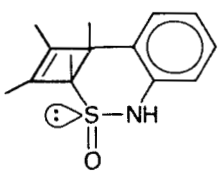
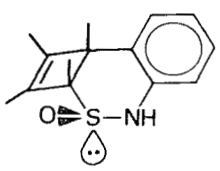
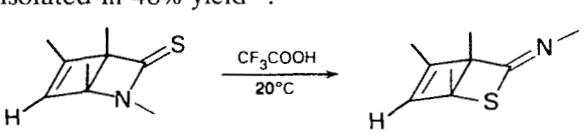
Complex	Cumulene	Product(s)	Yield (%)[a]
3	Ph—N=C=N—Ph	 **(73)**	68
3		 **(74)**	47
3	—N=C=S	 **(75)**	66
17·(Al_2Br_6)[b]	—N=C=S	 **(76)**	70

TABLE 6. *continued*

Complex	Cumulene	Product(s)	Yield (%)[a]
3	Ph—N=S=O	 **(77)**	30 ($T = -80°C$)[c]
3	Ph—N=S=O	 **(78a)**	74 ($T = -60°C$)[c]
3	Ph—N=S=O	 **(78a)**	49 ($T = 20°C$)[c]
		 **(78b)**	

[a] Yields are based on the amount of alkyne used.
[b] In this complex the $AlBr_3$ group has been replaced by Al_2Br_6.
[c] See text.

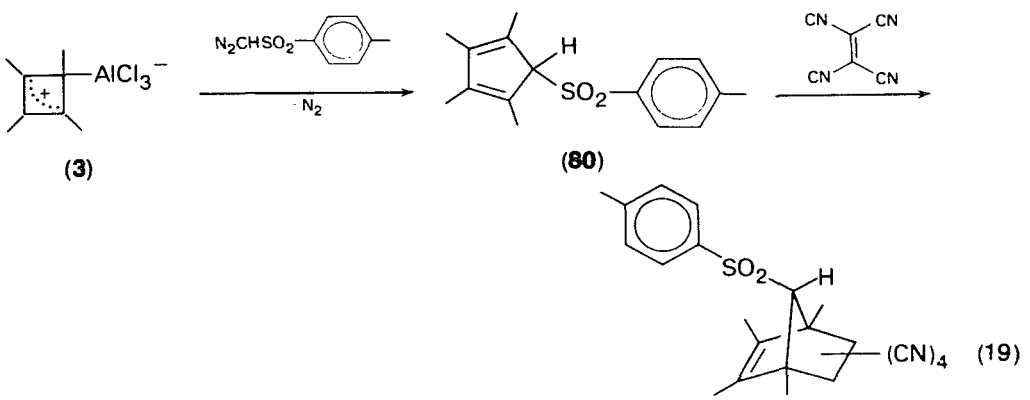
is therefore conceivable that in the latter case the temperature is high enough to induce a rearrangement by $AlCl_3$ of the initial addition product (with a C=S bond) to the observed product (with a C=N bond). When compound **76** is treated with trifluoroacetic acid at 20°C it also rearranges, and compound **79**, containing a carbon–nitrogen bond, is isolated in 48% yield[31].


(76) **(79)** **(18)**

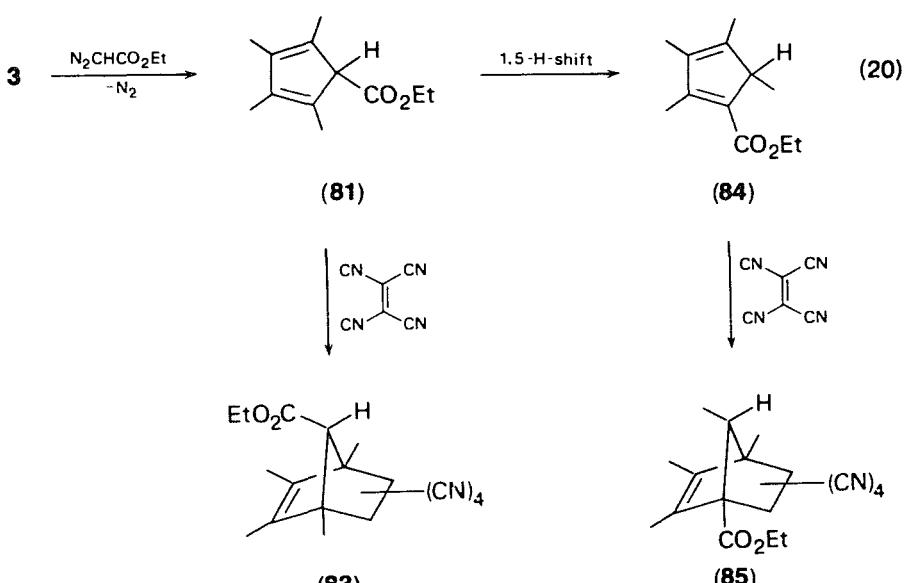
In the reaction of complex **3** with sulphinylaniline it has been shown that the nature of the product is strongly dependent on the temperature at which the reaction is carried out. When a mixture of complex **3** and sulphinylaniline at −80°C (^{13}C-NMR measurements reveal that no reaction occurs at this temperature) is quenched in alkaline water, pyrrole **77** is isolated in 30% yield. When the reagents are allowed to react at −60°C, ^{13}C-NMR measurements reveal the formation of **78a** and this compound has been isolated in 74% yield. When the reaction is performed at room temperature a mixture of isomers **78a** and **78b** (in a 2:1 molar ratio) is obtained in 49% yield (Table 6)[31].

5. *Miscellaneous reactions*

a. Reactions with diazo compounds. Complex **3** has been allowed to react with *p*-tolylsulphonyldiazomethane and ethyl diazoacetate to give, under expulsion of nitrogen, cyclopentadienes **80** and **81**, respectively (equations 19 and 20). These



(3) (80) (82) (19)

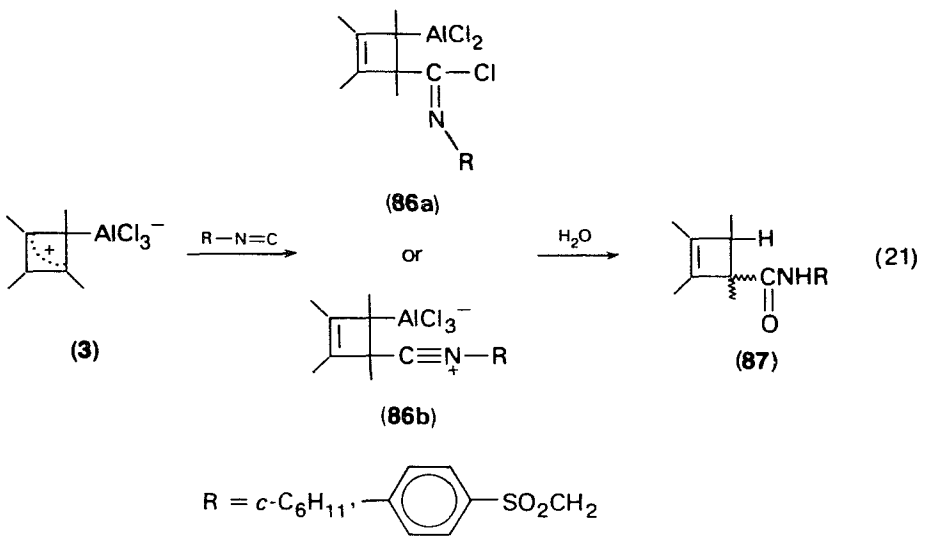


(81) (84) (20)

(83) (85)

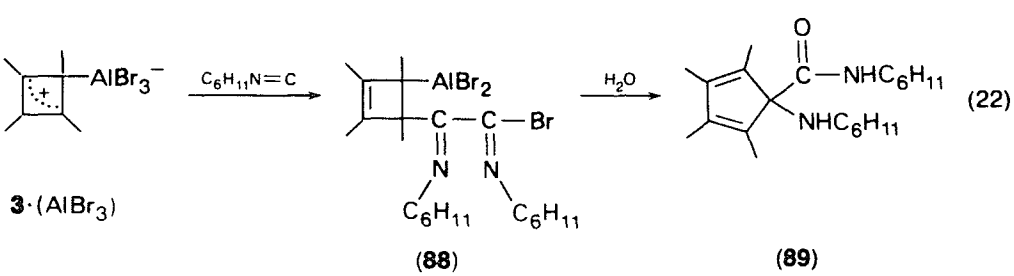
compounds react with TCNE to give Diels–Alder adducts **82** and **83** in 54% and 38% yield (based on used alkyne), respectively. In contrast to **80**, cyclopentadiene derivative **81** exhibits a 1,5 H-shift at room temperature to give **84**, which has been isolated as the Diels–Alder adduct **85** in 16% yield[31].

b. Reactions with isocyanides. When complex **3** is treated with cyclohexyl isocyanide in a 1:1 molar ratio, a new species is formed which still contains a carbon–aluminium bond (equation 21)[14,17]. ^{1}H-NMR, ^{13}C-NMR and IR measurements do not distinguish between **86a** and **86b**. Here as in the case of the isocyanates, the reaction takes place at the 2(4) carbon atom of the allylic cation. (The reactivity of the allylic cation moiety has also been observed with fluorine-substituted cyclobutenyl cations, which show electrophilic substitution reactions at benzene[59].) Addition of water results in cyclobutene derivative **87** (R = *c*-C_6H_{11}, one isomer) in 55% yield (equation 21). A similar

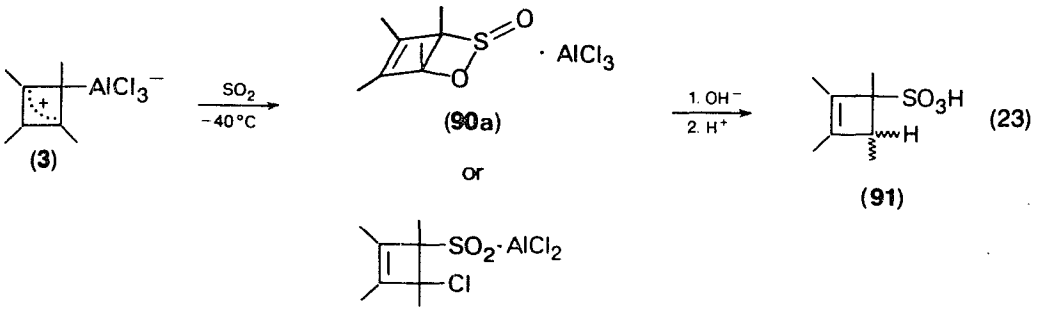


reaction is found with *p*-tosylmethyl isocyanide affording a mixture of two cyclobutene derivatives (*cis* and *trans*) **87** (R = *p*-$MeC_6H_4SO_2CH_2$) in 35% yield (equation 21).

When the corresponding complex **3**, bearing an $AlBr_3$ group is treated with cyclohexyl isocyanide in a 1:2 molar ratio, a new complex is observed to which, on the basis of ^{13}C-NMR and IR measurements, structure **88** has been assigned[17]. Upon hydrolysis the cyclopentadiene derivative **89** is isolated in 42% yield (equation 22).

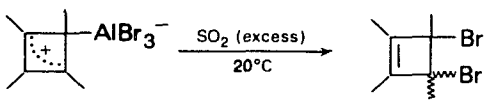


c. Reactions with sulphur dioxide. When SO_2 is added to complex **3** at −40°C, adduct formation takes place; ^{13}C-NMR measurements reveal the presence of a cyclobutene ring in the adduct, suggesting either structure **90a** or **90b**. After hydrolysis,

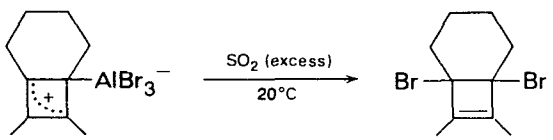


(3) (90a) or (90b) (91) (23)

the sulphonic acid derivative **91** (*cis* and *trans* isomers) is obtained in 50% yield (equation 23)[14]. Complex **3** · ($AlBr_3$) exhibits identical behaviour; however with excess SO_2 at 20°C (*cis* or *trans*)-3,4-dibromo-1,2,3,4-tetramethylcyclobutene (**92**)[7,9] is formed in 38% yield (equation 24). A similar reaction with complex **6a**·($AlBr_3$) gives a mixture of dibromides from which compound **93** has been isolated in 35% yield (equation 25)[14].

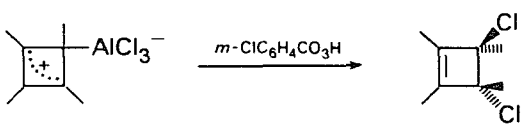


(3)·($AlBr_3$) (92) (24)



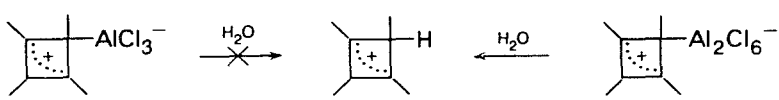
(6a)·($AlBr_3$) (93) (25)

d. Reaction with m-*chloroperbenzoic acid.* Complex **3** reacts with *m*-chloroperbenzoic acid to give compound **5** in 32% yield (equation 26)[31], also known from the BF_3-catalysed reaction of 2-butyne and chlorine (Section II.A).



(3) (5) (26)

e. Reactions with water. It has been demonstrated that the dynamic behaviour of complexes **3** and **3a** as manifested by ^{1}H-NMR line-broadening is quite different. Moreover, it has been observed that complexes **3** and **3a** diverge in their behaviour towards water. Complex **3** gives a mixture of unidentified products whereas complex **3a** is converted into cyclobutenyl cation **25** (equation 27)[13].

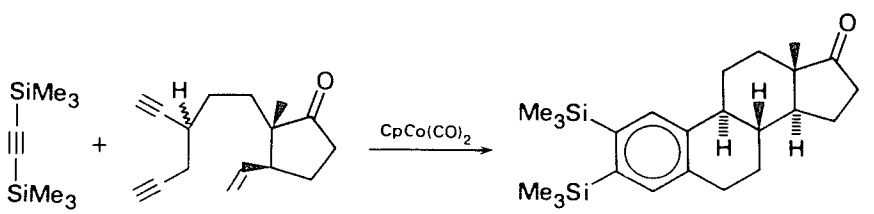


(3) (25) (3a) (27)

B. Comparison of Metallocyclopentadienes, Transition-metal π and Aluminium Halide σ Complexes of Cyclobutadienes

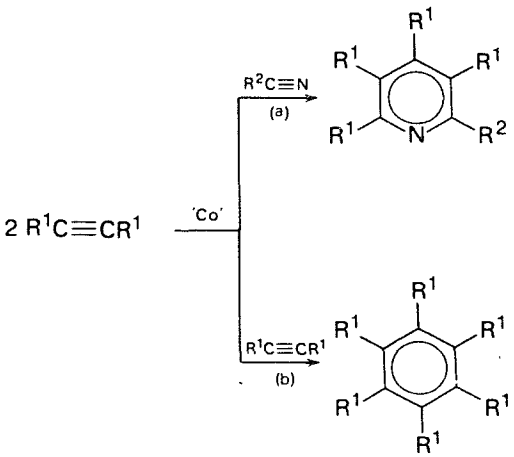
It has been found that complexes of type I, e.g. cobalt complexes, afford substituted benzenes, cyclohexadienes[67] and 2-(1*H*)-pyridones[36] in reactions with alkynes, alkenes and isocyanates, respectively. Rhodium complexes of type I show a similar behaviour towards alkynes; with alkenes, however, no reaction occurs[46]. The product formation in these reactions contrasts with the strained bicyclic products that are obtained in the reactions of the aluminium halide σ complexes of cyclobutadienes (Section III.A). Although the difference in products may in part be due to a difference in reaction temperature (the aluminium halide σ complexes react at or below room temperature, the rhodium and cobalt complexes require temperatures of 70°C and higher), the structure of complexes of type I makes the formation of a product, containing a cyclobutene fragment, i.e. a bicyclic product, less probable. The reactions of complexes of type II with alkynes and alkenes at room temperature affords also substituted (Dewar)benzenes and bicyclo[2.2.0]hexenes (see for instance References 26 and 68). Both aluminium halide σ complexes of cyclobutadienes (Section III.A) and cobalt complexes of type I[66] react with nitriles to yield pyridines.

The above-mentioned reactions are stoichiometric in nature. Catalytic (co)cyclotrimerizations have, however, also been extensively investigated. It is believed that transition-metal complexes of type I are intermediates in these cyclotrimerizations. For example, in the synthesis of substituted aromatic compounds Vollhardt[64] has cocyclotrimerized a variety of diynes with alkynes using $(\pi C_5H_5)Co(CO)_2$ as catalyst. With (bis)trimethylsilylacetylene, optimal results are obtained, which is caused by the fact that (bis)trimethylsilylacetylene does not cyclotrimerize itself. Furthermore, the trimethylsilyl group can easily be converted into other organic functionalities. More recently, Funk and Vollhardt[23,24] have elegantly applied this concept in the synthesis of *dl*-oestrone: compound **94** reacts with (bis)trimethylsilylacetylene to **95** using $(\pi C_5H_5)Co(CO)_2$ as catalyst (equation 28). Compound **95** is converted to *dl*-oestrone by regiospecific functionalization of the trimethylsilyl groups.



(94) (95) (28)

Bönnemann[2] has reviewed the catalytic cocyclotrimerization of alkynes and nitriles to pyridines by organocobalt derivatives (equation 29, path a). A large variety of mono- and di-substituted alkynes can be used, whereas cyclotrimerization of alkynes (equation 29, path b) is suppressed by performing the reaction at a low steady-state concentration of alkynes. The nature of the substituent R^2 can be alkyl or a sulphur-, nitrogen- or oxygen-containing organic group. It has been shown (Section II.A) that there is a preference for the *co*cyclodimerization of two alkynes, when treated with aluminium halides; in the catalytic cocyclotrimerization of acetylene, propyne and acetonitrile a mixture of mono-, di- and tri-substituted pyridines has been obtained, showing a poor selectivity for the intermediate cobaltocyclopentadiene complex Catalytic cocyclotrimerizations of alkynes with isocyanates[37] and carbodiimides[29,37]

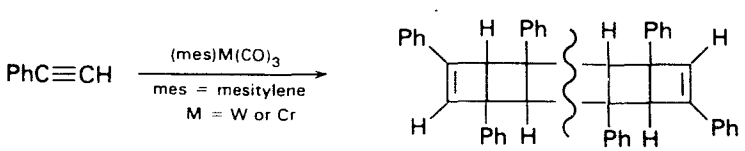


(29)

have been reported to yield 2-(1*H*)-pyridones and 2-imino-1,2-dihydropyridines, respectively.

Like the stoichiometric reactions of complexes of type I, the catalytic (co)cyclotrimerizations differ also from the aluminium halide σ complexes of cyclobutadienes in terms of product formation: whereas catalytic (co)cyclotrimerization leads to benzenes, 2-(1*H*)-pyridones and 2-imino-1,2-dihydropyridine, the aluminium halide σ complexes afford in similar cases (Dewar)benzenes, 3-oxo-2-azabicyclo[2.2.0]hex-5-enes and 2-aza-3-iminobicyclo[2.2.0]hex-5-enes respectively. A similarity in both types of reaction is found in the formation of pyridines.

Finally, the polymerization of phenylacetylene, using a (mesitylene)$M(CO)_3$ (M = W or Cr) catalyst, leads to a ladder polymer, which is probably formed by consecutive [2 + 2]cycloadditions (equation 30). In the polymerization of 2-butyne with (toluene)$Mo(CO)_3$, the presence of hexamethyl(Dewar)benzene has been detected[20].



(30)

IV. CONCLUSIONS

At the end of this review a number of summarizing remarks are appropriate with regard to the synthesis and chemical reactivity of aluminium halide σ complexes of cyclobutadienes. Because the scope of these complexes is still expanding, the conclusions present the state of the art at this moment.

(1) The use of alkynes in the synthesis of the σ complexes has been so far mainly limited to mono- and di-*alkyl*-substituted alkynes, although in some cases a heteroatom is allowed to be present in the substituent.
(2) The cyclic diynes used have shown a strong preference for *intra*-, rather than *inter*-molecular cyclodimerization.
(3) The cyclodimerization of monosubstituted alkynes is regioselective, e.g. the cyclodimerization of propyne with $AlBr_3$ leads to complex **15** only.
(4) There is a strong preference for *co*cyclodimerization of a *mono*- and a *di*-alkyl-substituted alkyne rather than the corresponding cyclodimerizations.

(5) With a few exceptions, the reactions of the σ complexes with unsaturated reagents, e.g. alkynes, alkenes and heterocumulenes, lead to strained bicyclic compounds.

(6) In the reactions of the σ complexes with unsaturated reagents, it depends on the nature of the reagent whether initial attack occurs at the allylic cationic moiety or at the carbon–aluminium bond.

(7) In general, the reactions of the σ complexes are stoichiometric in nature, with one notable exception, the cyclotrimerization of 2-butyne to hexamethyl(Dewar)benzene under the influence of a catalytic amount of $AlCl_3$.

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CHAPTER **24**

Structure of triple-bonded molecules

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I. INTRODUCTION

This chapter will review and summarize the results of structural determinations, both experimental and theoretical, and related spectroscopic measurements. Wherever possible, the most accurate structures will be indicated. It should be noted that in the present context, the structure of a molecule is taken to refer to its nuclear configuration, rather than its electronic configuration. Discussions of the latter can be found in another chapter.

II. DIATOMIC MOLECULES

In spite of the apparent simplicity of diatomic molecules there are still unresolved problems concerning the structure of many of relevance to the present volume. Since the theoretical aspects of such molecules have been discussed in another chapter only a brief summary of the structural features will be given here.

Although it is now established[1] that the ground state of the C_2 molecule is $^1\Sigma_g^+$, there is still doubt in the case of CN^+. The most recent calculations[2] favour a $^1\Sigma^+$ ground state for CN^+. The internuclear distances for C_2 and CN^+ are 1.2425 Å[1] and 1.1729 Å[3], respectively, while the vibrational frequencies are 1855[1] and 2033 cm^{-1} [3], respectively. Additional discussion of the CN^+ configuration problem can be found in another chapter.

III. TRIATOMIC MOLECULES

The microwave spectra and structure of HCN have been determined by Costain[4]. Centrifugal distortion constants and anharmonic potential constants have been obtained[5]. The lattice energy of hydrogen cyanide has been evaluated[6]. The force constants and ideal gas thermodynamic functions have been calculated[7]. A number of spectroscopic studies in the infrared have been carried out[8–9]. Rotational constants for HCN and DCN are available[10]. The bending-rotation Hamiltonian has been discussed with reference to HCN[11]. The molecular Zeeman effect has been observed in the $J = 0 \rightarrow 1$, $\Delta M = 0$ and ± 1 transitions in $H^{12}C^{15}N$ and the molecular g values, magnetic susceptibility anisotropies, and corresponding molecular quadrupole moments have been found[12]. Studies of the intermolecular interactions and self-association of HCN have been reported[13].

There has been considerable interest in hydrogen isocyanide for a number of years. HNC was first observed in the laboratory only in frozen matrices of Ar and CO_2, subsequent to photolysis of CH_3N_3 or HCN[14]. Calculations indicate an equilibrium mole fraction of HNC in HCN at 300 K of approximately 3×10^{-11}, which is below the limits normally detectable with a conventional microwave spectrometer. Hydrogen isocyanide was first observed when Snyder and Buhl discovered a strong emission line at 90665 (±1) MHz in the radio sources W51 and DR21[15]. This has been ascribed to the $J = 1 \rightarrow 0$ transition of HNC. It has been shown[16] that a mole fraction of approximately 10^{-8} can be detected, which sets a lower limit to the zero-point energy difference between HCN and HNC of 0.47 ± 0.02 eV (10.8 kcal mol^{-1}). Subsequently HNC was identified in the laboratory by two independent groups[17,18]. DC glow discharges in mixtures of cyanogen and hydrogen, cyanogen and acetylene, and nitrogen and acetylene were used as sources. The isotopic species $HN^{13}C$ was detected in a number of molecular sources[19], and the hyperfine structure of $HN^{13}C$ was determined[20]. Brown concluded that the deuterium enrichment in interstellar HCN and HNC must be due to isotopic effects that influence the formation processes rather than equilibria involving HCN or HNC[21].

TABLE 1. Structural features of some triatomic molecules, X—C≡N

Molecule	Bond lengths (Å)		Reference
	C≡N	X—C	
HCN	1.15535	1.06317	4
FCN	1.159	1.262	22
ClCN	1.159	1.631	22
BrCN	1.158	1.789	22
ICN	1.159	1.994	22

The structure of the cyanogen halides (or halogen cyanides) has been reported by Tyler and Sheridan[22] and is summarized in Table 1. The force constants in a number of linear triatomic molecules, including the cyanogen halides, have been evaluated[23,24]. The values obtained indicate that the CN bond is relatively insensitive to the nature of the attached atom. Ideal gas thermodynamic functions have been calculated for ClCN[25] for 298, 500 and 1000 K and for BrCN for a variety of temperatures[26]. The influence of the environment on the vibrational frequencies of C≡N bonds has been examined for BrCN and other nitriles[27].

IV. LINEAR MOLECULES CONTAINING —CN AND —C≡C—

The structures and spectra of a number of linear cyano compounds have been obtained. The microwave spectrum of cyanoacetylene (cyanoethyne) has been studied by Westenberg and Wilson[28] and by Tyler and Sheridan[29]. A summary of the microwave spectrum and related data is provided by Lafferty and Lovas[30]. Alexander, Kroto and Walton[31] have obtained the microwave spectrum, substitution structure and dipole moment of cyanodiacetylene (cyanobutadiyne). The microwave spectra of 1-cyano-2,4-pentadiyne[32] and of cyanohexatriyne[33] were published in 1978.

Oka[34] has demonstrated that values of B_0 for polyacetylene compounds can be successfully predicted by a numerical extrapolation of the series of rotational constants available for H—(C≡C)$_n$—C≡N, where n = 0, 1, 2 and 3.

The rotational spectrum of cyanobutadiyne has been observed in the range 26.5–40.0 GHz[35] and the emission spectra of the cations of cyanodiacetylene, methylcyanodiacetylene and ethylcyanodiacetylene in the gas phase have been detected using low-energy electron beam excitation[36]. The microwave spectrum of cyanohexatriyne has also been measured[37]. Table 2 summarizes the measured values of the rotational constants for the ground state.

Although not falling within the same group of cyano molecules just listed, *C*-cyanophosphaethyne(N≡C—C≡P) is, nevertheless, linear and thus should be included in the present section. This molecule has now been made from cyanogen azide (NCN_3) and phosphaethyne (HC≡P) and its microwave spectrum measured[38].

TABLE 2. Ground-state rotational constants

Molecule	B_0 (Mc/s)	Reference
HC≡CCN	4,549.06 ± 0.01	29
H(C≡C)$_2$CN	1,331.333 ± 0.002	35
H(C≡C)$_3$CN	564.00074 ± 0.00016	37
CH$_3$(C≡C)$_3$H	778.2445 ± 0.0005	32
CH$_3$(C≡C)$_2$CN	778.0401 ± 0.0008	32

TABLE 3. Experimental bond lengths in linear cyanides

Molecule	Bond lengths				Reference
	H—C	C≡C	C—C	C≡N	
Cyanoacetylene	1.058	1.205	1.378	1.159	29
Cyanobutadiyne	1.0569	1.2087	1.3623	1.1606	31
		1.2223	1.3636		
$CH_3(C{\equiv}C)_2CN$	—	1.2071	1.3629	1.1605	32
$H(C{\equiv}C)_3CN$	1.0569	1.2087	1.3623	1.1606	37
		1.2223	1.348[a]		
		1.2223	1.3636		

[a]Estimated value.

Considerable interest in linear cyano molecules has resulted from their detection in the interstellar medium. A substantial number of reports of the detection of these molecules can be found in the literature. Further discussion of these would unnecessarily enlarge the number of references. For additional details reference may be made to a list of interstellar molecules by Mann and Williams[39].

The availability of bond-length data for linear cyanides with increasing chain lengths provides an opportunity to examine the effect of electron delocalization on such structural parameters. Table 3 summarizes the information on bond lengths of such molecules. The addition of one acetylenic group to form cyanobutadiyne produces a marked elongation in the length of the C≡C bond closest to the cyano group, while both C—C bonds are shorter than that found in cyanobutadiyne. In cyanohexatriyne, the central C—C bond length was obtained by adjusting it to reproduce the observed value of B_0[37]. The estimated value of 1.348 Å is much smaller than the value of approximately 1.38 Å commonly found for the carbon–carbon single bond. Although such a shortened C—C bond is also found in $Me_3Si(C{\equiv}C)_4SiMe_3$[40], for which a value of 1.33 Å has been reported, the length of the central C—C bond in cyanohexatriyne is considerably shorter than those found in cyanobutadiyne[31].

Ab initio calculations on a variety of linear alkynes with both the STO-3G and the 6-31G basis sets have shown that the C—C and C≡C bond lengths depend on the length of the molecule, the position of the particular bond in the molecule and the presence or absence of substituents[41]. Although the trends are reproduced, the single-determinant calculations with either of these two basis sets are unable to reproduce the smallest C—C bond lengths found in the longer-chain alkynes, for example, cyanobutadiyne. Although small changes in the σ-overlap populations were found, it appears that the variations in bond lengths are primarily related to alterations in the π-overlap populations.

V. CYANAMIDES

The structure of cyanamide and its substituted derivatives has been of interest for many years, in part as a consequence of the uncertainty concerning the planarity of the molecule. In 1959, the structure of cyanamide was believed to be planar[42], and subsequent work[43], in 1961, was interpreted as confirming the earlier conclusion. However, in 1962, Millen, Topping and Lide[44] concluded, from their microwave studies, that the amine hydrogen atoms were slightly out of the plane defined by the remainder of the molecule. Further studies reported in 1968[45] supported the latter conclusion. An *ab initio* calculation reported in 1970[46] found a nonplanar

TABLE 4. Structures of cyanamides

Structural parameter	Molecule		
	H_2NCN[48]	F_2NCN[50]	$(H_3C)_2NCN$[52]
C≡N (Å)	1.160	1.158	—
N—C (Å)	1.346	1.386	1.351
R—N (Å)	1.001	1.399	—
RN̂R (deg.)	113.5	102.8	116
RN̂C (deg.)	—	105.4	—
NĈN (deg.)	—	173.9	—
Out-of-plane angle (deg.)	38	—	36

configuration of cyanamide to be more stable than a planar one. CNDO calculations[47] provided additional support for this contention. In 1972, Tyler, Sheridan and Costain confirmed the nonplanar structure of cyanamide[48] and found the out-of-plane angle for the HNH group to be 37° 58′ ±1°. Subsequent *ab initio* calculations with an STO-3G basis produced an out-of-plane angle of 49.7°[49].

The structure of a disubstituted cyanamide, difluorocyanamide, was reported in 1972[50]. With F_2NCN the pyramidal nature of the amide bonds is more evident than in cyanamide (Table 4). The RN̂R angle in F_2NCN is approximately 10° smaller than in H_2NCN. In addition the NĈN angle is not 180°, as expected, but 173°, with the cyano nitrogen bent away from the fluorine atoms. The N—C bond length is approximately 0.04 Å longer than that in H_2NCN and 0.05 Å shorter than that in F_2NCH_3[51]. The C≡N distance in F_2NCN is similar to that in H_2NCN.

The microwave spectrum of dimethyl cyanamide has been obtained[52]. With this molecule an out-of-plane angle of 36° was found for the amino group. A gas-phase electron diffraction study of dimethyl cyanamide[53] is in essential agreement with the microwave results.

VI. ACETONITRILES

Accurate structural data have been available for acetonitrile (methyl cyanide) for a number of years. Costain[54] has published its complete structural analysis (Table 5). The microwave spectrum of acetonitrile in excited vibrational states has been analysed[55,56]. The ground-state rotational spectrum of $^{12}CH_3{}^{12}C^{14}N$ has been investigated by sub-Doppler spectroscopy[57]. Consequently, values for all the sextic centrifugal distortion constants are now available. The spectrum of $^{12}CH_3{}^{12}C^{15}N$ has also been reported[58]. The ^{13}C isotopic forms of acetonitrile are of considerable astrophysical interest and importance[59]. The ground-state microwave spectra of

TABLE 5. Molecular structure of acetonitrile from various sources

C≡N (Å)	C—C (Å)	H—C (Å)	HĈC (deg.)	HĈH (deg.)	Reference
1.1572	1.4582	1.1120	109.27	109.67	61
1.157	1.458	1.103	109.5	—	54
1.1572	1.4596	1.094	—	108.93	62
1.153	1.465	1.095	109.7	—	63
1.1567	1.4617	1.0947	109.85	109.09	60

acetonitrile and acetonitrile-d_3 and their ^{13}C and ^{15}N isotopic species have been remeasured between 8 and 240 GHz. The quartic centrifugal distortion constants, rotational constants and structures have been derived[60]. The structural information from such work and that of others is summarized in Table 5.

VII. SUBSTITUTED ACETONITRILES

The structures of a number of halogenated acetonitriles have been studied by Graybeal and coworkers[64] and also by Morino and coworkers[66]. Graybeal and Cornwell[64] employed nuclear quadrupole resonance spectra to demonstrate that the cyano group, with its strong electron-withdrawing capabilities, changes the ionic character of the immediately adjacent bond, rather than altering the contribution of double-bond character to the bond. In monochloroacetonitrile[65,66] the length of the C—Cl bond (Table 6) is little different from that in either CH_3Cl or CH_2Cl_2, thereby suggesting little, if any, double-bond character in this bond. In contrast the C—C bond length is significantly shorter (Table 6) than that of the usual C—C single bond (1.54 Å), thus indicating either some double-bond character in the C—C bond, possibly arising from a contributing resonance form or as a result of the existence of some positive charge on the carbon atoms, again possibly from contributing resonance forms.

The microwave spectrum of monofluoroacetonitrile has been measured[67] but only the single common isotopic species was employed. If the H_2CCN skeleton structure obtained for monochloroacetonitrile[65] is assumed, the C—F bond length and CCF angle are 1.39 Å and 112°, respectively.

Structural parameters for bromoacetonitrile are listed in Table 6. Values of the quadrupole coupling constants have been interpreted as indicative of the absence of π bonding in the C—Br bond and approximately 4% ionic character in that bond.

Microwave spectral data have been used[69] to show that, in aminoacetonitrile, the amino and methylene groups adopt the *trans* orientation with respect to each other. Later results[70] from the measurement of the infrared and Raman spectrum of aminoacetonitrile support this conclusion. Although intramolecular hydrogen bonding may be responsible for the preferred orientation, large gas/liquid frequency shifts occur, possibly due to intermolecular hydrogen bonding in the liquid phase.

Measurements of the pure rotational spectrum of methoxyacetonitrile (CH_3OCH_2CN)[71] have shown that the *trans* and *gauche* conformations (with respect to rotation about the O—CH_2 bond) differ by approximately 5.7 kJ mol^{-1}, with the

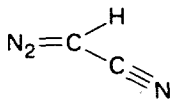
TABLE 6. Molecular constants of halogenated acetonitriles

Structural parameter	ClH_2CCN[65]	ClH_2CCN[66]	BrH_2CCN[68]
C—X[a] (Å)	1.767	1.7815	1.901
$C\hat{C}X$	111° 24′	111° 29′	111° 32′
C—C (Å)	1.472	1.458[b]	1.487
C—H (Å)	1.070[b]	1.0881	1.107
H···H (Å)	1.728	1.7812	1.718[b]
$C\hat{C}H$	109° 30′ [b]	107° 27′	102° 52′
C≡N (Å)	1.158[b]	1.158[b]	1.158[b]
$C\hat{C}N$	180°	180° [b]	180° [b]

[a]X = Cl, Br.
[b]Assumed.

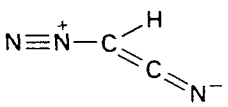
latter having the lower energy. The dihedral angle in the *gauche* conformer has been estimated to be approximately 69° from the *cis* orientation.

Costain and Yarwood[72] have measured the microwave spectrum, structure and dipole moment of diazoacetonitrile (**1**). Vibrational spectra of matrix isolated



(**1**)

diazoacetonitrile and several of its isotopic forms have been obtained[73]. The force constant for the CC stretch is larger than that expected for a CC single bond, while the C≡N stretching force constant is smaller than that for a typical CN triple bond. Both of these observations indicate the importance of the resonance structure **2**.



(**2**)

The experimentally measured CNN length in diazoacetonitrile is shorter than that in diazomethane and the HĈN in the former is more than 6° larger than the corresponding angle in the latter, thus suggesting significant interaction between the C≡N and the CNN groups. Measured values for bond lengths and angles of diazoacetonitrile and diazomethane are summarized in Table 7, along with calculated values for these two molecules as well as those for diazopropyne. The experimental C≡N bond length is approximately 0.006 Å longer than the 'normal' C≡N bond length. Mulliken[76] has estimated that an increase of 0.005 Å in the length of a triple bond can significantly alter the bonding in the remainder of the molecule. The C—C≡N chain in diazoacetonitrile is bent by approximately one degree, presumably due to the interaction between the two chain-like portions of the molecule. Costain and Yarwood[72] note that the available evidence supports a planar structure for diazoacetonitrile.

TABLE 7. Structures[a] of diazoacetonitrile, diazopropyne and diazomethane

	N_2CHCN[72]	N_2CHCCH	N_2CH_2[75]
C≡N	1.165 [1.159][b]	—	—
C—H	1.082[c] [1.081][b]	[1.082][b] [1.064][b] (≡C—H)	1.075 [1.079][b]
C—C	1.424 [1.439][b]	[1.173][b] (C≡C)	—
C=N	1.280 [1.303][b]	[1.298][b]	1.300 [1.282][b]
N—N	1.132 [1.180][b]	[1.184][b]	1.139 [1.190][b]
HĈC	117° [122.1][b]	[122.2][b]	—
CĈN	119° 32′ [119.9][b]	[120.7][b]	—
HĈN	123° 28′ [118.0][b]	[117.1][b]	117.0 [119.2][b]

[a]Calculated values (STO-3G) in square brackets; bond lengths in Å, bond angles in degrees.
[b]Reference 74.
[c]Assumed.

VIII. PROPIONITRILES

The microwave spectrum of propionitrile (ethyl cyanide) was first measured by Lerner and Dailey[77]. More recently, the ground-state rotational spectrum of propionitrile has been reinvestigated between 8 and 250 GHz[78] and the work since that of Lerner and Dailey has also been summarized. The structure of propionitrile is summarized in Table 8[79].

The infrared and Raman spectra of pentafluoropropionitrile (C_2F_5CN) have been measured and frequencies assigned to the 21 fundamental modes[80]. Ideal-gas thermodynamic properties have also been calculated. Lower C—C and C—F stretching constants have been obtained for C_2F_5CN than for CF_3CN. The C≡N stretching constants are 18.30 and 18.00 md/Å for the former and latter, respectively.

The microwave spectrum of 3-methoxypropionitrile ($CH_3OCH_2CH_2CN$) has been measured[81]. Only one rotational isomer (the fully-*trans* form) was found. This observation was rationalized in terms of a combination of polar and steric effects.

TABLE 8. Structure of propionitrile[79]

Bond	Bond length (Å)
C—C	1.525
C—CN	1.427
C≡N	1.168
C—H (methylene)	1.087[a]
C—H (methyl)	1.087[a]
Angle	**Bond angle (deg.)**
$C\hat{C}N$	180[b]
$C\hat{C}C$	110.9
$C\hat{C}H$ (methyl)	111.2
$H\hat{C}H$[c] (methyl)	107.6
$C\hat{C}H$ (methylene)	111.8
HCCH[d] (methylene)	59.8
$H\hat{C}H$[c] (methylene)	106.7

[a] C—H ≡ C—D.
[b] Assumed.
[c] Calculated from the other structure parameters.
[d] Dihedral angle formed by in-plane methyl H, the two ethyl C and methylene H.

IX. BUTYRONITRILE

The microwave spectra of *n*-propyl cyanide (butyronitrile)[82] and isocyanide[83] have been obtained. Both molecules can exist in two rotational isomers, *trans* (methyl *trans* to cyanide or isocyanide substituent) and *gauche*. The energy difference between the two cyanide conformations is estimated as probably less than 1 kcal mol^{-1}. The dihedral angle of the *gauche* form is estimated as approximately 60° from the *cis* orientation. Fuller and Wilson[83] have found the isocyanide *gauche* dihedral angle to be 61° (±2°) from the *cis* position and the isocyanide *gauche* conformer to be slightly more stable than the *trans* form. Wilson[84] has also reviewed and discussed the conformations of a variety of small molecules. *Ab initio* calculations with an STO-3G basis and geometry optimization have been performed on *n*-propyl cyanide and

isocyanide for four rotational conformations, *trans, cis* and *gauche* (dihedral angles of 60° and 90° from *cis*)[85]. For both the cyanide and isocyanide the *trans* and 60° *gauche* isomers are calculated to be the most stable, in agreement with the experimental data (Figure 1). Although the *trans* form is calculated to be 0.2 and 0.1 kcal mol^{-1} smaller than the 60° *gauche* form for the cyanide and isocyanide respectively, this difference is probably too small to permit any differentiation between the stabilities of these two conformers. Fuller and Wilson[83] found the 60° *gauche* ground state to be 0.3 ± 0.1 kcal mol^{-1} above the *trans* form. As can be noted from Figure 1, the *gauche* 90° and *cis* forms are calculated to be approximately 1.8 and 4.9 kcal mol^{-1},

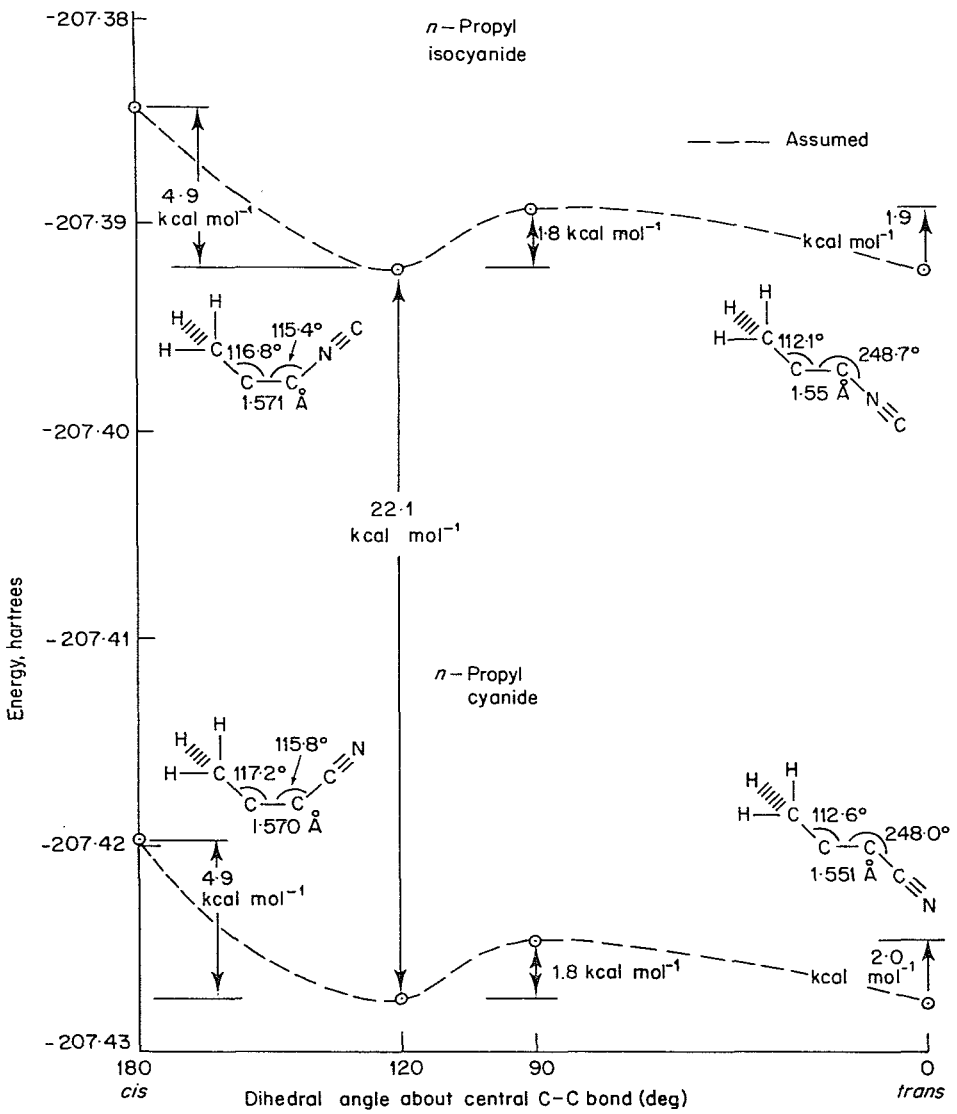


FIGURE 1. Energies of rotational isomers of *n*-propyl cyanide and *n*-propyl isocyanide. Reproduced by permission of Elsevier Scientific Publishing Company, Amsterdam from J. B. Moffat, *J. Mol. Struct.*, **44**, 237 (1978).

respectively, above the *gauche* 60° conformation for both the cyanide and isocyanide. It is of interest to note that with either the cyanide or the isocyanide the two framework angles (two CĈC angles in former case and one CĈC and one CĈN angle in latter case) are 4 degrees larger in the *cis* form than in the *trans* conformer.

It is interesting to note that in the case of *n*-propylacetylene[86] the experimental data indicate that the *trans* and *gauche* (65°) forms are the most stable, but the latter is the more stable of the two conformers mentioned.

X. NITRILES CONTAINING UNSATURATED SUBSTITUENTS

A. Vinyl Cyanide

The structures of vinyl cyanide (acrylonitrile)[87] and isocyanide[88] have been obtained from microwave spectra and are summarized in Table 9. *Ab initio* geometry-optimized

TABLE 9. Structures of vinyl cyanide and isocyanide

	Vinyl cyanide[87]	Vinyl isocyanide[88]
Bond	Bond length (Å)	
C=C	1.338	1.339
C—H	1.086	1.086
C—C	1.425	—
C—N	—	1.376
C≡N	1.163	1.165
Angle	Bond angle (deg.)	
$C^1\hat{C}^2H^3$ [a]	121.2	121.7
$C^1\hat{C}^2H^4$	121.2	121.7
$C^2\hat{C}^1H^5$	121.7	120.8
$C^6\hat{C}^1C^2$	122.6	—
$N^6\hat{C}^1C^2$	—	123.6

[a] C^1 and C^2 are ethylenic carbon atoms with the cyanide or isocyanide group attached to the former. H^3 and H^4 are attached to C^2 with the former *trans* to the cyanide or isocyanide group. C^6 and N^6 are the carbon and the nitrogen atoms of the cyanide and isocyanide group, respectively.

calculations[89] with the STO-3G basis sets and the 6-31G set have been carried out for both molecules. The extended basis provides bond lengths in better agreement with those obtained experimentally, while the smaller basis yields more acceptable values for the bond angles. The available data on the microwave spectrum of vinyl cyanide and derived molecular parameters have been reviewed[90].

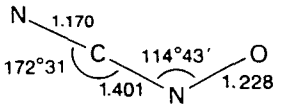
B. Substituted Vinyl Cyanides

The substituted propenes have been employed for studying the changes in the methyl group barrier to internal rotation resulting from adding various groups to the ethylene part of the molecule. Lowering of this barrier due to addition of various substituent groups has been attributed to conjugation. A number of these studies have

been concerned with cyanide group substitution. For example, the microwave spectrum of crotononitrile (1-cyano-2-methylethylene) has been measured, first by Laurie[91], and later by Suzuki and Kozima[92] and Hsu and Flygare[93]. *Ab initio* geometry-optimized calculations at the STO-3G level have also been done[94]. Studies of methacrylonitrile[95] have shown that the barrier to internal rotation of the methyl group is 2030 ± 60 cal mol^{-1}, considerably smaller than that found with the same molecule where the cyano group is replaced by a halogen atom, for example. Rationalization of this observation through a conjugation effect is discussed in more detail in the theoretical chapter of this volume.

XI. CYANIDES WITH NITROGEN IN THE SUBSTITUENT GROUP

Nitrosyl chloride and silver cyanide react at −30 to −20°C to form a blue-green gas which is stable at room temperature for several hours[96]. The microwave spectrum for this substance, nitrosyl cyanide (ONCN) was first reported in 1973[97]. The structure as given then (**3**) was obtained by assuming a planar molecule. The NCN bond is slightly bent and the C≡N bond is somewhat longer than normal. However the C—N bond is only 1.401 Å in length.



(**3**)

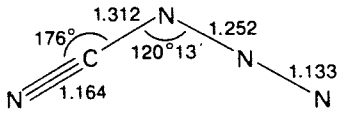
Gowenlock and coworkers have employed an electron impact method to obtain the R—NO bond strengths in some *C*-nitroso compounds[98] and a number of halogenated *C*-nitroso compounds[99]. They have predicted that the governing factor in the R—NO bond energy is the reorganizing energy of the liberated nitric oxide and that there is no correlation between the bond dissociation energy and the bond length. This prediction has been tested and confirmed by measuring the bond energy in NC—NO by an electron impact method[100]. A value of 28.8 ± 2.5 kcal mol^{-1} is obtained, apparently the smallest so far obtained for any *C*-nitroso compound. Since the C—N bond is short and the bond energy is relatively small, there appears to be no direct correlation between bond energy and bond length.

The vapour-phase infrared spectrum of nitrosyl cyanide has been measured in the region between 4000 and 250 cm^{-1} [101]. Ideal gas thermodynamic properties have also been calculated for temperatures from 100 to 2100 K.

Ab initio calculations on nitrosyl cyanide[102] rationalize the electron reorganization energy for NO, released through the dissociation of NCNO, as resulting from the change from a σ-bonded fragment, with an sp^2-hybridized nitrogen atom, to a π radical.

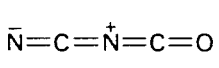
The pure rotational far-infrared absorption spectrum of nitrosyl cyanide has been measured in the range 20–100 cm^{-1} [103]. The infrared spectra of nitrosyl cyanide and eight isotopically substituted species have been obtained[104]. Force constants have been obtained both from the experimental data and *ab initio* calculations. Both the N=O and the C—N stretching force constants are found to be relatively small.

The microwave spectra of cyanogen azide, NCNNN, and two isotopic species have been measured between 11 and 37 GHz[105]. The observed data are consistent with a planar V-shaped structure (**4**). The rotational spectrum of cyanogen azide has also been studied by Bolton, Brown and Burden[106].

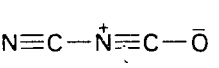


(4)

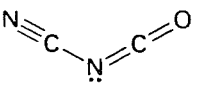
Cyanogen isocyanate (NCNCO) has only recently been prepared for the first time[107,108]. The infrared spectrum of cyanogen isocyanate has been interpreted as showing that the molecule is bent in the solid phase but linear in the gas[107]. The microwave spectrum has been obtained by Hocking and Gerry[109,110]. Since only one isotopic species was studied, only two structural parameters were calculated, after assumption of values for all others. The two calculated values are 1.283 Å and 140° for the NC—NCO bond length and the CN̂C angle, respectively. These authors conclude that, of the three most probable resonance forms, two are linear (**5a,b**) and the third is bent (**5c**), with the bent form presumably being the most important.



(**5a**)



(**5b**)



(**5c**)

Theoretical studies of cyanogen isocyanate and its isomers[111] provide semiquantitative support for the bent structure and the existence of resonance delocalization. For example, the C=O bond in cyanogen isocyanate is calculated to be 1.176 Å (STO-3G) while that in the parent molecule, isocyanic acid (HNCO), is predicted to be 1.183 Å. Further, the calculated NC—N bond length, 1.382 Å, is considerably shorter than that expected for the usual C—N single bond.

XII. CYCLIC MOLECULES

The microwave spectrum of cyclopropyl cyanide has been investigated by a number of workers[112–115]. Some years ago a theory of strained hydrocarbons was outlined[116]. The energy per CH_2 group is assumed to be a function of a hybridization parameter ξ [where the angle $(\pi - 2\xi)$ is the angle between two hybrid orbitals of a carbon in a field of symmetry C_{2v}] and the energy is minimized with respect to this parameter. The hybrid orbitals are written as linear combinations of the atomic 2s, 2pσ and 2pπ orbitals of carbon. For cyclopropane a value of 38° is obtained for ξ. This can then be interpreted as showing that the angle between the orbitals binding the carbon atoms is 104°, even though the angle between the C—C directions is 60°. Since the C—C bonds must then be displaced outward from the centre of the ring, the internuclear distance between carbon atoms should be decreased. In addition, the CCC bond angle is reduced from the tetrahedral value 109° through an increase in the amount of p character in the hybrid bonds, thus decreasing the strain. This leads to an increase of the HĈH angle above the tetrahedral value because of increased s character. For cyclopropane the HĈH angle is predicted to be 116°. The resonance energy is calculated as 3.3 eV. The cyclopropyl ring is more electrophilic and more conducive to conjugation with substituents as a result of the delocalization of the C—C bonding electrons relative to that in unstrained hydrocarbons.

Friend and Dailey[112] have obtained the microwave spectra and rotational constants for cyclopropyl cyanide and two deuterated species. Their results provide support for the Coulson–Moffitt theory[116]. A C—C distance of 1.513 Å is found, 0.037 Å shorter than the C—C distance in the ethyl halides. The HĈH and HĈCN

angles have been determined to be 114.6° and 119°, respectively. The conjugating ability of the cyclopropyl ring seems to lie between that of benzene and ethylene.

Hofmann has suggested[117,118] from the Walsh model for cyclopropane[119] that substitution with a cyano group, for example, that is, a good π acceptor ligand, will produce a net strengthening of the 2,3 bond and a corresponding weakening of the 1,2 and 1,3 bonds. In contrast, substitution with a π-electron donor is predicted to weaken all three ring-bonds.

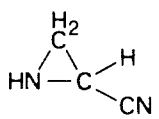
The microwave spectrum of the normal isotopic species of cyclopropyl cyanide and of the isotopic species with ^{13}C substituted in the ring has been obtained[113]. The C(1)—C(2,3) and C(2)—C(3) bond lengths are found to be 1.528 Å and 1,500 Å, respectively, compared with 1.510 Å[120] and 1.514 Å[121] for either length in cyclopropane. Therefore, in agreement with the predictions of Hoffmann[117], substitution with a π-electron acceptor shortens the bond opposite the substituent and lengthens the two adjacent ones. However, the predicted effect with π-electron donors was not observed.

The results of *ab initio* calculations (4-21G) for cyclopropyl cyanide[123] in comparison with those for other substituted cyclopropanes provide evidence for a conjugative interaction between the π orbital of the substituent and the σ orbital of the ring. For example, the calculated values for C(1)—C(2,3) and C(2)—C(3) are 1.525 and 1.505 Å, in good agreement with the experimental results[113]. In addition, the length of the C—CN bond is predicted to be 1.435 Å, significantly shorter than expected for a C—C single bond.

Most recently, Brown, Godfrey and Ottrey[115] have analysed the quadrupole hyperfine structure of six selected rotational transitions of cyclopropyl cyanide. Coupling constants were derived and slightly revised rotational constants were obtained.

The microwave spectrum of cyclopropane-1,1-dicarbonitrile has been measured and the 2,3 C—C bond length is found to be 1.485 A[122]. This may be compared with the values of 1.500 Å found in cyclopropyl cyanide[113] and 1.515 for cyclopropane[121]. This provides further support for Hoffman's contention[117].

Brown, Godfrey and Ottrey have also measured the microwave spectrum of 2-cyanoaziridine (**6**)[124]. No evidence could be found for the rotational transitions of



(6)

the *trans* isomer of this molecule. Consequently these workers concluded that if the *trans* isomer is present, then the rotational transitions must be an order of magnitude weaker than those of the *cis* isomer. A lower limit of 11 kJ mol^{-1} was calculated for the free energy difference between the two configurations. These authors note that the *trans* configuration was found to be the predominant invertomer from NMR and infrared investigations of 2-substituted aziridines[125,126] and consequently suggest that the difference may be due to a significant dipole–dipole interaction between the amino and nitrile groups. However, it has been suggested that the relative stability of isomers in molecules such as hydroxyacetonitrile may be influenced by electron-exchange terms between groups. The authors[127] predict the inversion barrier height of 2-cyanoaziridine to be of the order of 16.7–19.1 kcal mol^{-1}.

The far-infrared spectrum of cyanocyclobutane has been obtained[128] and the potential function for the ring-puckering vibration of cyanocyclobutane determined. Since

only one minimum was found in this function it was concluded that only one ring-conformation was stable. However, it was not possible to determine whether the cyano group was in the axial or equatorial ring-position. The microwave spectrum from 18.0 to 40.0 GHz was recorded[129] for one isotopic species of cyanocyclobutane. By a comparison of the results with those obtained earlier for chlorocyclobutane[130], it appeared that only the equatorial form would fit the observed moments of inertia.

The infrared spectra and assigned frequencies for benzonitrile[131–133] and benzonitrile-d_5[133,134] have been reported. A number of infrared absorption frequencies and their tentative assignments of benzonitrile-*p*-d have been published[134,135]. A normal coordinate analysis for the in-plane vibrations has also been carried out[136]. The results of microwave studies are also available[137,138]. The results of the measurement of the microwave spectrum of benzonitrile and nine isotopic species[139] show that the substitution of cyano group on benzene shortens the ring C—C bond. However, the structural changes are small, the largest being the decrease of 0.01 Å found for the C(1)—C(2) bond.

The spectra and assignment for a series of *para*-substituted benzonitriles have also been reported[140]. Infrared and Raman spectra of *p*-methylbenzonitrile are available, together with assignment of frequencies and the results of calculations of ideal gas thermodynamic properties[141–143].

Spectra in the ultraviolet visible region have been reported for cyanobenzene[144–147], dicyanobenzenes[148], cyanopyridines[146], dicyanopyridines[149], and tetracyanobenzene[150]. Semiempirical calculations have been employed to predict spectral transitions for these molecules[151]. An improved parameterization has recently been proposed for such calculations on cyanoarenes[152].

The microwave spectrum of 2-cyanopyridine has been observed and assigned[153]. Perturbations of the pyridine ring structure by a cyano group substituted adjacent to the nitrogen have been considered[154]. The microwave spectrum and dipole moments of all three of the cyanopyridines has recently been reported[155]. It was concluded that the pyridine ring must be distorted, but no quantitative information could be supplied.

XIII. DICYANO MOLECULES

A. Dicyanoketene and its Isomers

Although cyanoketenes are considered as both highly reactive and unstable[155], the first preparation of dicyanoketene was claimed in 1978[156]. *Ab initio* STO-3G calculations were carried out on dicyanoketene and five of its isomeric forms[157]. It was shown that the dicyanoketene structure is the most stable of all the isomers considered, the next most stable form NC—CC—NCO being 26.2 kcal mol^{-1} higher in energy. The heats of formation of dicyanoketene and dicyanooxirene were calculated to be 56.5 and 119.5 kcal mol^{-1} respectively. The generation of free dicyanoketene in the gas phase has been reported recently[158]. MNDO calculations were used to predict heats of formation of 52 and 118 kcal mol^{-1} for dicyanoketene and dicyanooxirene, respectively, in good aggreement with the values calculated earlier[157]. However the MNDO calculations on the isomer NC—CC—OCN produced a heat of 101 kcal mol^{-1} [158] as contrasted with a value of 88.5 kcal mol^{-1} from the *ab initio* calculations[157]. Although no details of the MNDO calculations were given it appears that these authors[158] assumed a linear structure for NC—CC—OCN, whereas the geometry-optimized STO-3G calculations[157] predict a nonlinear molecule. Further the latter calculations predict that the isomer NC—CC—NCO is 5.8 kcal mol^{-1} more stable than NC—CC—OCN.

Dicyanothioketene has also been detected in the gas phase[159] and the heat of formation has been estimated as 110 kcal mol^{-1}.

B. Methylene Cyanide

The first spectroscopic studies of methylene cyanide were done many years ago. The Raman spectrum[160] and the infrared spectrum, with a normal coordinate analysis[161], have been reported. The microwave spectrum and structure have been obtained[162,163]. The rotational spectrum in excited vibrational states was also reported by Hirota[164]. Centrifugal distortion effects in the microwave spectrum have also been studied[165].

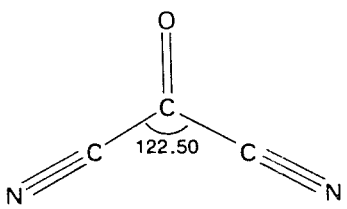
The structure of methylene cyanide, as determined by Hirota[163], shows values of structural parameters similar to those found in related molecules. However the CCN group is bent by $3.67 \pm 2.9°$.

C. 1,1-Dicyanoethene

The microwave spectra of 1,1-dicyanoethene and its deuterated species $CD_2C(CN)_2$ have been reported for their ground and lowest excited vibrational states[166]. The infrared spectrum of the normal isotope of 1,1-dicyanoethene has been studied and the Urey–Bradley force constants for the in-plane vibrations have been calculated[167]. Vibrational Raman frequencies and the centrifugal distortion constants determined from the microwave rotational spectrum have been used to calculate a harmonic force field[168]. Values for structural parameters were assumed.

D. Carbonyl Cyanide

The spectrum of carbonyl cyanide (7) has been of interest for a number of years[169–174]. Most recently the molecular structure has been obtained from gas-phase



(7)

electron diffraction[175]. These authors[175] note that carbonyl cyanide is a small molecule with conjugated double and triple bonds which may produce electron delocalization effects. Since the C—C single bond lies between a double and a triple bond, some effect should be observable. Kuchitsu and coworkers[176] have termed this the 'secondary environment effect'. According to these authors, the C—C single-bond length in carbonyl cyanide should be longer than that found for acetyl cyanide. However these values are found from experiment to be 1.469[175] and 1.477 Å[176], respectively. Typke and coauthors[175] suggest that the π systems of the cyano groups and the carbonyl group can interact, leading to the shortening of the C—C bond lengths.

E. 1,2-Dicyanotetrafluoroethane

The infrared spectra of 1,2-dicyanotetrafluoroethane have been obtained in the vapour, glassy solid and crystalline solid states[177]. Raman spectra have been measured for the liquid and crystalline solid[177]. In the crystal, only the *trans* form has been identified, whereas *trans* and *gauche* forms coexist in the vapour, liquid and in the amorphous solid with the *trans* conformer dominating.

F. Cyanogen

Gas-phase electron diffraction has been employed to find the internuclear distances in cyanogen[178-180]. The more recent results give 1.154 and 1.389 Å for C≡N and C—C, respectively.

The force constants for cyanogen have been calculated from frequency shifts of isotopic forms[179,181-184].

XIV. TRICYANO MOLECULES

Ab initio calculations performed on cyanoform $HC(CN)_3$ and its isomer, dicyanoketene imine $(NC)_2C{=}C{=}NH$[185] have shown that the former is approximately 10 kcal mol^{-1} lower in energy than the latter. Subsequent microwave spectroscopy[186] appears to demonstrate the existence of cyanoform.

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CHAPTER **25**

NMR spectra of acetylenes

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Acetylenes exhibit an axis of symmetry on account of the triple bond and in dimethylacetylene the rotational barrier around the bond between the unsaturated and terminal carbons is less than 0.1 kcal mol^{-1} [1].

I. ^{1}H CHEMICAL SHIFTS

The free circulation of electrons, which in spherically symmetrical atoms and molecules such as benzene gives rise to diamagnetic effects, also occurs around the triple bond in acetylenes (or nitriles) when the axis is parallel to an applied magnetic field and has the effect of inducing a magnetic moment. As a consequence of this diamagnetic circulation around the acetylenic axis the protons in acetylene absorb at higher field than anticipated on the basis of hybridization. Thus for ethane, ethylene and acetylene the relevant chemical shifts are 0.88, 5.30 and 1.49 ppm.

The anomalously high field absorption of alkyne protons was calculated[2] to be ca. 10 ppm, and more recent calculations of local anisotropic contributions of protons

adjacent to alkyl groups have been made.[3] The ^{13}C tensors of but-2-yne have previously been shown[4] to exhibit considerable anisotropy and are probably similar to those for acetylene. From these values the high field local anisotropic shifts of protons in alkynes have been calculated to be ca. 4.44 ppm. An 'inherent' shift of a —C≡C—H system based on the electron-withdrawing character of the alkyne group and estimated to be ca. 7 δ based on acid strengths of *inter alia* propiolic acid gives, when corrected for the local anisotropy, a value of ~ 2.6 δ, which is close to a cited experimental value of 2.88 δ.

Chemical shifts of acetylenic protons of a large number of monosubstituted acetylenes have been determined by Drenth and his collaborators[5]. The values of a representative number of compounds, determined in carbon tetrachloride and extrapolated to infinite dilution are given (in ppm from TMS) in Table 1.

A broad correlation exists between the ^1H acetylenic chemical shifts and the electronegativity parameter of Dailey and Schoolery[6], as long as correction is made for anisotropy effects, with the restriction that the substituent is part of subgroup H—C≡C—CH_2X, i.e. that one is dealing with propyne derivatives. However, when the substituent is capable of mesomeric electron donation to the ethynyl system such as may occur with HC≡C—NEt_2 or H—C≡C—OEt more pronounced shielding of the acetylenic proton is now apparent and can be rationalized on the basis of contributions from structures **1b**. Similarly, a shielding effect is noted in

$$\underset{\textbf{(1a)}}{H—C{\equiv}C—O—Et} \longleftrightarrow \underset{\textbf{(1b)}}{H—\bar{C}{=}C{=}\overset{+}{O}—Et}$$

butadiyne and cyanoethyne where mesomeric charge transfer is essentially precluded; here the ring currents of C≡C and the substituent X are considered to be coupled with a consequent increase in the diamagnetic anisotropy effect.

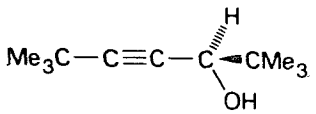
By way of contrast a deshielding of the acetylenic proton is now manifest when X = Ph, PR_2 or $P(O)R_2$ and transfer of electrons from the triple bond is postulated in suitable cases[7].

In the case of phenylacetylene an earlier postulated transfer of charge from the phenyl ring occurs with concomitant expansion of the p orbitals of C(1) attended by a lessening of the anisotropic contribution. It is also noted[8] that solvent change only marginally affects the ^1H chemical shift of the ethynyl proton in PhC≡CH.

The ethynyl-*t*-butyl group of 1,3-di-*t*-butylpropargyl alcohol (**2**) was assigned to the absorption at δ 1.23 ± 0.02 and the alkyl-*t*-butyl group to that at δ 0.97 ± 0.03, the

TABLE 1. Proton chemical shifts in some monosubstituted acetylenes, HC≡C—X

X	δ (ppm)	X	δ (ppm)
H	1.80	CO_2H	3.02
Me	1.76	C≡CEt	1.78
CH_2OH	2.33	$SnEt_3$	2.07
CH_2Cl	2.40	CN	2.48
CH_2CN	2.15	NEt_2	2.15
CMe_3	1.87	PEt_2	2.70
CF_3	2.80	$AsPh_2$	2.82
$CH{=}CH_2$	2.92	OEt	1.33
Ph	2.93	SEt	2.64
$C_6H_4NO_2$-*p*	3.21	F	1.57
COMe	3.50		



(2)

former value being very similar to the corresponding protons of *t*-butylacetylene[9]. The relative deshielding of the ethynyl-*t*-butyl group allows an experimental delineation of the deshielding and shielding zones to be partially made. This result contrasts with predictions based on treatment of the triple bond as a point dipole centrally located[10] and also a subsequent analysis based on location of point dipoles at the ends of the triple bond[11], in that the size of the deshielding zones is larger than calculated.

By means of a set of gauge-invariant atomic orbitals a number of ^1H chemical shifts have been accounted for[12], and in particular, the qualitative trend of chemical shifts relative to methane accounted for; the values obtained in ppm, and with experimental values in parentheses are: CH_4 (0); C_2H_4 −6.20 (−5.20); C_2H_2 −2.27 (−1.35); propyne, methyl protons −1.35 (−1.54); ≡CH −2.38 (−1.58).

An average value $\Delta\chi = -25 \times 10^{-6}$ cm^3 mol^{-1} [13] for the magnetic anisotropy of the carbon–carbon triple bond (see also Reference 8) was employed[14] in an investigation of the effect of an electric field on ^1H chemical shifts. The concurrence of two independent sets of calculations of ^1H chemical shifts of *inter alia* 4-cyano-and 4-ethynylstyrene by two independent methods, viz. CNDO/2 and Buckingham's field effect model with the experimental shifts in hydrocarbon solvent, extrapolated to infinite dilution, indicated decisively the role of electric effects.

Mohanty[15] has examined with precision the chemical shifts of acetylene brought about by isotopic substitution. For the ^1H spectrum $\delta(C_2H_2) - \delta(H^{13}CCH)$ is 0.000 ± 0.002 ppm and in $H_a—^{13}C—C—H_b$, $\delta(H_a) - \delta(H_b)$ is 0.001 ± 0.002 ppm; in doubly labelled acetylene the value $\delta(C_2H_2) - \delta(H^{13}C^{13}CH)$ is 0.000 ± 0.002 ppm. These values are refinements of earlier values[16]. The proton chemical shift anisotropy $\Delta\sigma = \sigma_{\parallel} - \sigma_{\perp}$, where $\sigma_{\parallel}$ and $\sigma_{\perp}$ are components of the shielding tensor parallel and perpendicular to the molecular axis, was found to be 22 ± 2 ppm using a liquid crystal technique.

The magnetic anisotropy of *inter alia* acetylene has been calculated[17] to be ca. -8×10^{-6} e.m.u. mol^{-1} with broadly similar values for the isoelectronic molecules HCN and N_2. However the anisotropies of -36×10^{-6} e.m.u. mol^{-1} have previously been determined for the triple bonds C≡C and C≡N[18,19], and it is pointed out[17] that the local paramagnetic contribution, difficult to quantify and frequently neglected, may significantly affect proton chemical shifts.

II. ^{13}C CHEMICAL SHIFTS

In general acetylenic compounds absorb in the region 65–90 ppm downfield from tetramethylsilane; however wide variations are known for particular acetylenes (*vide infra*). The ^{13}C chemical shift of 1,2-^{13}C-acetylene absorbs 56.6 ppm to high field of benzene[15]. Shieldings of sp-hybridized carbons of acetylenes are given in References 20 and 21 and only a few representative values are given in Table 2 (in ppm downfield from TMS); other values are mentioned where relevant. Thus downfield shifts of 54–61 ppm are exhibited for the sp-hybridized carbon with respect to the corresponding alkane. Using the same comparison carbons bonded to an ethynyl carbon are shielded by 10–14 ppm; this latter shielding may have origins in the diamagnetic anisotropy of the triple bond and is not reproduced[22] by calculation of σ_g, which yields a contribution of only 4 ppm, using an admittedly contentious value of $\Delta\chi$.

TABLE 2. ^{13}C-NMR chemical shifts of alkyne carbons in acetylenes

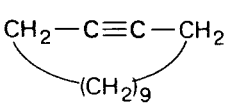
	C(1)	C(2)
Acetylene	73.2	—
But-1-yne	67.3	85.0
Hex-1-yne	68.6	84.0
Pent-1-yne	68.2	83.6
Oct-3-yne	111.5 C(3)	112.8 C(4)
3,3-Dimethylbut-1-yne	66.9	92.1
Phenylacetylene	83.3	77.7
Phenylpropyne	86.4 C(2)	80.4 C(3)
Diphenylacetylene	89.7	—

The shielding at β and γ carbons is rather irregular, although conformational differences may be responsible for variations at γ and more remote carbons. The γ parameter which is of the same sign and magnitude as for alkanes, although of uncertain origin, allows, at a phenomenological level, for the unambiguous assignment of the absorption of sp-hybridized carbons in alkynes where the triple bond is removed from the end of the chain by not more than three sp^3-hybridized carbons.

^{13}C-NMR spectra of a number of heteroatom-substituted acetylenes have been determined[7] where the heteroatom is O, S, P and Ge. In the case of ethoxyethyne, contributions of the resonance form H—$\bar{C}$(1)=C(2)=$\overset{+}{O}$—Et are proposed from the high field chemical shift of 22.0 ppm for C(1), and a value of 88.2 ppm for C(2). In accord with this interpretation the methylene carbon absorbs at 71.2 ppm compared with 66.8 ppm in diethyl ether. Conversely in di-*s*-butylethynylphosphine, C(1) now absorbs at 91.5 ppm which supports the significance of the resonance form H—$\overset{+}{C}$=C=$\bar{P}$(Bu-*s*)$_2$.

In order to assess the effect of a triple bond ^{13}C chemical shifts of a number of diynes and a triyne were determined[22], the former case exemplified by 3,5-octadiyne where the absorptions occur at C(1), 12.8; C(2), 12.2; C(3), 77.6 and C(4), 64.5 ppm. The interior C(4), C(5) carbons are then shielded by ca. 13 ppm from the corresponding monoalkyne (Table 2); thus the shielding effect of a triple bond at an α carbon is essentially independent of the nature of the hybridization at that carbon. The spectra of 1,7-octadiyne and 1,7,13-tetradecatriyne show that the β and γ carbons are shielded by only ca. 1 ppm with respect to the corresponding carbons in oct-1-yne. In conjugated diynes assignment of the 'inner' carbons is facilitated since these absorptions exhibit a smaller peak height, on account of attenuation of the Nuclear Overhauser Effect (N.O.E.) for carbons with no adjacent protons. In cyanoacetylene C(2) absorbs at 57.1 ppm; this is ca. 17 ppm upfield from the value in acetylene whereas the terminal carbon is only slightly deshielded[23]. This shift of C(2) is in contrast to the small α effect observed in saturated nitriles.

Incorporation of the acetylene moiety into a cyclic system affects the chemical shifts of sp carbons only marginally[24]; thus in **3** the acetylenic carbons absorb at 80.4 ppm and in tetradeca-1,7,13-triyne sp-hybridized carbons absorb at C(1), 68.2; C(2), 83.2



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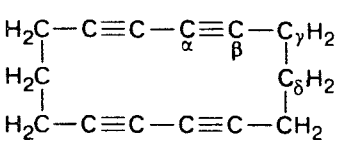


(4)

and C(7), 80.1 ppm. Carbons α to the triple bond now absorb ca. 10 ppm upfield from the other sp^3-hybridized carbons.

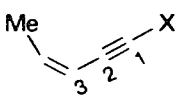
Also examined were a number of polyynes, exemplified by tetradeca-1,3,8,10-tetrayne (**4**). Calculations suggest that, based on the anisotropy of the triple bond, C_α and C_β in **4** should be deshielded by the transannular pair of triple bonds. Experiment shows this to be the case by 2.9 ppm and 2.4 ppm respectively with respect to the corresponding carbons of tetradeca-1,6,8,13-tetrayne. However the deshielding of 1.9 ppm experienced by C_γ of **4** is not predicted definitively by the calculation, since C_γ lies close to the boundary of the shielding and deshielding zones. The relative deshielding of C_δ in **4** by 2.0 ppm though is in accord with the calculation. The role of electric field effects in determining chemical shifts is considered to be important only when a large electric dipole exists within the molecule and as such probably do not have a major influence in acetylenes.

^{13}C chemical shifts of 28 propargylic alcohols have been reported[25] with the terminal carbon again at higher field than C(2); the hydroxymethyl group deshields the bonded sp-hybridized carbon by ca. 10 ppm, about half the value in alkyl alcohols.

A γ effect of the hydroxylic group γ^{π}_{OH}, operating via the π bond at C(1) is deshielding by ca. 6.5 ppm, and is appreciably greater than the corresponding γ^{π}_{Me} effect, ca. 0.65 ppm, and also deshielding, observed[22] in linear alkynes. A much smaller β^{σ}_{OH} deshielding effect is observed at the closer sp-hybridized carbon; this effect is also much smaller than that of ca. 10 ppm observed in alkanols.

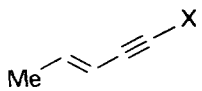
In diacetylenic alcohols both α and β sp-hybridized carbons are shielded by ca. 4.5 ppm with respect to the corresponding ethynyl compound as a consequence of mutual shielding interaction between the conjugated triple bonds[26]; a γ^{π}_{OH} effect is again evident and deshields the 'interior' sp-hybridized carbon by ca. 5 ppm with respect to the methyl analogue.

The olefinic bond of both the *cis* and *trans* isomers **5** and **6** strongly deshields the terminal carbon C(1) while shielding the interior carbon C(2). Thus in **5** the relevant absorptions occur at C(1), 82.1 and 80.3 ppm and in **6** respectively at 75.8 and 82.5 ppm; these values are to be compared with those of pent-1-yne (Table 2). The olefinic carbon C(3) in **5** and **6** experiences an α shielding effect of 18 ppm from the triple bond, nearly twice that observed at an sp^3 carbon α to the carbon–carbon triple bond. When a $SiMe_3$ group is introduced, as in **7** and **8**[26], the acetylenic carbons α and



(**5**) X = H

(**7**) X = $SiMe_3$



(**6**) X = H

(**8**) X = $SiMe_3$

β to it are deshielded by ca. 17 and 22 ppm respectively. The deshielding of the β carbon is rationalized via a postulated mixing of carbon sp orbitals with d orbitals on silicon.

Trimethyl(phenylethynyl)silane (**9**) shows absorptions for C_α, 92.5 ppm; ^1J ^{13}C—^{29}Si, 83.6 Hz; C_β, 104.4 ppm; ^2J ^{13}C—^{29}Si, 16.1 Hz[27]; with the couplings instrumental in the assignments; the chemical shift of 3-phenylpropyne is given in Table 2 for comparison. The greater than 18 ppm deshielding of C_β in **9** with respect to the corresponding carbon in 1-phenylprop-1-yne is attributed to a significant ground-state contribution from the resonance form **9a**.

$$Ph-C_\beta\equiv C_\alpha-SiMe_3$$

(**9**)

$$Ph-\overset{+}{C}=C=\bar{S}iMe_3$$

(**9a**)

The effect of alkyl substituents on the shifts of sp-hybridized carbons in aliphatic alkynes has been examined via 55 linear and highly branched alkynes. The shifts range over 25 ppm with limiting values noted for *t*-butylacetylene where C(1) and C(2) absorb at 66.9 and 92.1 ppm respectively, and are discussed[28a] in terms of the authors' DARC protocol[28b]. Alkyl groups influence chemical shifts of the sp-hybridized carbons independently, and such influence is attenuated with increased alkyl branching. Small values of γ_π effects (< 0.8 ppm) are indicated; indeed δ_π effects may be larger in certain cases up to a maximum of 1.2 ppm although the origin of these effects is uncertain.

^{13}C chemical shifts of all acetylenic carbons in ***inter alia*** the pentayne **10** have been assigned as indicated[29]. The same group have investigated several polyyne aldehydes and ketones[30], e.g. **11**, where the acetylenic carbon δ to carbonyl, C(5) in **11**, absorbs ca. 10 ppm downfield with respect to the corresponding alcohol **12**; this is attributed to extended conjugation with the carbonyl group.

$$(CH_3)_3C-C\equiv C-C\equiv C-C\equiv C-C\equiv C-C\equiv C-C\equiv C-C(CH_3)_3 \quad \textbf{(10)}$$

30.3 28.5 88.5 64.6 62.3 62.1 56 1.8

$$OHC-C\equiv C-C\equiv C-CH_2OAc \quad \textbf{(11)}$$

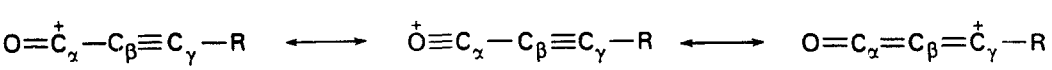
$$HOCH_2-C\equiv C-C\equiv C-CH_2OAc \quad \textbf{(12)}$$

The nature of alkynylcarbenium ions (**13**) has been investigated by ^{13}C-NMR in order to assess the significance of structures **13a** and **13b**[31]. With respect to the

(13a) **(13b)**

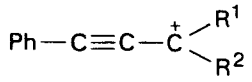
propargyl alcohol precursors, C_α and C_γ in **13** are markedly deshielded. Thus in the case where $R^1 = R^2 = R^3 =$ Me, C_α and C_γ shifts are 269.0(204.0) and 219.1(141.4) ppm respectively, values of the alcohol shifts are given in parentheses; clearly mesomeric structures of type **13b** are significant. Aromatic substitution at C_α and C_γ, e.g. **13**, $R^1 = R^2 =$ Ph, R^3 = Me and **13**, $R^1 = R^3 =$ Ph, R^2 = Me results in less deshielding at C_α and C_γ as positive charge is delocalized into the aromatic ring, preferentially the C_α ring where possible.

The same group[31] has envisaged resonance structures **14a–c** for a series of alkynoyl cations, prepared from the respective fluorides. Here C_α and C_β are shielded, 124.1(141.7) and 48.9(69.1) ppm with respect to the precursor fluoride in the case of **14**, R = H; by contrast C_β in the ion is now deshielded by 110.7(82.4) ppm. These data indicate that oxonium form **14b** is a major contributor to the ionic structure with the mutual shieldings of the C_α and C_β contributing to the observed high field shifts of these carbons. The authors[31] point to a parallel with ethynylbenzenes and benzonitriles where a similar shielding is observed for the C *ipso* absorption. It is also noted that consistent with the importance of **14b** as a resonance contributor it is not possible to prepare carbenium ions of the type $H-C\equiv C-\overset{+}{C}R_2$ (R = alkyl or aryl), whereas **14** is quite stable.



(14a) **(14b)** **(14c)**

The ^{13}C chemical response of all carbons, including those of an aromatic nucleus, have been examined in *inter alia* arylethynyl carbenium ions of type **15**[32]. With respect to phenylcarbenium ions, ions of type **15** show less scatter in the ^{13}C chemical shifts of the *ipso* and *ortho* carbons, demonstrating that through-bond and through-space effects are important.



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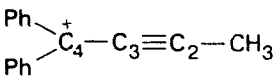

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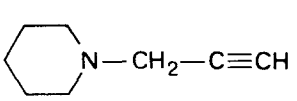
The acetylenic carbons of **16** have been assigned C(2), 165.1; C(3), 93.2; C(4), 195.7 ppm; which indicates an appreciable mesomeric vinyl cation contribution to the structure[31]; in parallel vein appreciable nitrenium ion character is shown in α-cyanocarbenium ions[33].

In **17** C(2) absorbs at 79.3 ppm and shows second-order coupling, ^2J C(2)≡C(3)—H, 48.5 Hz; ^2J H—C≡C, 7.5 Hz; the terminal carbon C(3) absorbs at 72.9 ppm with ^1J C—H, 247 Hz and ^3J H_2C—C≡C, 4 Hz. The propargylic carbon absorbs at 47.7 ppm, ^1J C—H, 135 Hz[34]. In amine oxides the acetylenic absorptions are inverted such that in **18** C(1) absorbs at 78.8 ppm, C(2) at 74.4 ppm with the propargylic carbon now deshielded to 63.2 ppm.



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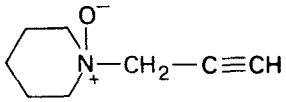

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The acetylenic carbons of 1-phenylpropyne Ph—C(3)≡C(2)—$C(1)H_3$ absorb at 85.7 and 79.8 ppm and have been variously assigned[34,35]; the assignment in which C(2) absorbs at 86.4 ppm and C(3) at 80.4 ppm[36] is supported both by specific labelling and partial proton decoupling. Additionally a C≡C bond is less efficient than a C=C bond in transmitting a substituent effect, a finding confirmed in the ρ values for β-carbon shifts in substituted phenylacetylenes (ρ = 3.6 ppm) as compared with styrenes (ρ = 4.73 ppm).

From the ^{13}C-NMR spectra of 41 alkynes a series of incremental shifts at α, β, γ and δ carbons has been made[37].

III. CALCULATIONS OF ^{13}C CHEMICAL SHIFTS AND ANISOTROPIES

Gauge-invariant atomic orbitals have been employed in INDO calculations in order to calculate ^{13}C chemical shifts of *inter alia* acetylenes; these indicate that in propyne the terminal and methyl-substituted sp-hybridized carbons deviate from experimental values by 16.7 and 14.7 ppm respectively[38]. From the same INDO calculations the main ^{13}C shielding tensor elements have been obtained and these reveal appreciable anisotropies for acetylenes; the values obtained are σ_{xx}, −130.00; σ_{yy}, −130.00; σ_{zz}, 36.53 ppm.

By means of a CNDO/2 method the charge density on the sp-hybridized carbons of diphenylacetylene, which absorb at 89.7 ppm, is calculated to be -64×10^{-3} e.u.[39]. Also in diphenylbutadiyne Ph—C_α≡C_β—C_β≡C_α—Ph, C_α absorbs at 81.50(66.30) ppm and C_β at 74.37(67.5) ppm, where the parenthesized figures refer to butadiyne; in diphenylbutadiyne the respective charges at C_α and C_β are now -83×10^{-3} e.u. and $+14 \times 10^{-3}$ e.u., respectively. By comparison with allenic

systems it is concluded that the large difference in diamagnetic anisotropy between the cumulenic and acetylenic π systems accounts for the ca. 15 ppm difference of the C(1) phenyl carbons in tetraphenylcumulenes and diphenylacetylenes. The anisotropy difference is also largely responsible for the ca. 70 ppm upfield shift experienced by butadiyne (or diphenylbutadiyne) with respect to butatriene as the CNDO/2 calculations indicate little disparity in the relative charge densities at the β carbons.

Ditchfield[40] has calculated the shieldings for the carbons in propyne $C(3)H_3—C(2)\equiv C(1)$ using gauge-invariant atomic orbitals; values found are C(1), 92.3(72.4); C(2), 84.4(84.7); C(3), 6.6(7.3).

A slightly extended set of orbitals was then used in SCF calculations of the ^{13}C chemical shift of acetylene[41]. The method gives a value for acetylene of 75.2 ppm downfield from methane, compared with an experimental value of 76 ppm.

For fluoroacetylene $F—C(1)\equiv C(2)—H$, C(1) and C(2) are now calculated[41] to absorb at 82.5 and 26.9 ppm, respectively, in good agreement with the experimental values of 90.8 and 16.3 ppm.

More recently gauge-invariant atomic orbital basis sets and semiempirical wave functions embracing all valence electrons have accounted for the major ^{13}C shielding trends of hydrocarbons[42]. Good agreement has been reached between the experimental, 74.6 ppm, and calculated 75.9 ppm shifts of acetylene. For propyne $C(3)H_3—C(2)\equiv C(1)$ shifts are calculated to be C(1), 86.76(70.98); C(2), 102.43(82.24); C(3), 11.77(4.89) ppm. In 1,3-butadiyne the shifts of the terminal and central carbons are calculated to be 64.64(69.27) and 99.15(70.98) ppm respectively; experimental values are given in parentheses. Together with cyclopropane, the errors in the calculations of the chemical shift of acetylene with respect to the internal carbons of diacetylene are ascribed to three-centre terms; in particular the internal carbons in diacetylene are calculated to be shielded by ca. 25 ppm with respect to those of acetylene, cf. an observed value of ca. 5 ppm.

^1H, ^{13}C and ^{19}F chemical shifts have been calculated for *inter alia* $H—C(2)\equiv C(1)—F$ using SCF linear combination gaussian orbitals[43]. With respect to hexafluorobenzene the ^{19}F chemical shift is calculated to be 96.9 ppm, compared to an experimental value of 100.1 ppm. ^{13}C chemical shifts are calculated to be ca. 8 ppm for C(1) and ca. 90 ppm for C(2).

^{19}F screening constants and their anisotropies have been calculated[44] *inter alia* for a number of fluorinated acetylenes, including some for which data are not available. For $F_3C—C\equiv C—CF_3$ the ^{19}F chemical shifts in the INDO and CNDO/S calculations have been calculated to be 435.8 and 461.1 ppm, respectively, compared with an experimental value of 486 ppm (expressed as low frequency with respect to F_2).

As part of a study of the variation of the local diamagnetic shielding term in ^{13}C chemical shifts values of the local diamagnetic shielding σ_d^A have been calculated[45] for acetylene by an extended Flygare method. The value obtained is 261.50 ppm, or −0.08 ppm when referenced to methane; this latter value compares with a figure of −0.26 ppm from X-ray photoelectron spectroscopy. For carbon in a representative series of environments agreement is generally good.

^{13}C screening constants have been calculated for a group of unsaturated molecules[46] using Pople's gauge-dependent atomic orbitals and INDO/3 parameterization. For acetylene the calculated screening tensor of 122.1 ppm is made up of σ_{loc}^d 260.67 ppm, σ_{loc}^p −134.45 ppm and σ_{nonloc}^p; the experimental σ value is 120.0 ppm[47]. The experimental σ_{obs} is derived from $-(\delta_x - \delta_{ethylene}) = +74.0$ where δ_x is given relative to TMS and 74.0 ppm represents the *ab initio* ^{13}C screening of ethylene.

Calculations have been carried out on ethane, ethylene and acetylene with the INDO approximation using SCF finite perturbation theory when the molecules are subjected to the fields caused by positive or negative monopoles or dipoles juxtaposed with the hydrocarbon in a large number of geometrical arrangements[48]. When the

monopole is located along the carbon–carbon axis of acetylene for maximum effect, a chemical shift difference of 12.3 ppm is estimated between C(1) and C(2); for a dipole the largest calculated difference, predictably, is smaller, 4.46 ppm. These values are rather larger than reported in conformationally mobile systems. A monopole or dipole shifts the two carbons in opposite senses but by different amounts; the sense of the shift of a particular carbon is reversed either when the sign of the monopole or the sense of the dipole is reversed. The behaviour is in accord with that expected from an electric field.

The flow of electron density in σ and π systems of acetylene in response to electric field effects has been considered[48]; interpretation based solely in terms of polarizability and charge densities is considered too facile. Although the polarizability of carbon–carbon triple bonds is larger than that of the corresponding double bonds a larger electric field effect is exhibited in the latter case. A linear relationship is shown between ^{13}C shifts and π-electron densities in acetylenes and ethylenes.

Previous work has been concerned with the ^{13}C chemical shift anisotropies of acetylene, propyne and 1,3-butadiyne[49,50], the last molecule has also been considered in the solid state[4]. The value for acetylene has been calculated to be 237.1 ppm (cf. 215.7 ppm[50]) and the observed value is 269 ± 11 ppm (cf. 245 ± 20 ppm[15]). For propyne $C(3)H_3—C(2)\equiv C(1)H$ the anisotropies found by the gradient method together with the calculated values in parentheses are for C(2), 251 ± 9 (271.3 ppm) and C(1), 191 ± 10 ppm (211.1 ppm). In dimethylacetylene the anisotropy of C(2) is 160 ± 7 ppm (calc. 237.6 ppm). The experimental values change by 80–90 ppm for the acetylenic carbon in $HC\equiv CH$, $MeC\equiv CH$ and $MeC\equiv CMe$ whereas the calculations indicate a smaller range, though with the correct trend, with emphasis on the change in anisotropic shielding along the axis of the triple bond.

Cyanopropyne, $H_3C(1)—C(2)\equiv C(3)—C(4)\equiv N$, oriented in a nematic phase of *p-n*-butyl-*p'*-methoxyazoxybenzene orients preferentially[51] with its long axis parallel to the optical axis of the nematic solvent, as found for other acetylenes except acetylene itself[52]. It has been suggested[53] that a bond exists between the acetylenic hydrogen and the π orbitals of the aromatic rings of the liquid crystal.

In diacetylene the axially symmetric shielding anisotropy $\Delta\sigma = \sigma_{\parallel} - \sigma_{\perp}$ has been found to be 218 ppm[54] from proton-enhanced nuclear induction spectroscopy at low temperature and the isotropic shift obtained from melting the sample; the value compares with $\Delta\sigma \approx 240$ ppm for acetylene from the liquid crystal method[15]. Parenthetically, a C—H internuclear distance of 1.094 a.u. is reported from the dipolar splitting of C(1) in the $\sigma_{\perp}$ region of the two-dimensional pattern[54].

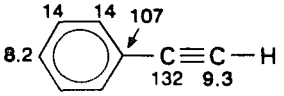
The same group[55] has determined ^{13}C shielding parameters for *inter alia* dimethylacetylene. For the methyl carbon at −186°C, $\sigma_{11} = \sigma_{22} = 113 \pm 6$ ppm and $\sigma_{33} = 127 \pm 6$ ppm; the acetylenic carbon has $\sigma_{11} = \sigma_{22} = -29 \pm 6$ ppm and $\sigma_{33} = 173 \pm 17$ ppm.

Values of σ^{d}_{loc}, 316 ppm; σ^{p}_{exp}, −195 ppm (converted to ethylene reference using $\delta_{TMS} = +122.8$ ppm) enable a paramagnetic shielding to be estimated for *inter alia* acetylene. From this an 'average electronic excitation energy' ΔE of 9.45 eV which reproduces the shieldings is calculated[56].

Complex formation between $PhCOC\equiv CH$ or $PhC\equiv CH$ and a number of aromatic solvents has been demonstrated with a 1:1 stoichiometry demonstrated[57], and equilibrium constants measured.

IV. RELAXATION TIMES

^{13}C spin-lattice relaxation times, T_1, of the carbons of phenylacetylene (**19**) have been measured[58]. In deuterated degassed acetone at 25.2 MHz the various T_1 (± 5–10%) are given in seconds. T_1 values for *para* carbons are, as is customary, shorter than those



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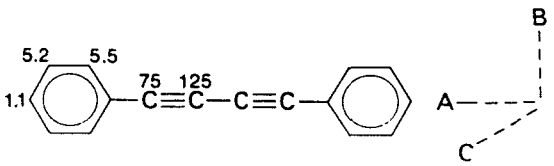


(20)

of *ortho* and *meta* carbons of the same ring; rotation around the C_2 symmetry axis does not lead to any effect on T_1 of the *para* carbon.

In diphenyldiacetylene (**20**) the motional anisotropy is such that T_1 for *para* carbons is now ca. 5 times less than that for the *ortho* and *meta* carbons. This value corresponds to the rate of rotation about the long molecular axis, A, being ca. 17 times those around the short axes B and C. For comparison, if the ratio of the rates of rotation about the longer and shorter axes in an axially symmetric molecule is very great then the ratio $T_1^{o,m}/T_1^{p}$ tends towards a theoretical limit of 64. In phenylacetylene the tumbling modes are less anisotropic than in **20**.

Diphenyldiacetylene (DPDA) is the only compound where the carbons are predominantly relaxed by the chemical shift anisotropy mechanism at 23.5 kG at ambient temperature. At a concentration of 30% w/v in acetone-d_6 (degassed) the T_1 values for C_α and C_β are respectively 82 and 136 s. For C_β, which is >3 Å distant from an available proton, T_1 is $>10^2$ that for the *para* carbon. Indeed so long is the C_β T_1 that the value can be determined outside the magnetic field, save for initial polarization and final measurement. This weak-field determination gives $T_1 = 340 \pm 70$ s, in accord with over 60% of the C_β relaxation deriving from the chemical shift anisotropy (CSA) method. At high field, 63 MHz, the T_1 values for C_α and C_β are now 15 and 30 s respectively, in particular C_β is now relaxed by the CSA mechanism to the extent of 90%; generally the importance of the CSA mechanism is enhanced at lower temperatures also. The chemical shift anisotropy is calculated to be 270 ppm for C_β in **20** for which the competing spin-rotation relaxation is insignificant.

The C_β of DPDA gives an NOE effect of 0.5 ± 0.1 η; this together with the T_1 value for C_β enables the components of relaxation to be dissected (at 23 kG with a 30% sample): T_1^{CSA} 200 ± 80 s, T_1^{DD} 500 ± 100 s, T_1^{other} 500–>5000 s, where DD refers to dipole–dipole interactions.

A method of calculating ^{13}C relaxation times from those of a directly bonded ^{2}H has been developed and, when relaxation of ^{13}C occurs via dipole–dipole interaction agreement is generally good[58]. Such is the case with phenylacetylene where in PhC≡CD, T_1 for D is 0.25 s; this leads to a value of 7.8 s for the ^{13}C T_1 as compared with an experimental value of 9.3 s for a degassed sample.

If D and ^{13}C T_1 values are known then the ^{2}H quadrupole coupling constant may be calculated; here although a good correspondence is shown in general, an exception is phenylacetylene where a discrepancy now exists since here the ^{13}C relaxation time contains substantial contributions from chemical shift anisotropy.

V. COUPLING CONSTANTS

Coupling constants in acetylenes fall into four classes: (1) proton–proton, (2) proton–carbon, (3) carbon–carbon and (4) those involving a heteroatom with either a proton or carbon. Coupling constants are presented in the form $^{n}J_{XY}$ where X and Y are the coupled nuclei and the superscript n indicates the number of bonds separating X and Y. In the main the numbering system of the original paper is preserved.

A. Mono- and Poly-acetylenes; Non-heteroatom-substituted Acetylenes

The values for acetylene were determined by two groups[59,60] and the values obtained were $^1J_{CH}$, 248.7 (249.0); $^2J_{CH}$, 49.7(49.3); $^2J_{HH}$, 9.8(9.55) (see also References 15 and 61); $^1J_{CC}$, 170.6(171.6) Hz; parenthesized values refer to Reference 60. At the same time a number of acetylene derivatives *inter alia* were examined[34] and these gave values Ph—C(2)≡C(1)—H, $^1J_{C(1)C(2)}$, 175.9 Hz; Ph—C(3)≡C(2)—C(1)H_3, $^1J_{C(1)C(2)}$, 68.6 Hz; PhC(3)≡C(2)—C(1)≡N, $^1J_{C(1)C(2)}$, 155.8 Hz. It was concluded[34] that the C, C coupling constant was proportional to the product of the s character of the relevant carbon atoms and it was also noted[60] that the values of $^1J_{CC}$, $^1J_{CH}$ and $^2J_{CH}$ increased markedly along the sequence ethane, ethylene and ethyne.

A correlation between H,H and C,H coupling as a function of hybridization at carbon has been proposed by Karabatsos' group[62] and takes the form

$$J_{CH} = a.J_{HH}$$

where for sp carbon $a = 0.6$; corresponding values for sp^2- and sp^3-hybridized carbons are 0.4 and 0.2.

The earlier studies involving coupling to ^{13}C were often carried out using isotopically enriched materials, frequently at multiple sites, but subsequently the advent of Fourier transform techniques has made such procedures less necessary, save for experiments concerned with the determination of signs of coupling constants.

Roberts' group[63] found a value of $^1J_{C(2)C(3)} = 67.4$ Hz in propyne together with a geminal carbon–carbon coupling $^2J_{C(1)C(3)} = 11.8$ Hz, considered to be positive by analogy with the carbon–proton coupling in acetylene where the sign of J_{HH} has been calculated to be positive[64].

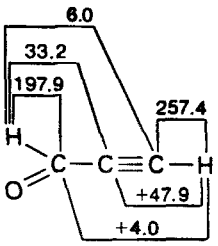
In propyne the three couplings between the acetylenic proton and ^{13}C are positive in sign whereas the sign of those involving methyl protons alternates[65]. For propyne the couplings between ^1H and ^{13}C have recently been reported[66]; thus for C(3)H_3C(2)≡C(1)H_a values of $^1J_{C(3)H}$, 131.55; $^3J_{C(3)H}$, 3.41; $^1J_{C(1)H}$, 248.1; $^3J_{C(1)H}$, 4.65; $^2J_{C(2)H_a}$, 50.11; $^2J_{C(2)H}$, −10.43 Hz have been obtained.

By means of SCF theory in the INDO approximation a coupling constant $^1J_{CH} = 122.0$ Hz within the methyl group has been calculated for propyne[67]. Also cited are one-bond coupling constants $^1J_{CH}$ involving an acetylenic proton[67]: PhC≡CH, 251.0; HC≡C—CMe_2OH, 253.0; HC≡C—CH_2OH, 248.0 Hz, which are quite well reproduced by the calculations. The same group[68] has calculated $^1J_{C(2)C(3)} = 67.4$ Hz in propyne together with other *trans* triple-bond carbon–carbon couplings: PhC≡CH, 156.3 (exptl. 175.9 Hz); PhC≡C—C≡N, 148.7 (exptl. 155.8 Hz).

The ^{13}C-NMR spectrum of dimethylacetylene has been analysed as an $A_3A_3{}^1X$ system[66] and from this has been obtained $^1J_{CH}$, +130.64; $^4J_{CH}$, +1.58; $^2J_{CH}$, −10.34; $^3J_{CH}$, +4.30 Hz; also in this molecule $^5J_{HH}$ is +2.79 Hz. Certain couplings such as ^2J for the H—C≡C fragment between acetylene and methylacetylene and the $^3J_{CH}$ couplings of the H—C—C≡C fragment together with ^2J for H—C—C≡ are, where appropriate, essentially transferable between acetylene, methylacetylene and dimethylacetylene. Thus all the ^1H, ^{13}C spin coupling constants through the triple bond are positive as has been found for HC≡C—CH_2Cl[69] and HC≡C—CHO[70] where the coupling constants are as shown in **21**.

The $^1H^1H$ coupling constants are of alternating sign in acetylene, methylacetylene and dimethylacetylene with magnitudes little different from those of saturated compounds.

By means of methyl tetrolate (**22**) labelled at carbons C(1), C(3) and C(4) the



(21)

$$H_3C^{5}-C^{4}\equiv C^{3}-C^{2}O_2C^{1}H_3^{6\,7}$$

(22)

carbon–carbon couplings have been determined[71]. These are $^3J_{C(1)C(4)}$, + 1.84; $^2J_{C(1)C(3)}$, +20.33; $^1J_{C(3)C(4)}$, +65.15 Hz; cited values for propyne $H(5)_3C(4)—C(3)\equiv C(2)H$ (numbering from Reference 71) are $^1J_{C(3)C(4)}$, 67.4; $^2J_{C(3)H(5)}$, −10.6; $^1J_{C(4)H(5)}$, +131.4 Hz. More elegantly the C(1) monolabelled methyl tetrolate has been employed for the same end by means of selective population transfer and off-resonance methods[72]; similar results have been obtained and a value of $^1J_{C(1)C(2)}$ = +127.5 Hz given. The signs of the coupling constants have been determined relative to $^4J_{C(1)H(5)}$, −1.96 Hz. Additional couplings involving the ester group have been determined: $^3J_{C(1)H(7)}$, +4.17; $^2J_{C(1)C(6)}$, −2.28 Hz. Neither group makes reference to $^1J_{C(2)C(3)}$ in methyl tetrolate.

In diacetylene ($HC\equiv C—C\equiv CH$) $^5J_{HH}$ is 2.2 Hz[61] and a calculated π-electron contribution of 0.95 Hz from finite perturbation theory or 1.39 Hz from modified Karplus equation have been estimated[73].

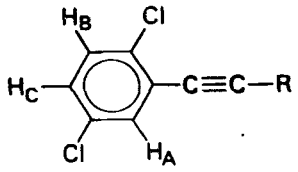
The spin–spin coupling between ^{13}C nuclei have been determined in totally ^{13}C-labelled diacetylene, together with the bis(trimethylsilyl) derivative[74]. Thus in diacetylene, values of $^1J_{C(1)C(2)}$, 194.0; $^1J_{C(2)C(3)}$, 154.8; $^2J_{C(1)C(3)}$, 18.9; $^3J_{C(1)C(4)}$, 15.9 Hz were found; thus $^1J_{CC}$ coupling between acetylenic carbons is ca. 22 Hz greater in diacetylene than in acetylene. This suggests that an interpretation based solely on π electrons is too facile since the π electron density of the triple bond is higher in acetylene. Rather the Fermi contact contribution, associated with σ electronic effects, is shown by INDO calculations to be responsible for the difference with orbital–dipolar and spin–dipolar terms essentially constant. The natural abundance spectrum gives the following CH couplings: $^1J_{CH}$, 259.1; $^2J_{CH}$, 52.3; $^3J_{CH}$, 6.5; $^4J_{CH}$, 0.4 Hz. From the values of $^2J_{CC}$ in diacetylene (18.9 Hz) and propyne (11.8 Hz) it is postulated that an intermediate value should be obtained for the corresponding coupling in vinylacetylene.

In the triacetylene **23** a long-range proton–proton coupling $^9J_{HH}$, = 0.4 Hz was measured[61,75] and the π-electron contribution to the proton coupling in triacetylene was calculated to be 0.32 Hz[73]. More recent calculations in the INDO and CNDO approximations[76] have reproduced the coupling constants for a number of acetylenes with reasonable accuracy. Thus for a number of compounds the H,H coupling constants experimental and calculated (in the CNDO and INDO approximations) respectively are propyne, 2.9–3.6 (0.06, −2.29); but-2-yne, 2.7 (2.34, 3.29); 1,3-pentadiyne, 1.27 (0.00, 0.97); 2,4-hexadiyne, 1.3 (0.87, 1.38); 2,4,6-octatriyne 0.4 (0.00, 0.58) Hz. Homologation of propyne and penta-1,3-diyne only slightly affects the coupling constants, although that (J_{HH}) for butadiyne is almost twice those of the mono and bis homologues. The authors consider that except for acetylene the coupling constants are transmitted via the π system.

$$H_3C—C\equiv C—C\equiv C—C\equiv C—CH_2OH$$

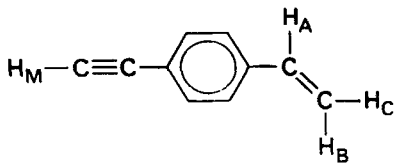
(23)

The long-range proton–proton coupling constants are given for 2,5-dichlorophenylacetylene (**24**) (J_{HAHM}, +0.29; J_{HBHM}, −0.07; J_{HCHM}, +0.33 Hz), its homologue (**25**) (J_{HAHM}, −0.30; J_{HBHM}, +0.15; J_{HCHM}, −0.26 Hz) and 4-vinylphenylacetylene (**26**) (J_{HAHM}, 0.10; J_{HBHM}, +0.11; J_{HCHM}, +0.14 Hz); the coupling constants are well reproduced by INDO calculations[77]. The acetylene group is ca. half as effective as a methyl group in transmitting spin information from a phenyl π electron system and almost as effective as a vinyl group. The signs of the long-range coupling constants are entirely consistent with transmission of spin information via the π system.



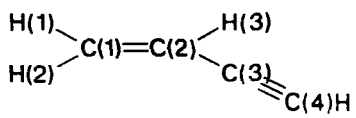
(24) R = H_M

(25) R = CH_3(M)



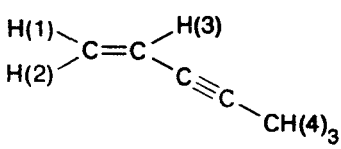
(26)

^{1}H, ^{13}C coupling constants in butenyne (**27**) (and their ^{13}C chemical shifts) have been determined; in particular: $^3J_{C(3)H(1)}$, 16.3; $^3J_{C(3)H(2)}$, 9.5; $^3J_{C(4)H(3)}$, 4.0; $^4J_{C(4)H(1)} \equiv {}^4J_{C(4)H(2)}$, < 1.0 Hz. A coupling constant $^2J_{C(1)H(3)} = 8.8$ Hz is also reported[78] compared with a value of $^2J_{CH} = -2.4$ Hz in ethylene corresponding to an increment of 11.2 Hz for the —C≡CH substituent; this value of 8.8 Hz does not accord with the corresponding value of 3.7 Hz found for $^2J_{C(1)H(3)}$ in *Z*-1-methoxybut-1-en-3-yne for which a value of 16.5 Hz has been calculated[79]. These authors conclude, without the benefit of direct evidence, that the value of $^2J_{C(1)H(3)}$ reported previously[78] is in error.



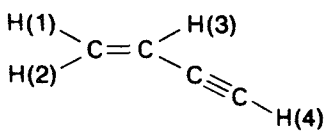
(27)

The ^{1}H^{1}H coupling constants of pent-1-en-3-yne (**28**) have been reported[80]. Thus a value of $^2J_{H(1)H(2)} = 2.28$ Hz was found and the other values were referred to this coupling taken as positive: $^3J_{H(1)H(3)}$, 11.11; $^6J_{H(1)H(4)}$, −0.56; $^3J_{H(2)H(3)}$, 17.49; $^6J_{H(2)H(4)}$, −0.71; $^5J_{H(3)H(4)}$, 2.30 Hz. In vinylacetylene (**29**), $^5J_{H(1)H(4)}$, 0.92; $^5J_{H(2)H(4)}$, 0.70 and $^4J_{H(3)H(4)}$, −2.17 were found. The reversal of sign with an approximate retention of magnitude indicates that π coupling is the prevailing mechanism of these



(28)

couplings with the reservation that a π coupling should result in values of *J* which are geometrically invariant. By way of contrast, replacing the olefinic proton H(3) in **29** by a methyl group to give **30** results in $^5J_{H(3)H(4)} = 0.3$ Hz, i.e. a diminution of ca. 7. This



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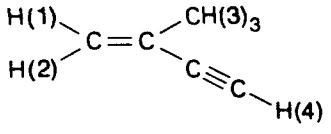
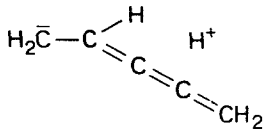


(30)

is understood in terms of a hyperconjugative model such that whereas the methyl group and both the double and triple bonds are involved in a resonance structure **31** of **28**, a structure such as **32** involves the methyl group and the double, but not the triple, bond.



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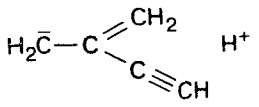
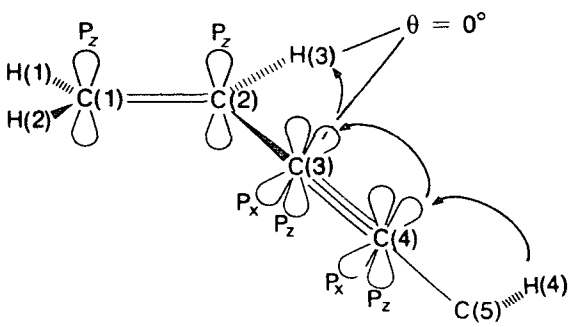


(32)

The spin information of the methyl group in **28** can be transmitted through the π system of the triple bond via carbon p_x or p_z orbitals; the latter case is favoured since the C(2)—H(3) bond forms a dihedral angle, $\theta = 0°$ with the p_x orbitals (**33**) and the effectiveness of the coupling follows a $\cos^2\theta$ relationship. In the corresponding diene, *trans*-penta-1,3-diene, the analogous coupling $^5J_{H(3)H(4)}$ is now only 0.4 Hz since the angle θ is here 90°. Previously the $^1H^1H$ coupling constants of vinylacetylene have been investigated by two groups[81,82].



(33)

B. Heteroatom-substituted Acetylenes

In $(HC{\equiv}C)_2PNPh_2$ and $HC{\equiv}CP(OEt)_2$ respective values of $^1J_{PC}$, −9.8 and −50 Hz, have been found, the negative sign also being found for saturated and aromatic phosphines and thus being independent of the hybridization at carbon, a parallel which can be extended *inter alia* to $HC{\equiv}C{-}P(O)Ph_2$ where $^1J_{PC} = +164.6$ Hz is found[83]. In $HC{\equiv}C{-}P(OEt)_2$ a small negative value ($^3J_{PH} = -2.42$ Hz) is found, whereas in fragments P—C—C—H, P—O—C—H, P—N—C—H and P—C=C—H, containing a three-coordinate phosphorus, $^3J_{PH}$ is positive.

In acetylenic phosphine oxides $^1J_{PC}$ and $^2J_{PC}$ are positive and larger than in saturated and aromatic phosphine oxides. It is suggested that in this series $^1J_{PC}$, $^2J_{PC}$ and $^3J_{PH}$ to which $^1J_{PC}$ and $^2J_{PC}$ are linearly related[84] are mainly dependent on the Fermi contact

term, though not exclusively, as a plot of $^1J_{PC}$ or $^2J_{PC}$ vs. $^3J_{PH}$ does not pass through the origin.

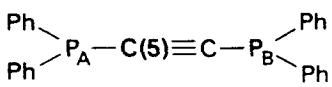
In P(III) acetylenic derivatives $^1J_{PC}$ and $^2J_{PC}$ are, in contrast to the P(IV) counterparts, not related to the electron-withdrawing power of substituents bonded to phosphorus, and the indication is that the orbital coupling mechanism, possibly with the spin dipolar term, is more independent than the Fermi contact term.

$^3J_{PH}$ is positive in acetylenic phosphine oxides, as is general for coupling via three bonds, whereas in $R_2P(O)C{\equiv}CMe$ $^4J_{PH}$ is negative, presumably since the observed value mainly reflects π contributions. However in acetylenic phosphines $^3J_{PH}$ is negative, exemplified by a value of −2.4 Hz for $(EtO)_2P{-}C{\equiv}CH$, the first such acyclic example. In propynylic phosphines $^4J_{PH}$ is positive, though precedent here contains examples of both signs. $^1J_{P(IV)C(sp)}$ is positive in both acetylenic and propynylic phosphine oxides.

An NMR study at 165 K of $H{-}C{\equiv}P$, prepared in addition to *inter alia* $HC{\equiv}CH$, which served as an adventitious standard, from passage of PH_3 through a carbon arc gave $\delta(^{31}P)$, 32.0 ppm to high field of external 85% H_3PO_4; $^2J_{HP}$, 43.9 Hz, $\delta(^{13}C)$, 154 ppm downfield of external Me_4Si; $^1J_{PC}$, 54.0; $^1J_{CH}$, 211 Hz[85]. This last coupling implies 43% s character of this bond; however this is a minimum value since electropositive atoms decrease the value of $^1J_{CH}$. The high value of both one- and two-bond couplings in HCP indicates a high s character in the bonds transmitting the coupling. Polarization is thought to be in the sense $H\overset{\delta-}{C}{\equiv}\overset{\delta+}{P}$.

In $P(C{\equiv}C{-}CF_3)_3$ a coupling $^4J_{PF}$ = 6.4 Hz has been determined, with no evidence for hindered rotation; the F absorption is 112.05 ppm to low field of C_6F_6[86]. In the As and Sb analogues the ^{19}F chemical shift is similar.

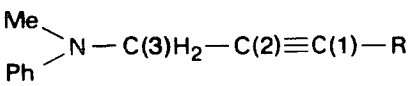
The ^1H decoupled ^{13}C- and ^{31}P-NMR spectrum of **34** has been analysed as an ABX system. In $CDCl_3$ $^3J_{PP}$ is found[87] to be 5.5 Hz with $^3J_{PA\,C(5)}$, 15.9 Hz and $^2J_{PB\,C(5)}$, 1.46 Hz; very small ^{13}C isotope shifts are reported on ^{31}P nuclear shieldings.



(34)

In disubstituted acetylenes exemplified by $Me_3Sn{-}C{\equiv}C(2){-}C(1)H_3$ $^1J_{C(1)H}$ is 130 Hz; for $PhSe{-}C(3){\equiv}C(2){-}C(1)H_3$, values of $^1J_{C(1)H}$, 132.8; $^2J_{C(2)H}$, 10.4; $^3J_{C(3)H}$, 5.8 Hz have been found[65]. In general for this class of compound the magnitude of the coupling constants varies little whereas in monosubstituted acetylenes a much greater range is observed. Thus the following values have been obtained: for $Me_3Si{-}C(2){\equiv}C(1)H$, $^1J_{CH}$, 236.2 and $^2J_{C(2)H}$, 42 Hz and for $PhO{-}C(2){\equiv}C(1)H$, $^1J_{C(1)H}$, 269 and $^2J_{C(2)H}$, 61 Hz[65].

The ^{13}C-NMR spectra of ^{15}N-labelled propargylamines **35** and **36** have been determined[88]. $^2J_{HC(2)} = {}^3J_{NC(1)}$ = 0.9 Hz in **35**, and in **36**: $^1J_{NC(3)}$, 36.2; $^2J_{NC(2)}$, 5.5;



(35) R = H

(36) R = Me

$^3J_{NC(1)}$, < 0.5 Hz. The experimental values are greater than those obtained using Binsch's equation (equation 1) which relates the coupling to the product of the per-

centages of s character S_C and S_N in the hybrid orbitals forming the C—N bond. This indicates that the Fermi contact term is not alone in its contribution to the coupling.

$$80|{}^1J\ {}^{15}N\ {}^{13}C| = S_N \times S_C \quad (1)$$

In the INDO approximation using either fixed atomic values for the integrals, or integrals allowed to vary according to the molecular environment, the respective calculated values[89] for $^2J_{NC(1)}$ in **35** are 0.458 and −0.431 Hz. The magnitudes of the coupling constants of **36** are well reproduced by the calculations.

In the complex *trans*-[Pt(C≡C—$CR^1_2OR^2$)$_2$(PMe_2Ph)$_2$] **(37)**, $R^1 = H_\alpha$, the coupling $^4J_{PtH_\alpha}$ was found to be in the range 11.5–12.4 Hz[90]. When R^1 = Me, R^2 = H, $^1J_{PtC}$ is 892 Hz, which is much greater than the corresponding value of 594 Hz in *trans*-[$PtPh_2(PEt_3)_2$, probably on account of a hybridization change of the carbon bonded to platinum.

In the analogue of **37** with arsenic as a ligand, $^1J_{PtC}$ is now 915 Hz; the increase from 892 Hz is attributed to greater Pt—C bond strength in the arsine complex. In **37**, R^1 = Me, R^2 = H, J_{PtC} decreases along the carbon chain from 892 Hz to $^2J_{PtC}$, 255 and $^3J_{PtC}$, 20.6 Hz.

^{13}C data have been reported for a number of Pt(II) compounds, in particular *trans*-[di-*t*-butylacetylene–$PtCl_2$. NC_5H_4X-*p*], **(38)** and *trans*-[methylacetylene–Pt.NC_5H_4X-*p*], **(39)**[91]. In **38** with di-*t*-butylacetylene numbered $(C(3)H_3)_3C(2)$—C(1)≡$CC(CH_3)_3$, values of $^1J_{PtC}$, 183.5 Hz; δ C(1), 76.40 ppm and $^2J_{PtC(2)}$, 15.7 Hz; δ C(2), 29.58 ppm were found. In *trans*-[*p*-$Me(CH_2)_3OC_5H_4Pt(Me_2PhP)_2$–C(1)≡C(2)—$C(3)H_3$] observed parameters were now $^1J_{PtC(1)}$, 1238 Hz, δ C(1), 59.66 ppm; $^2J_{PtC(2)}$, 359.1 Hz, δ C(2), 100.46 ppm. In the *p*-CN pyridyl analogue $^3J_{PtC(3)}$ is 27 Hz; broadly similar data were obtained when halogen replaced pyridyl as a ligand.

Tungsten–carbon coupling constants have been observed recently; thus from the acetylenic complex $(CO)_3WC_5H_5C(1)H_2$—C(2)≡C(3)H in perdeuterotoluene $J_{WC(1)}$, 29.5 Hz, δ C(1), − 33.2 ppm and for $(CO)_4BrW$≡C(1)—C(2)H=C(Ph)NMe_2 values of $J_{WC(1)}$, 168.5 Hz, δ C(1), 283.9 ppm; $J_{WC(2)}$, 34.0 Hz, δ C(2), 108.5 ppm[92]. In $(CO)_4BrW$≡C—C≡C—Ph, $J_{WC(1)}$, 185.5 ppm, δ C(1), 230.6 ppm; $J_{WC(2)}$, 53.5 Hz, δ 105.8 ppm; $J_{WC(3)}$ ∤ 10.0 Hz, δ C(3), 72.2 ppm. There does not appear to be a very precise correlation between ^{13}C–^{183}W coupling and hybridization at carbon.

$^1J_{CC}$ coupling constants between acetylenic carbons have been measured in mono- and di-substituted silyl- and stannyl-acetylenes[93] and are given in Table 3. It is noteworthy that even the highest value is as low as 130.9 Hz. Entry 4 in Table 3 shows a value of $^1J_{CC}$ = 81.0 Hz, little higher than that for ethylene, thereby indicating a large contribution from the resonance form **40b**. The ratio of $^2J_{MC(1)}$ is 1.6 for entries 1 and 3 and 2.2 for entries 2 and 4 consonant with a significant change in π-electron density of the triple bond on further substitution with R_3Si and R_3Sn.

TABLE 3. Coupling constants (Hz) in ^{13}C-labelled silyl- and stannyl-acetylenes R^1—M—C(2)≡C(1)—R^2 in acetone

Entry	Compound	$^1J_{C(1)C(2)}$	$^2J_{MC(1)}$
1	Et_3SiC≡CH	130.9	18.6[a]
2	Bu_3SnC≡CH	119.8	61.5[b]
3	Et_3SiC≡C$SiEt_3$	101.4	11.5[a]
4	Bu_3SnC≡C$SnBu_3$	81.0	28.2[b]

[a] M = ^{29}Si.
[b] M = ^{119}Sn.

$$R_3M-C\equiv CH \longleftrightarrow R_3\bar{M}=C=\overset{+}{C}H$$

(40a) (40b)

However it has previously been claimed that d_π–p_π interaction between tin and the acetylenic triple bond is unimportant[94]. It might be pointed out here that introduction of R_3Sn and R_3Si groups also causes deshielding of the α and β carbons[93,95].

Wrackmeyer[96] has determined coupling constants for a large number of silicon-, tin- and lead-substituted acetylenes. Thus whereas in $Me_3CC\equiv CH$ $^1J_{CC}$ is 168.7 Hz, the corresponding value drops to 151.6 Hz in $Me_3SnC\equiv COEt$ and the further reduced values of $^1J_{CC}$ = 127.6 Hz for $Me_3SnC\equiv CMe$ and 112.0 Hz for $Me_3SnC\equiv CSiMe_3$ are observed, although no specific interpretation is proposed.

VI. DEUTERIUM QUADRUPOLE COUPLING

From the ^{2}H-NMR spectrum of non-1-yne-1-d, in a nematic phase, the deuterium quadrupole coupling constant has been calculated from the quadrupolar deuterium and dipolar ^{13}C–D splittings[97], the first such application to an acetylenic deuteron. After correction for vibrational averaging a value of 205 ± 3 kHz has been determined.

Deuterium quadrupole coupling constants have been determined in nematic liquid crystal solutions for a number of small molecules, in particular C_2D_2[98]. The value of e^2qQ/h along the bond axis is 198 ± 7 kHz. In this work are cited, with references, corresponding values in $CH_3C\equiv CD$, 199.4 ± 2.0, 208 ± 10; $ClC\equiv CD$, 226 ± 8, 175 ± 20; $FC\equiv CD$, 212 ± 10; $PhC\equiv CD$, 215 ± 5 kHz. A subsequent paper gives the deuterium quadrupole coupling constant of 227 ± 4 kHz at 299 K in the case of phenylacetylene[99] by combining measurements of deuteron spin-lattice relaxation times in a compound with deuterium bonded to carbon C_α together with T_1^{DD}, the ^{13}C dipole relaxation time for C_α in the undeuterated molecule. A value of 230 ± 14 kHz is cited for *p*-dideuteroethynylbenzene.

The deuterium quadrupole coupling constant in cyanoacetylene determined from spin-lattice relaxation times has a value of 200 ± 2 kHz; the analogous value for the ^{14}N nucleus is 4.14 ± 0.05 MHz[100].

In acetylene the experimental coupling constant $^1J_{CH}$ is 249.0 Hz compared with values of 156.2 and 125.0 Hz in ethylene and ethane respectively; the corresponding calculated isotropic coupling constants are 141.9, 80.1 and 64.6 Hz respectively[101]. The calculated anisotropies, $J_{xx} - \frac{1}{2}(J_{yy} + J_{zz})$ are 18.0, 24.5 and 33.0 Hz respectively, where the *x* axis of the coupling tensor is parallel to the C—H bonds. Although agreement is only moderate, the trend is consistent with that anticipated from changes in hybridization and their effect on the Fermi contact and spin dipolar cross-term. The experimental isotropic J_{CC} is 66.5 Hz; the Fermi term contributes 56.1 Hz.

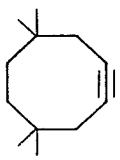
VII. CARBON–BROMINE COUPLING

In bromoacetylene $BrC\equiv CH$, ^1J $^{13}C^{79}Br$ is 266 Hz between −11 and −50°C, the near constancy indicating that relaxation via spin rotation (SR) interaction is negligible. The spin rotation coupling constants in bromoacetylene are calculated to be ca. −0.9 kHz, and at −11°C T_1^{SR} is ca. 1350 s, and contributing less than 0.4% of the relaxation, is considered negligible, as is the chemical shift anisotropy (CSA) where T_1^{CSA} is ca. 550 s[102]. The predominant relaxation mechanism is presumably scalar coupling, since the resonance frequency is similar to that of bromine which is rapidly relaxed by quadrupole interaction.

In bromoacetylene the quadrupole coupling constant is 648.0 MHz for ^{79}Br and 541.4 MHz for ^{81}Br. The magnitude of the coupling constant $^{1}J\ ^{13}C^{79}Br$ varies linearly with the s character of the carbon hybridization indicating a predominant role for the Fermi contact interaction; however a plot of J against s character does not pass through the origin, for reasons which are not clear. Also $^{1}J_{CH}$ in bromoacetylene is 261 Hz, larger than the value in acetylene.

VIII. CONFORMATIONAL MOBILITY

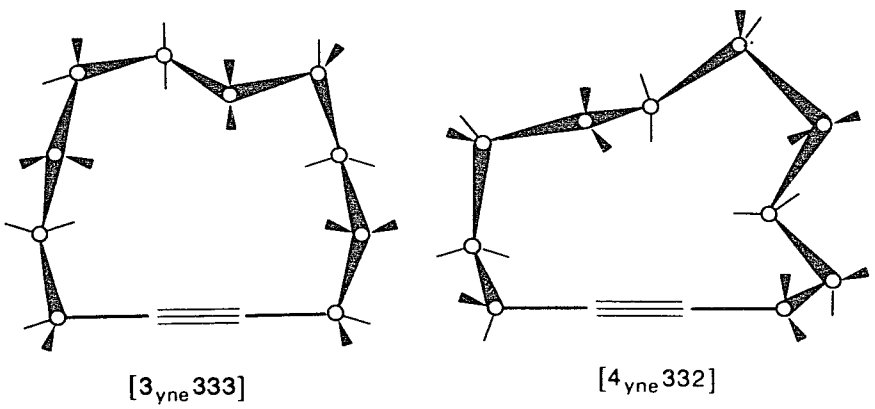
Whereas three sharp signals are observed in the ^{1}H-NMR spectrum of 4,4,7,7-tetramethylcyclooctyne (**41**) at lower temperature the α and γ methylene and the methyl protons split[103], and from the CH_2 and CH_3 protons similar values of $\Delta G^{\neq} \approx 12$ kcal mol^{-1} have been determined. This value associated with conformational mobility is appreciably less than that for cyclooctene, though resolution of **41** into optical isomers does not appear possible. Nevertheless, the



(**41**)

mobility of **41** is surprisingly high, due in part to the ready deformation of the C≡C—C angle, manifestation of which comes from a shielding of ca. 0.3 ppm of the α methylene protons in **41** with respect to those of a linear analogue bearing the grouping —CH_2—C≡C—CH_2— since the α protons in **41** are moved toward the shielding zone of the triple bond.

More recently the α methylene ^{1}H resonances of cyclododecyne (**42**) in the 251 MHz spectrum have been shown to broaden at low temperature[104] with a 'coalescence



(**42**)

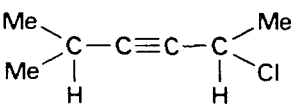
temperature', T_c, of −107°C in an unspecified conformational process with $\Delta G^{\neq} \approx 7.8 \pm 0.3$ kcal mol^{-1}. Maximum broadening in the ^{13}C-NMR spectrum is achieved at −95°C, and at −133°C three sharp lines, with idealized intensity 1:4:1, are observed, indicative of two conformations, one symmetrical and the other

unsymmetrical. The symmetrical conformation is assigned the [3_{yne} 333] structure (for nomenclature see footnote 8 in Reference 104 and Reference 105; note that the numbers refer to the number of bonds, *not* carbons).

Force field calculations identify the [4_{yne}332] and [3_{yne}333] conformations as the most stable in that order although the strain energy difference is given as only 0.8 kcal mol^{-1} (± 1 kcal mol^{-1}). The minor conformer is thus tacitly assigned the [4_{yne}332] structure and a conformational energy barrier of 7.9 ± 0.3 kcal mol^{-1} at −95°C between this and the [3_{yne}333] conformation is found from the ^{13}C spectrum. However this interconversion corresponds to a C_2 time-averaged symmetry; in contrast the ^{1}H spectrum of cyclododecyne corresponds to C_{2v} time-averaged symmetry. It is thus concluded that a further conformational process exists with a magnitude ca. 8 kcal mol^{-1}.

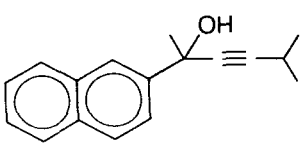
The phenomenon of time-averaged anisochrony of geminal groups which remain symmetry non-equivalent under conditions of rapid conformational inversion, and under the constraint that all conformers are equally populated, has been considered critically[106]. Such molecules are of type **43** where CU_2V is designated the sensor group.

(43)



(44)

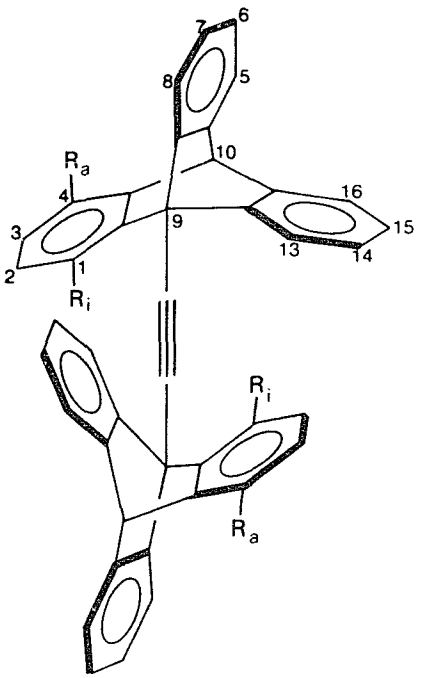
The first example was provided by 2-chloro-5-methylhex-3-yne (**44**) where in the ^{1}H decoupled spectrum[107] an anisochrony of 0.011 ppm was observed for the methyls of the isopropyl group. In the ^{1}H decoupled ^{13}C-NMR spectrum of a mixture of *meso* and *racemic* isomers of **44** the methyl and acetylenic carbons gave distinct absorptions. It had previously been calculated that intrinsic diastereotopic discrimination was likely to be extremely small and 'experimentally insignificant' for nuclei of low atomic number[108]. Notwithstanding this, the ^{1}H-NMR spectrum of 2-(2-naphthyl)-5-methylhex-3-yn-2-ol (**45**) at 300 MHz showed two methyl doublets $\Delta\delta$, 1.3×10^{-3}

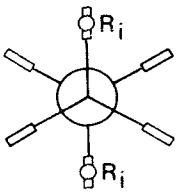


(45)

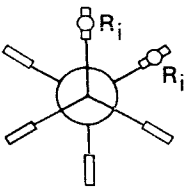
ppm, though the authors[106] add that 'the question now remains to what extent the observed anisochrony can be associated with a freely rotating species'.

Investigation of the low-temperature NMR of ditriptycenylethyne (**46**) at low temperatures gives no indication of hindered rotation[109] whereas the internal methyl groups of the tetramethyl derivative (**47**) show two singlets whose intensity is temperature-dependent, broadening, T_c = 10°C, to give ultimately a singlet at 70°C. The low-temperature behaviour is ascribed to two conformers of which the more stable is antiperiplanar (**48**) together with a syn-clinal counterpart (**49**). The hindered rotation is essentially due to a nonbonded interaction between methyl substituents such that for conversion of **48** → **49**, $\Delta G^{\neq}$ = 65.2 kJ mol^{-1} and for conversion of **49** → **48**, $\Delta G^{\neq}$ = 63.1 kJ mol^{-1}; the related ethenes and ethanes have also been considered.





(48)



(49)

(**46**) $R_a = R_i = H$

(**47**) $R_a = R_i = Me$

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CHAPTER **26**

Preparation and synthetic applications of cyano compounds

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I. INTRODUCTION

In the past decade, the chemistry of the cyano group, usually second in abundance and diversity to that of the amino group, has achieved parity and is moving ahead rapidly to new frontiers. Today, there is hardly any branch of organic, organometallic, inorganic or physical chemistry wherein cyano compounds are not employed. The discovery of organic metals, introduction of the phase-transfer reaction, and the synthesis of new heterocyclic systems, organic and organometallic semiconductors and conducting polymers are but a few topics wherein cyano compounds are involved. Such electron acceptors as tetracyanoethylene (TCNE) and tetracyanoquinodimethane (TCNQ); oxidants, e.g. 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ); organic reagents, e.g. the synthons acrylonitrile, malononitrile, or cyanocarbons; organometallic cyano reagents, e.g. α-phosphoryl (Wittig reagents) and 2-trimethylsilyl (Peterson reagents); and inorganic reagents, e.g. sodium cyanoborohydride, are but a few areas wherein the present trend is proceeding. All of these topics will be covered in this review; in addition, pertinent, recent methods for the preparation of nitriles are also discussed.

During the past decade, synthetic applications of cyano compounds have grown enormously, and the field is expanding rapidly. Consequently, it is, in a single review, impossible even to attempt to cover all of the recent synthetic developments in cyano chemistry exhaustively.

Owing to limitations of space, and the extensive literature on the subject, the present survey of new, synthetic applications will be thorough, but not exhaustive. An effort has, however, been made to provide the reader with all of the major developments in synthetic applications of cyano compounds achieved during the past ten years (1970–1980); this has not, however, proved an easy task as several thousand references had to be considered. The chemistry of the cyano group has been reviewed in an extensive monograph[1] and two books[2,3]. Four recent accounts deal with the chemistry of cyanamides[4], cyanocarbons[5], cyanoethylation[6] and cyanohydrins[7,8]. The chemistry of malononitrile and related cyano compounds has been reviewed[9,10].

A monograph by Freeman[11] discusses in considerable detail malononitriles, ylidenemalononitriles, cyanocarbon acids and dimers and trimers of malononitrile. Two recent reviews by Freeman[12,13] deal with recent developments in the chemistry of ylidenemalononitriles[12] and new reactions of substituted malononitriles[13]. Two other

reviews have discussed the reactions of halogen derivatives of nitriles[14] and the properties of the dicyanomethylene group, e.g. the analogy between the oxygen atom and the $C(CN)_2$ group[15].

II. NEWER METHODS FOR SYNTHESIS OF NITRILES: SOME OF THEIR REACTIONS

Since the last comprehensive survey of the chemistry of the cyano group[1], a large number of reports has appeared on new and improved procedures for the synthesis of cyano compounds.

The present article surveys recent methods by which a nitrile group is introduced either by substitution or addition and those by which the nitrile group is formed *in situ* by the elimination of elements or groups. Because of the specificity of various new reagents used in preparing nitriles, this survey treats, as separate topics, the preparation of unsaturated nitriles or enaminonitriles, saturated nitriles and aromatic and heterocyclic nitriles, stereospecific and asymmetric synthesis of nitriles and cyanoethylation and cyanomethylation reactions. The continual discovery of new synthetic reagents makes it extremely difficult to assess the claims of new methods for the general synthesis of nitriles, as compared to standard, classical methods. Indeed, the purpose of this article is, in part, to demonstrate the ongoing, new methodology and to point out new trends in the chemistry of the cyano compounds of the future.

A. PREPARATION OF NITRILES BY ELIMINATION

1. *Conversion of aldehydes and ketones, via their aldoximes, into nitriles*

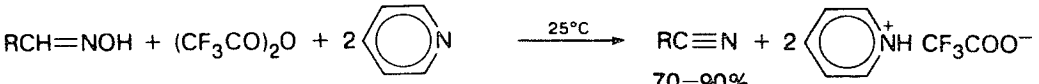
Over the years, a number of methods have been described for the conversion of aldehydes into nitriles via the dehydration of the corresponding oximes (equation 1)

$$RCHO \xrightarrow{H_2N-OH} RCH{=}NOH \xrightarrow[-H_2O]{} RC{\equiv}N \qquad (1)$$

with such reagents as acetic anhydride, acetyl, benzoyl and thionyl chloride, and phosphorus petaoxide, and all of these, and other classical methods, have been surveyed[16–20]. However, development of new reagents and methods in synthetic organic chemistry are indisputable facts today[21,22].

The known methods leading to nitriles from aldoximes often present some disadvantages, such as vigorous reaction conditions, tedious processing, unsatisfactory yields, limited adaptability, and, most important, a lack of generality for both the aliphatic and aromatic aldoximes[23–29]. Recent preparative methods[23–29] for the transformation of aldoximes to nitriles stress mildness, versatility, convenience (e.g. one-flask conversion), and high yield of the product.

a. Trifluoroacetic anhydride. Trifluoroacetic anhydride and pyridene at ambient temperature is a mild dehydrating system for the efficient preparation of nitriles from aldoximes (equation 2)[30]. The reagent has also been used for preparation of nitriles



(2)

from primary amides. In this fashion[31], a series of *trans*-(*E*)- and *cis*-(*Z*)-aldoximes was converted into nitriles in 80–99% yield. The usefulness and versatility of the method was demonstrated by the efficient dehydration of a structurally complicated and

sensitive substrate, i.e., *all-trans*-retinaldoxime (80–85% conversion). By the same procedure, some dioximes were converted into the corresponding dinitriles in 62–98% yield[31].

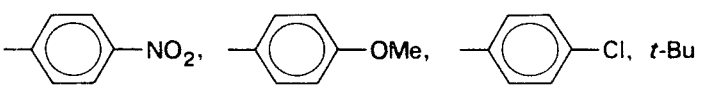
The dehydration of aldoximes may occur by a base-promoted, bimolecular mechanism in which stereochemical factors must play a most important role in determining the different reactivities (*anti* stereochemistry favoured)[32].

b. Trifluoromethanesulphonic anhydride and other mild reagents. Nitriles are obtained in excellent yield from either *syn*- or *anti*-oximes by treatment with trifluoromethanesulphonic anhydride (triflic anhydride) as a dehydrating agent (equation 3)[26]. Aldoximes, (*E*)- and (*Z*)-, are converted into the corresponding nitriles by treatment with *N*,*N*′-carbonylbis(imidazole) (CBI) in dichloromethane at room temperature or under reflux (equation 4)[33]. Alkyl and aryl oximes have successfully been converted into

$$RCH{=}NOH \xrightarrow{(F_3C-SO_2)_2O/NEt_3/CH_2Cl_2,\ -78\ \text{to}\ +20^\circ C} \underset{84-94\%}{RC{\equiv}N} \qquad (3)$$

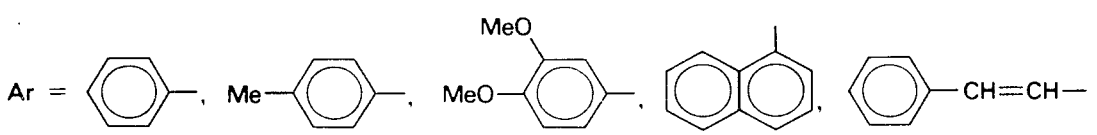
R = alkyl, aralkyl, aryl

$$RCH{=}NOH \xrightarrow{CBI/CH_2Cl_2} \underset{75-99\%}{RC{\equiv}N} \qquad (4)$$

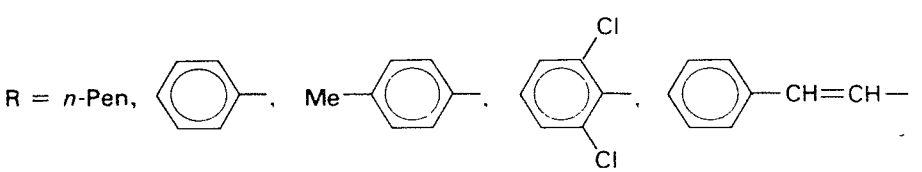
R = 

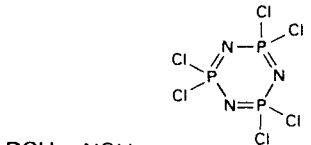
nitriles with such mild reagents as trichloroacetonitrile (equation 5)[36], *N*-ethylacetonitrilium fluoroborate (equation 6)[34,35], or phosphononitrile dichloride trimer (1,1,3,3,5,5-hexachlorocyclotriphosphatriazene) and an excess of triethylamine at room temperature (equation 7)[36].

$$ArCH{=}NOH + Cl_3CCN \xrightarrow[75-95\%]{\nabla} ArCN + Cl_3C-\overset{\overset{O}{\|}}{C}-NH_2 \qquad (5)$$

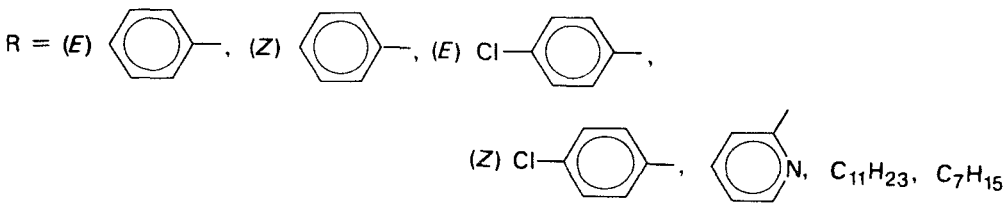
Ar = 

$$RCH{=}NOH + MeC{\equiv}\overset{+}{N}HEt\ BF_4^- \xrightarrow[-HBF_4]{} \left[\text{cyclic intermediate}\right] \xrightarrow[56-88\%]{} RCN + MeCONHEt \qquad (6)$$

R = *n*-Pen, 



$$RCH{=}NOH \xrightarrow[72-92\%]{} RC{\equiv}N \qquad (7)$$



c. Selenium dioxide. Another mild and versatile method for the conversion of aldoximes into nitriles in high yield uses selenium dioxide in chloroform[29] (equation 8). It is surprising that this reaction occurs so readily, since in some previous investigations[37], selenium dioxide with dioximes yielded heterocyclic compounds of the selenadiazole type.

Sosnovsky and coworkers[38] have described an interesting one-flask conversion of aldehydes into nitriles by hydroxylamine hydrochloride and selenium dioxide (70–89%) (equation 8). The method was successfully used with aldehydes containing

$$RCH{=}NOH \xrightarrow[\substack{R = \text{alkyl; } 20-23^\circ C \\ R = \text{aryl; reflux}}]{SeO_2/CHCl_3} RC{\equiv}N \qquad (8)$$

$$68-100\%$$

R = Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$, *n*-Pr, *n*-Hex, *n*-Hep, *c*-Hex

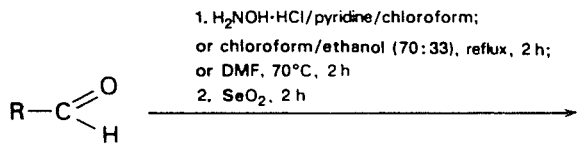
either allylic hydrogen atoms, such as vitamin A aldehyde, or a hydroxyl group, without affecting these moieties (equation 9).

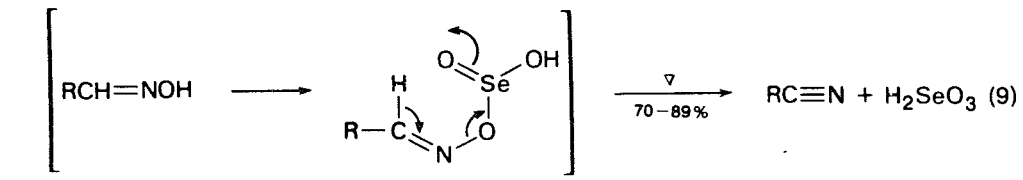
d. Trimethylamine–sulphur dioxide complex and chlorosulphonyl isocyanate. Olah and Vankar[28] have reported the preparation of nitriles from aldoximes via dehydration with the trimethylamine–sulphur dioxide complex. The method appears to be general for both aryl- and alkyl-substituted aldoximes (equation 10). Olah and coworkers[39a] have also found chlorosulphonyl isocyanate to be efficient in the conversion of aldoximes (and amides) into nitriles in good yield (equation 11). The same group[39b] have also utilized sulphonyl chloride fluoride ($ClSO_2F$) in the preparation of nitriles from aldoximes.

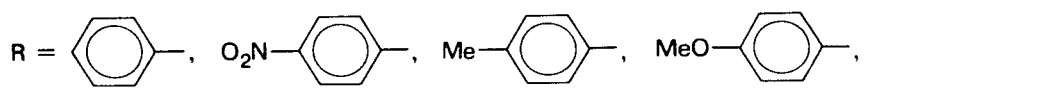
Shah and Bhatt[40] have dehydrated oximes to nitriles with phenyl isocyanate (70–80%) (equation 12).

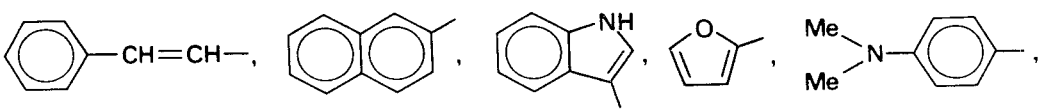
e. Acetonitrilium salts and carbodiimides. As reported by Ho[41], aldoximes are dehydrated to nitriles when treated in acetonitrile with *N*-ethylacetonitrilium tetrafluoroborate (8 h at 20°C, and then 0.5 h at 80°C) (equation 13). The aldoximes are also dehydrated with dimethyliminium salts in refluxing chloroform in excellent yields (equation 14)[42]. Carbodiimides are effective for the dehydration of aldoximes to nitriles, generally in 70–96% yield (equation 15)[43].

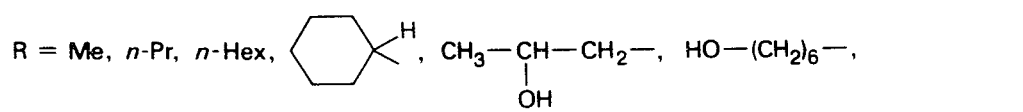
f. Dehydration of aldoximes by phase-transfer catalysis. Aldoximes (also amides and thioamides) are dehydrated to nitriles by dichlorocarbene, generated *in situ* from

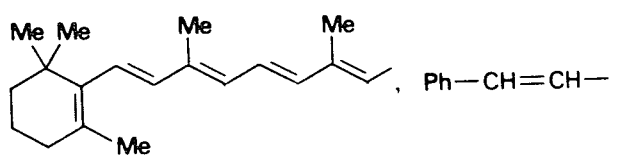


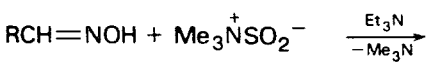


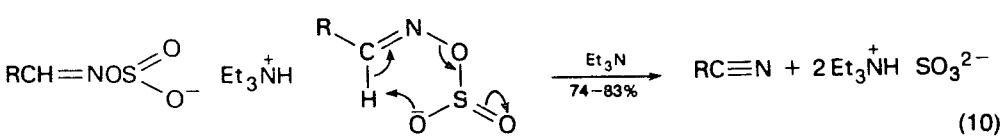






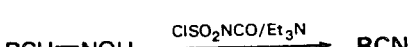






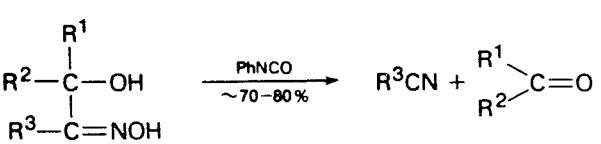
(10)

R = *n*-Pen, *n*-Hex, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, $PhCH{=}CH_2$, 2-furyl



(11)

R = **Subst. Ph**, *n*-Pen, *c*-Hex

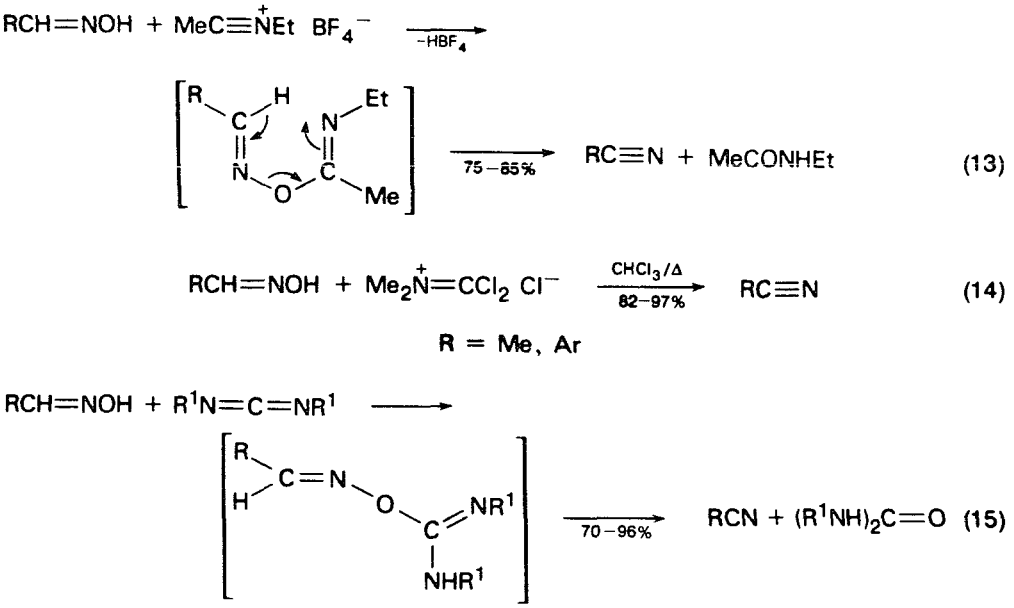


(12)

R^1, R^2 = H, alkyl, Ph

R^3 = Ph, alkyl

R^1, R^2 = cyclic



$$RCH{=}NOH + MeC{\equiv}\overset{+}{N}HEt\ BF_4^- \xrightarrow{-HBF_4}$$

$$\left[\begin{array}{c} R \\ H \end{array}\!\!>C{=}N{-}O{-}C(Me){=}\overset{+}{N}HEt\right] \xrightarrow[75-85\%]{} RC{\equiv}N + MeCONHEt \qquad (13)$$

$$RCH{=}NOH + Me_2\overset{+}{N}{=}CCl_2\ Cl^- \xrightarrow[82-97\%]{CHCl_3/\Delta} RC{\equiv}N \qquad (14)$$

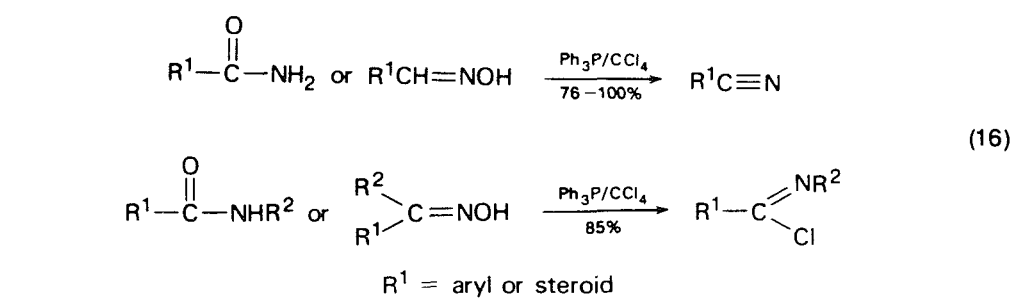
R = Me, Ar

$$RCH{=}NOH + R^1N{=}C{=}NR^1 \longrightarrow \left[\begin{array}{c} R \\ H \end{array}\!\!>C{=}N{-}O{-}C(NHR^1){=}NR^1\right] \xrightarrow[70-96\%]{} RCN + (R^1NH)_2C{=}O \qquad (15)$$

R = Ph, 4-MeC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 1-$C_{10}H_7$, PhCH=CH

chloroform and aqueous NaOH in the presence of a phase-transfer catalyst, e.g. benzyltriethylammonium chloride (TEBA). Yields range from 50 to 85%. Substrates cannot be sensitive to alkalis or contain groups that react with dichlorocarbene[44].

g. Triphenylphosphine–carbon tetrachloride system. Primary amides[45,46] and aldoximes[46] react readily with triphenylphosphine and carbon tetrachloride to give nitriles. Secondary amides[47] and ketoximes[48] react with the same reagent to give imidoyl chlorides. A system of a polymer-supported phosphine and carbon tetrachloride has been reported[49] to be better for conversion of aldoximes or ketoximes into nitriles, or imidoyl chlorides, respectively. The advantage of the polymer-supported reagents[50,51] is the simplified processing, i.e. isolation of the product. The polymer-supported reagent (Ph_3P–CCl_4)[49] is also efficient in the conversion of amides into nitriles (76–100% yield), and particularly useful in the reaction with ketoximes to yield moisture-sensitive imidoyl chlorides (equation 16).

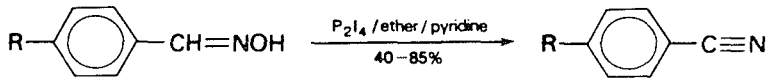


$$R^1{-}C(=O){-}NH_2 \text{ or } R^1CH{=}NOH \xrightarrow[76-100\%]{Ph_3P/CCl_4} R^1C{\equiv}N$$

$$R^1{-}C(=O){-}NHR^2 \text{ or } \begin{array}{c} R^2 \\ R^1 \end{array}\!\!>C{=}NOH \xrightarrow[85\%]{Ph_3P/CCl_4} R^1{-}C(=NR^2){-}Cl \qquad (16)$$

R^1 = aryl or steroid

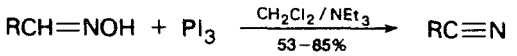
h. Dehydration of oximes by diphosphorus tetraiodide. Diphosphorus tetraiodide (P_2I_4) converts both aliphatic and aromatic aldoximes into nitriles under mild conditions in ether at room temperature, in moderate to good yields (equation 17)[52].



(17)

R = Cl, MeO, NO_2, Me_2N

i. Dehydration of oximes by phosphorus triiodide. PI_3, a powerful deoxygenating agent efficiently transforms aldoximes into nitriles under mild conditions[53] at room temperature in dichloromethane (equation 18).



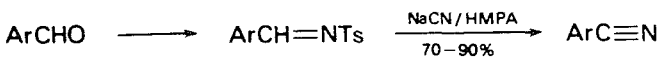
(18)

R = $C_{10}H_{21}$, $PhCH_2$, Ph

j. Additional methods for preparation of nitriles via oximes. Recent methods found for the conversion of both aliphatic and aromatic aldehydes into nitriles in a one-flask procedure include the use of *O*-(2,4-dinitrophenyl)hydroxylamine[25], hydroxylamine-*O*-sulphonic acid[54] and a mixture of hydroxylamine hydrochloride and formic acid[55].

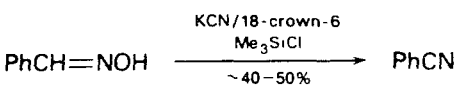
Other mild methods for conversion of aldoximes into nitriles involve the application of phosphonylimidazolide[56], dichloro-*N*,*N*-dimethylmethaniminium chloride[57], dialkyl (or diphenyl) hydrogen phosphite–carbon tetrachloride[58], trichloro-1,3,5-triazine–pyridine[59], phenyl chlorosulphite–ether–*N*,*O*-bis(trifluoroacetyl)hydroxylamine[60], phosphorus tris(dimethylamide)[61]; also, potassium cyanide–phase-transfer catalyst[62]. titanium(IV) chloride[63] or *O*-(4-chlorophenyl)carbonochloridothiolate–ether or –dichloromethane[64].

Conversions of aldoximes into nitriles that require heat or an elimination process involve the use of dicyclohexylcarbodiimide[43,65], methyl isocyanate–*N*,*N*-dimethylformamide[66], phenylchlorocarbonate[67], trichloroacetonitrile[68], 1-amino-2-pyridone[69]; also, 1,2-elimination of *O*-substituted aldoximes[25,54] or 1,2-elimination of a Schiff-base tosyl group (equation 19)[70].

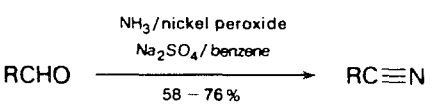


(19)

k. Special methods. Nitriles are prepared by treatment of aldoximes with potassium cyanide in the presence of a crown ether (equation 20)[71]; also from aldehydes via ammonia–nickel peroxide treatment (equation 21)[20] or from benzyl chloride analogues via oximes and dehydration steps (equation 22)[73].

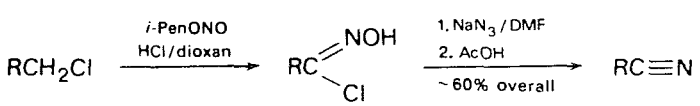


(20)



(21)

R = Subst. Ph, *n*-octyl, furyl



(22)

R = heterocyclic

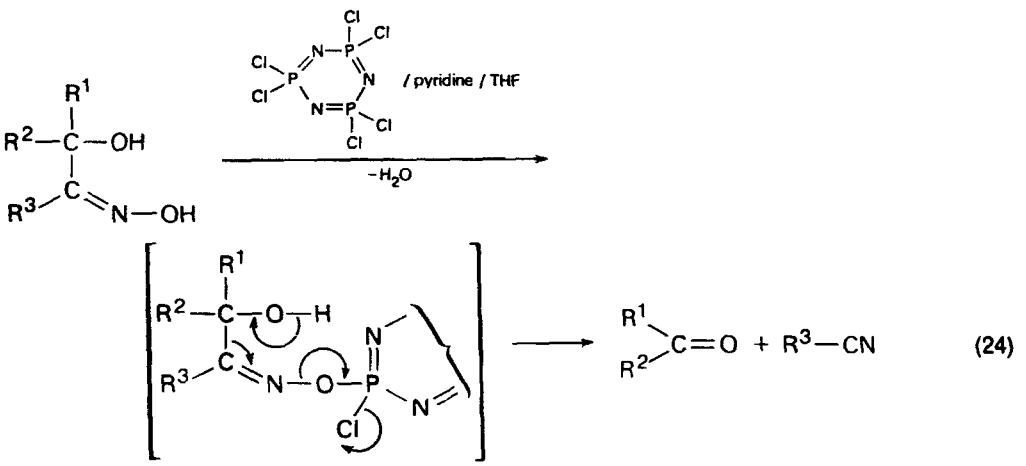
2. *Nitriles from ketoximes via an abnormal Beckmann rearrangement*

Although ketoximes cannot normally be converted into nitriles, α-oximino ketones or acids or β-keto ether oximes undergo fragmentation or an abnormal Beckmann rearrangement[3,74], giving nitriles. This rearrangement is brought about by strong acids, acid chlorides, acylating agents, bases, or heat alone. The abnormal Beckmann rearrangement of ketoximes with an adjacent carbonyl or carboxyl group, or ketoximes bearing an amino or ether substituent at the β-position, or transformation of α-keto acids to nitriles has been discussed[3,74,75].

a. The Beckmann fragmentation of oxime ortho ester adducts. The oxime ortho ester adducts are generally stable under neutral conditions[76]. However, in the presence of various acid catalysts, they give nitriles, esters and alcohols (equation 23)[77]. The fragmentation probably involves reversible formation of a conjugate-acid intermediate, followed by formation of an oxime alkoxycarbonium ion and subsequent fragmentation of the latter[77].

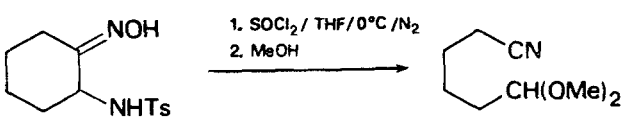
$$R^1CH{=}NOCR^2(OR^3)_2 \xrightarrow{H^+} R^1CN + R^2COOR^3 + R^3OH \qquad (23)$$

b. Fragmentation of α-hydroxyketoximes. Phosphonitrile dichloride reacts at room temperature with aldoximes to give nitriles[36,78], but in the presence of pyridine it causes the fragmentation of α-hydroxyketoxime to give ketone (or aldehyde) and nitrile in almost quantitative yields (equation 24)[79]. The reaction is assumed to proceed as a Beckmann fragmentation[74,79].



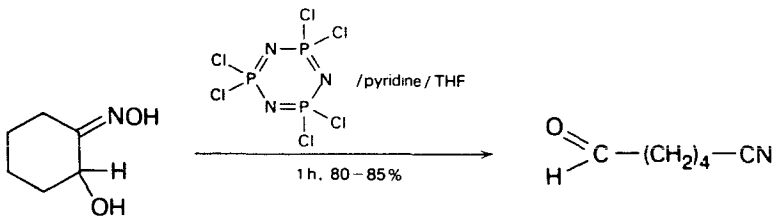
(24)

c. Ring-opening of cyclic oximes. Frequently, under Beckmann rearrangement conditions, cyclic oximes undergo ring-opening[80] to yield cyanocarboxylic acid derivatives, e.g. acetals (equation 25)[81] or esters[77]. Rosini and Medici[79] have also found that synthetically important[82] ω-cyano aldehydes are readily obtained from oximes of cyclic acyloins by treatment with phosphonitrile dichloride–pyridine. Thus,



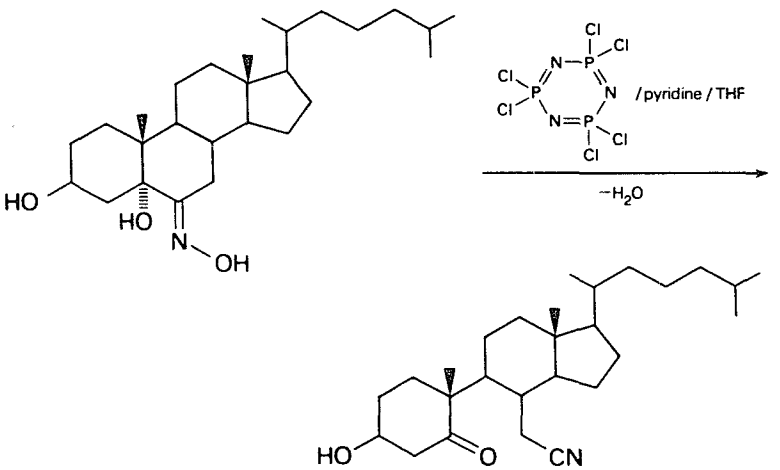
70%

(25)



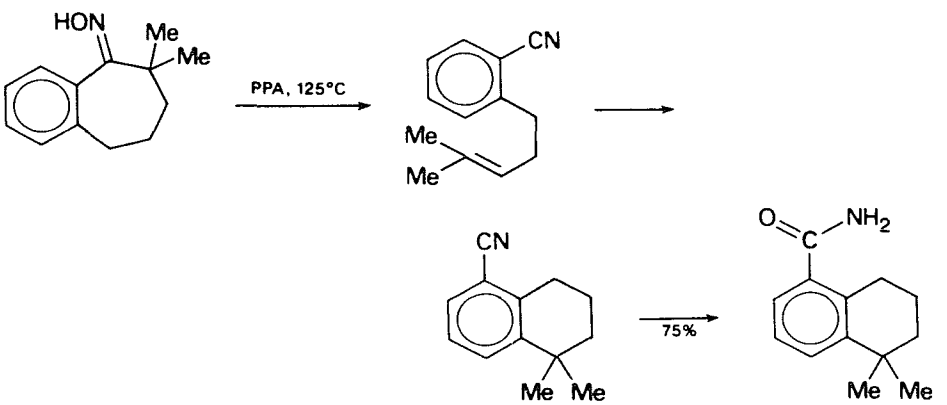
(26)

2-hydroxycyclohexanone oxime is cleaved to give 6-nitrilohexanal (equation 26). The method[79] is also useful in steroid chemistry. Thus, 3β, 5α-dihydroxy-6-oximinocholestanone is cleaved by the reagent, to give 3-hydroxy-6-nitrilo-5-oxo-5,6-secocholestane in 80–85% yield; the free 3β-hydroxyl group is not affected (equation 27). Previously, 2-alkoxycycloalkanone oximes were cleaved by phosphorus(V) chloride to give ω-cyano aldehydes; this is the only report[83] on record.



(27)

d. Ring-expansion of cyclic oximes, and exceptions thereto. Although simple 2,2-disubstituted cycloalkanone oximes undergo cleavage (Beckmann fragmentation) under Beckmann rearrangement conditions[74,75,84] to produce nitriles, the corresponding 2,2-disubstituted 1-indanone, tetralone or benzosuberone oximes reportedly



(28)

undergo, almost exclusively, ring-expansion[85], with the formation of 7-membered-ring amides.

However, on treatment of 6,6-dimethylbenzosuberone oxime with warm poly(phosphoric acid) (PPA), an amide was obtained by Amit and Hassner[86], probably through Beckmann fragmentation of the oxime in PPA, to give the 2-(3-alkenyl)benzonitrile, which by acid-catalysed cycloaddition and hydrolysis may give the amide (equation 28). This constitutes a useful, synthetic pathway to the (otherwise difficultly accessible), substituted tetralin system.

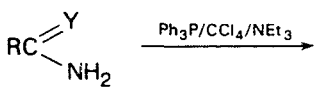
B. Conversion of Carboxylic Acids via their Amides or Thioamides into Nitriles

The most important method for the conversion of carboxylic acids into the corresponding nitriles consists in the dehydration of their amides or thioamides (equation 29) with common dehydrating agents[17–19].

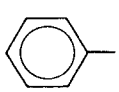
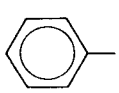
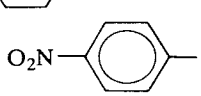
$$\begin{aligned} RCONH_2 &\xrightarrow{-H_2O} RC{\equiv}N \\ RCSNH_2 &\xrightarrow{-H_2O} RC{\equiv}N \end{aligned} \qquad (29)$$

1. New reagents and methods

Often, new reagents used for the dehydration of oximes to nitriles are also found to be effective for the dehydration of amides to nitriles. Thus, the dehydration of amides or thioamides with triphenylphosphine, carbon tetrachloride and triethylamine provides a convenient method for the preparation of nitriles under mild conditions (equation 30)[45,46]. Similar transformations have been achieved with triphenylphosphine



(30)

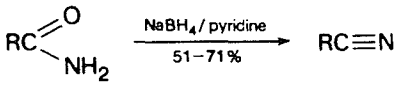
Y	R	Yield (%)
O	H	51
O	Me	92
S	Me	89
O		90
S		60
O		71

and carbon tetrachloride (80–100%)[45,87], with trifluoroacetic anhydride (70–90%)[30], titanium(IV)chloride (66–91%)[63], phosphononitrile dichloride trimer (83–100%)[36,88], dichlorocarbene (40–95%)[44,89] or zinc chloride (60–80%)[90a], and quite recently, with cyanuric chloride[90b].

The use of polyphosphoric acid ethyl ester in chloroform, in certain cases, is superior to other dehydration procedures (53–93%)[91].

2. Sodium borohydride reagent

Amides are resistant to mild reducing agents such as sodium borohydride. However, primary amides that are not substituted at nitrogen may be dehydrated by sodium borohydride in refluxing pyridine (10–20 h) (equation 31); *N,N*-disubstituted amides are instead converted into amines. Monosubstituted amides do not react under these conditions[92,93].

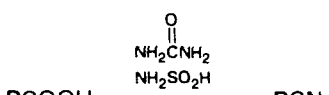


(31)

R = Me, Et, Ph

3. Urea–sulphamic acid reagent

Cyclohexanecarboxylic and benzoic acids have been converted into nitriles by treatment with urea and then with sulphamic acid (equation 32)[90].

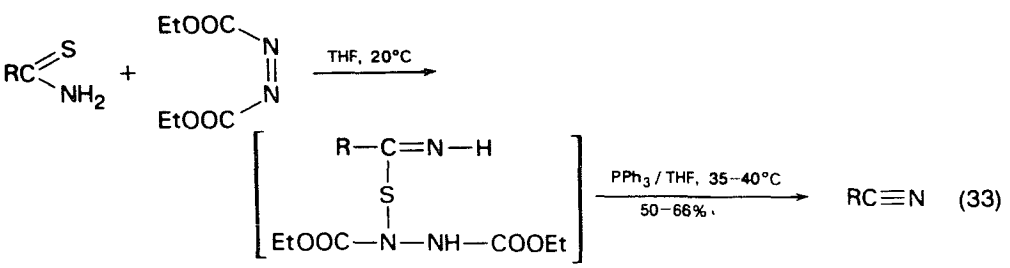


(32)

R = C_6H_{11}, Ph

4. Diethyl azodicarboxylate–triphenylphosphine reagent

Thioamides give nitriles with a combination of diethyl azodicarboxylate and triphenylphosphine. The reactions involve the formation of a 1:1 adduct which is then desulphurized by triphenylphosphine to generate the nitriles. The method is apparently specific for thioamides (equation 33)[94].



(33)

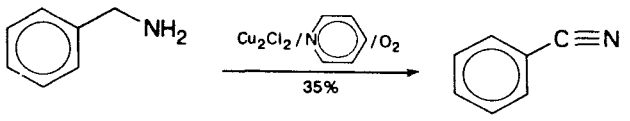
R = Me, Ph, pyridyl

C. Synthesis of Nitriles from Amines, Hydrazones and their Derivatives

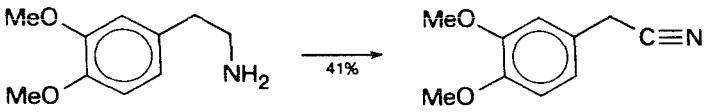
1. Oxidation of amines

The oxidation of amines to nitriles has been achieved with various oxidizing agents, such as nickel peroxide[95], lead(IV) acetate[96], silver(III) oxide[97] or silver(II) picolinate[98].

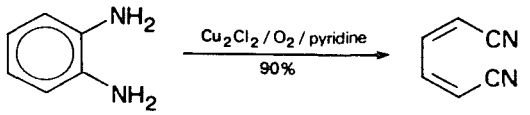
a. Copper(I) chloride reagent. A new procedure[99] reports mild oxidation of amines to nitriles by the use of copper(I) chloride in pyridine under an atmosphere of oxygen. In this way, benzylamine is oxidized to benzonitrile (equation 34) and 3,4-



(34)



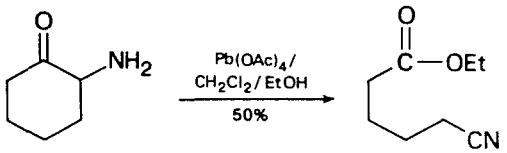
(35)



(36)

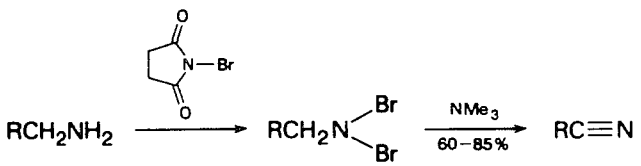
dimethoxyphenetylamine to 3,4-dimethoxybenzyl cyanide (equation 35). Similarly, *o*-phenylenediamine is oxidized to *cis,cis*-mucodinitrile in high yield (equation 36)[100].

b. Lead tetraacetate reagent. Degradation of 2-aminocyclohexanone with lead tetraacetate in dichloromethane–ethanol leads to a ω-cyanoethyl ester (equation 37)[101].



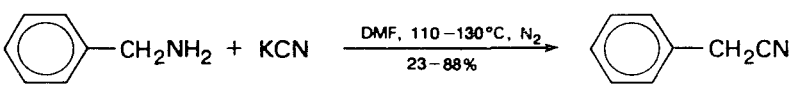
(37)

Other procedures include bromination of amines, followed by treatment with triethylamine (equation 38)[102], alkylation of a cyanide ion with substituted benzylamines (equation 39)[103], diazotization of aniline (equation 40)[104], chlorination of dimethylaniline (equation 41)[105] and dehydration of a 2-

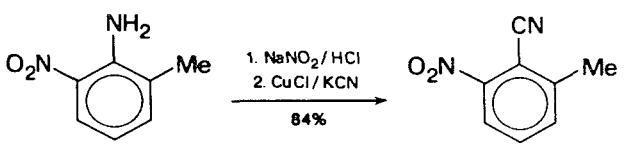


(38)

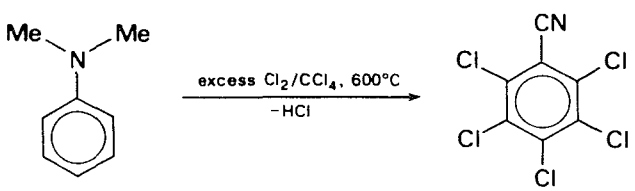
R = alkyl, aryl



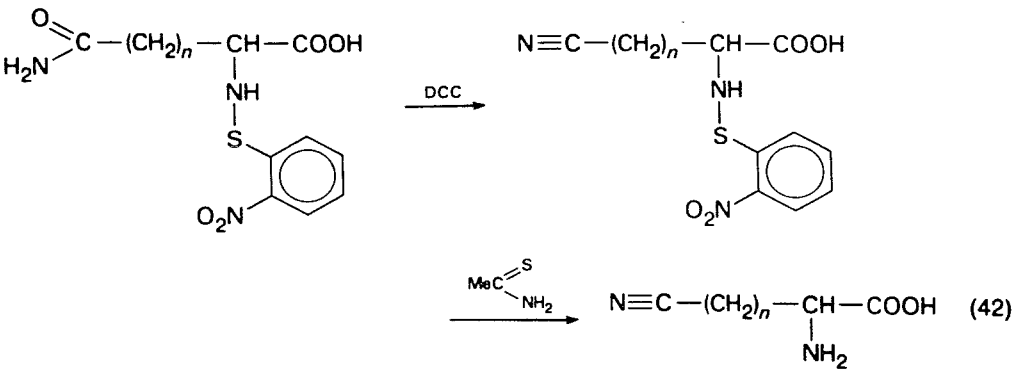
(39)



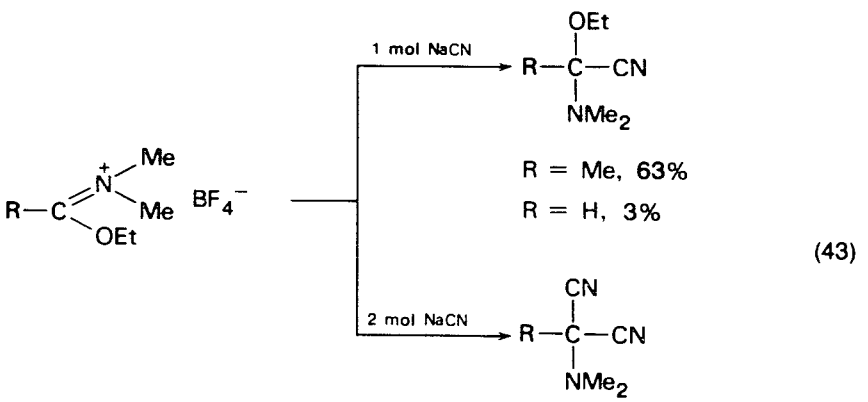
(40)



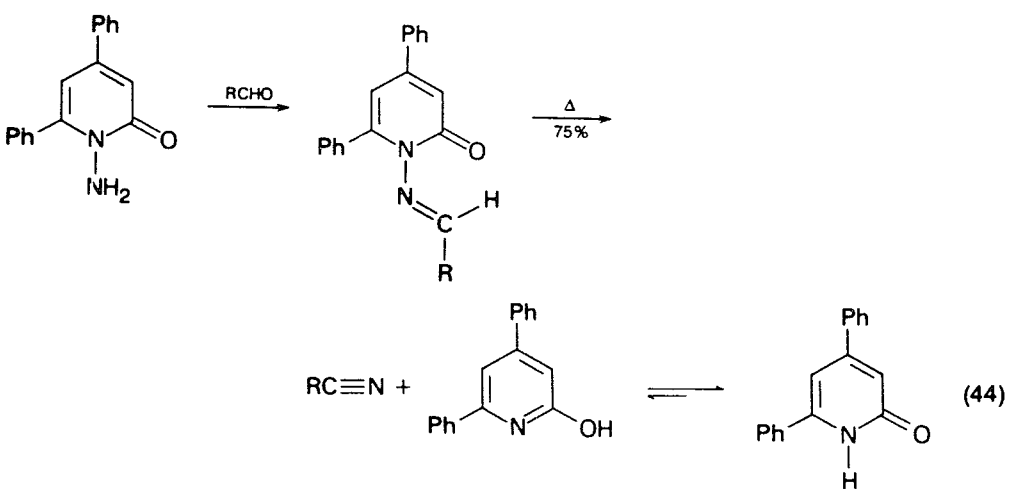
(41)


DCC
n = 1, 70%
n = 2, 78%

(42)


1 mol NaCN
2 mol NaCN
R = Me, 63%
R = H, 3%
R = Me, 66%
R = H, 51%

(43)


RCHO
75%

(44)

amino-ω-aminocarbonylcarboxylic acid with dicyclohexylcarbodiimide (equation 42)[106]. Additional methods include cyanation of (dimethylamino)ethoxymethylcarbonium tetrafluoroborate (equation 43)[107], thermal decomposition of pyridone[108a] or quinazolinone[108b] aldimines (equation 44), reaction of aldehydes with cobalthexammine complexes, followed by oxidation with bromine (equation 45)[109] and thermal decomposition of an azide (equation 46)[110].

$$RCHO + Co(NH_3)_6X_2 \xrightarrow{MeCN}$$

$$\left[\begin{array}{c}(R-CH{=}NH)_n \\ \downarrow \\ Co(NH_3)_{6-n}\end{array}\right] X_2 \xrightarrow[70-100\%]{Br_2} RCN \qquad (45)$$

R = Ph, X = $Co(CO)_4$

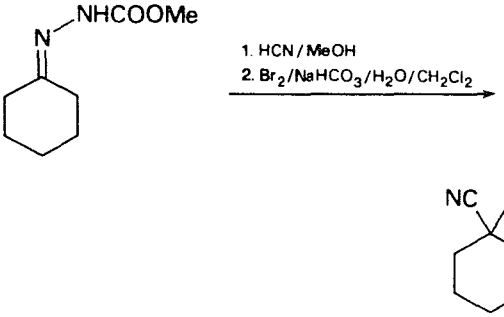
$$R^1-CH{=}C(-C(=O)-R^2)(-N_3) \xrightarrow[75\%]{\Delta} R^1-CH(-CN)-C(=O)-R^2 \qquad (46)$$

R^1 = *p*-MeC_6H_4, R^2 = Me

2. *Conversion of aldehydes and ketones via their hydrazones into nitriles containing additional carbon atoms*

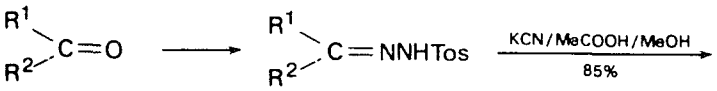
The currently accepted method involves the reaction of the hydrazones with hydrogen cyanide (or potassium cyanide); the hydrazones used are methoxycarbonylhydrazone[111], tosylhydrazone[112] and 2,4,6-triisopropylphenylsulphurylhydrazone[113]. This method is superior to any procedure involving dehydration followed by catalytic hydrogenation of the cyanohydrins initially formed.

In the procedure of Ziegler and Wendler[111], a ketone was first treated with methyl carbazate, to give methoxycarbonyl hydrazone, and then, successively, with hydrogen cyanide (to yield the hydrazide), dehydrated with bromine to *N*-methoxycarbonyldiazene, and, finally, with sodium methoxide to afford the nitrile (equation 47). Caglioti and coworkers[112] showed that *p*-toluenesulphonylhydrazones



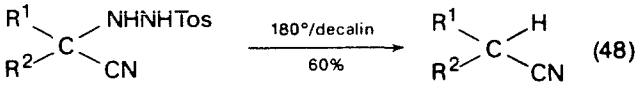
(47)

(of cyclohexanone and 4-heptanone) react with hydrogen cyanide to give the corresponding adducts; on heating, the desired nitriles are obtained (equation 48). Reese



$R^1 = R^2 = n\text{-Pr}$

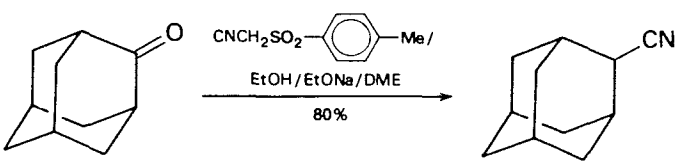
$R^1 = R^2 = -(CH_2)_5-$



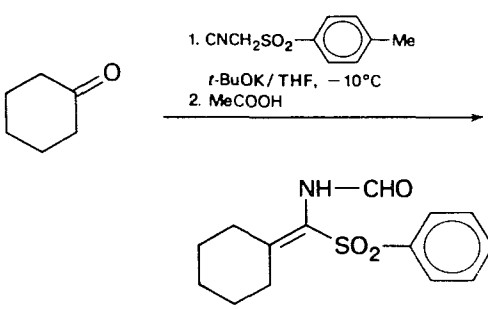
(48)

and coworkers[113] allowed the reaction to proceed in the presence of an excess of potassium cyanide in refluxing methanol, so that the high-temperature decomposition of the hydrogen cyanide adduct was avoided.

a. p-Tolylsulphonylmethyl isocyanide reagent. Oldenziel and van Leusen found[114] that, when adamantanone was treated with *p*-tolylsulphonylmethyl isocyanide and sodium ethoxide in 1,2-dimethoxyethane–ethanol at 0°C, 2-cyanoadamantane was obtained (equation 49). Similarly, benzaldehyde, pivaldehyde, cyclohexanone (equation 50)[115] or 1-tetralone[116] have been converted into the corresponding nitriles.



(49)

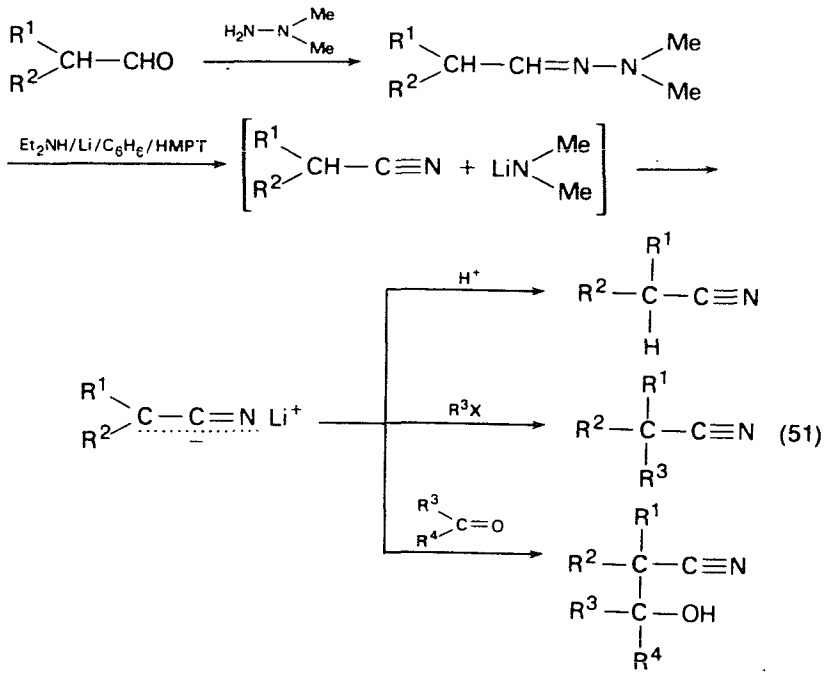


(50)

3. *Synthesis of nitriles via metalation of hydrazones*

A convenient synthesis of nitriles from hydrazones involves their reaction with active amides, prepared from diethylamine plus lithium in hexamethylphosphoric triamide (HMPT). As shown by Normant and coworkers (equation 51)[117,118], lithium *N,N*-dimethylamide metalates the nitrile at a position α to the cyano group; protonation of the anion then gives a nitrile (H^+, hydrolysis). The lithium salt may also react with various electrophiles, including various alkylating agents (e.g. dimethyl sulphate, to give trisubstituted nitriles) or with aldehydes and ketones (to give 3-hydroxynitriles) (equation 51)[118]. This provides a convenient, one-flask procedure for a direct synthesis of nitriles from aldehydes (77–94% yield).

a. N,N-Dimethylhydrazine + oxirane reagent (e.g. $H\bar{N}\text{-}\dot{N}Me_3CH_2CH_2OH$). A new mild method for converting aldehydes into nitriles involves the reagent prepared from *N,N*-dimethylhydrazine and oxirane[119]. A previously reported method[120] for the conversion of aldehydes into nitriles involves the 1,2-elimination of the trimethylamino group in $RCH = N - NMe_3^+ I^-$ by a base.



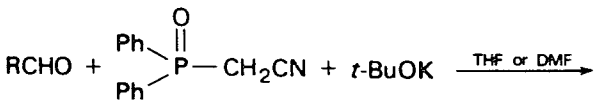
D. Stereoselective Synthesis of Unsaturated Nitriles

1. Synthesis of 2-alkenenitriles

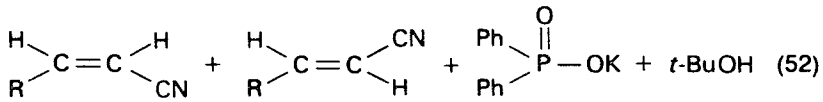
The preparation of α,β-unsaturated nitriles is of considerable importance[17,121,122]. The stereoselective synthesis of 2-alkenenitriles from aldehydes has been realized via several routes: (*a*) the Doebner condensation of aldehydes with cyanoacetic acid[123], which usually leads to a mixture of *Z*(*cis*) and *E*(*trans*) isomers; (*b*) the carbonyl olefination of aromatic aldehydes with cyanomethylenetriphenylphosphorane[124,125] (the Wittig reagent), which gives the *E*(*trans*) isomers in good yields; and (*c*) the carbonyl olefination of aldehydes with diethyl cyanomethanephosphonate anion[126] (the Wittig–Horner reaction), which affords 2-alkenenitriles (90%), the *E*(*trans*) selectivity being ≥ 70% in the case of aromatic aldehydes, but poor for aliphatic aldehydes. A new procedure entails reaction of an organometallic substrate with, for example, cyanogen chloride, phenyl cyanate or 2-alkynenitriles.

a. trans-*2-Alkenenitriles from aldehydes*. A new method[127], suitable for transforming aromatic and some aliphatic aldehydes into 2-alkenenitriles, employs cyanomethyldiphenylphosphine oxide [**2**, $(Ph)_2P(O)CH_2CN$] as the alkenating agent. The reaction of the aldehyde **1** (R = *i*-Pr, Ph) is performed in THF in the presence of potassium *t*-butoxide (**3**) at room temperature. Compound **2** is thus converted into potassium diphenylphosphinate (**6**), which makes product separation easier. The yields are 82–95%, with the *E*(*trans*)-2-alkenenitrile (**5**, R = Ph) predominant (90%) and less of the *Z*(*cis*) isomer (**4**, R = Ph) (10%) (equation 52). Some similar reactions are summarized in Table 1.

b. Stereospecific synthesis of vinyl nitriles from vinyl halides. Vinyl bromides are converted into nitriles by potassium cyanide in benzene in the presence of Pd(0) catalyst and 18-crown-6. The reaction is highly stereospecific (equation 53)[128].



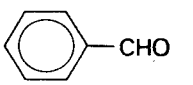
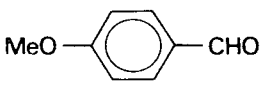
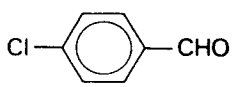
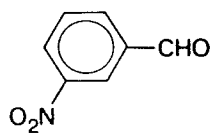
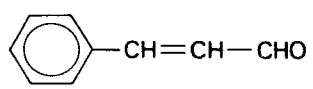
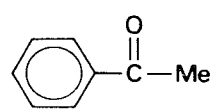
(1) (2) (3)

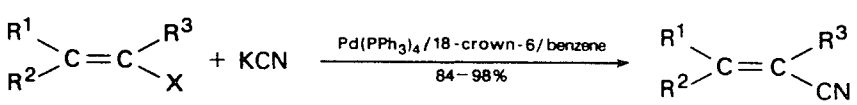


Z (cis) E (trans)

(4) (5) (6) (52)

TABLE 1. 2-Alkenenitriles from aldehydes (and acetophenone) (1) and cyanomethyldiphenylphosphine oxide (2)[127]

Reaction component	Solvent	Yield (%)	Z/E Ratio
	THF DMF	95 90	3:97 10:90
	THF DMF	90 90	5:95 10:90
	THF DMF	93	5:95 10:90
	THF	95	5:95
	THF		10:90
i-PrCHO	THF or DMF	94	17:83
	THF	82	6:94

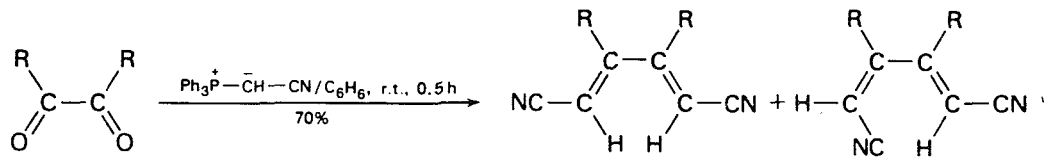


(53)

R^1 = H, Bu
R^2 = H, Me, Bu, Ph
R^3 = H, Ph
X = Br, Cl

2. 3,4-Disubstituted muconononitriles from 1,2-diketones via the Wittig reaction

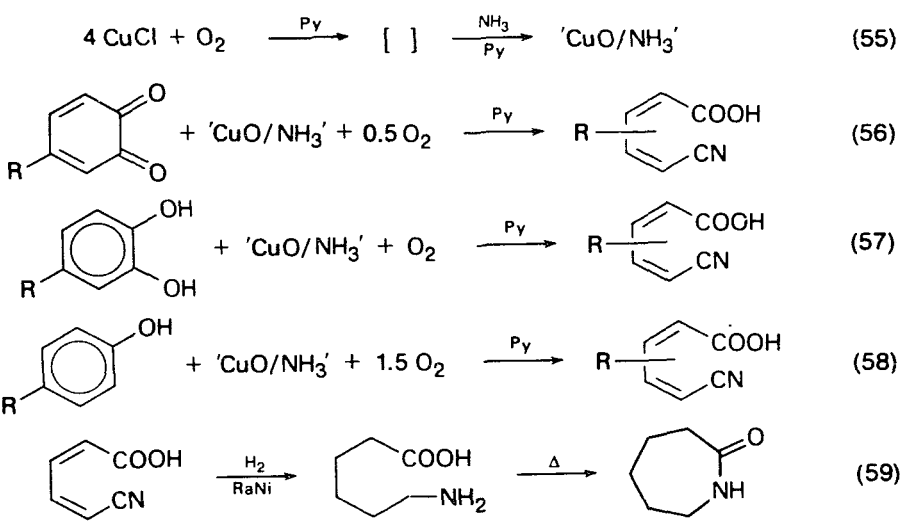
The more reactive 1,2-diketones can be readily transformed into muconic acid derivatives via the Wittig reaction. It has also been found[129] that several, less reactive 1,2-diketones (e.g. 2,3-butanedione or 1,2-cyclohexanedione) can undergo the transformation with an excess of the Wittig reagent. Thus, 2,3-butanedione (**7**, R = Me) reacts with 3 mol. equiv. of cyanomethylenetriphenylphosphorane ($Ph_3P{=}CHCN$) in benzene solution at room temperature to give *E,E*(*trans, trans*)-3,4-dimethylmuconononitrile (**8**, 70%); the *E,Z*(*trans, cis*) isomer (**9**) is not observed in this reaction (equation 54). Similar reaction with 3,4-hexanedione gives a mixture of (*E,E*)- and (*E,Z*)-muconononitriles; however, benzil is not affected by the reagent.

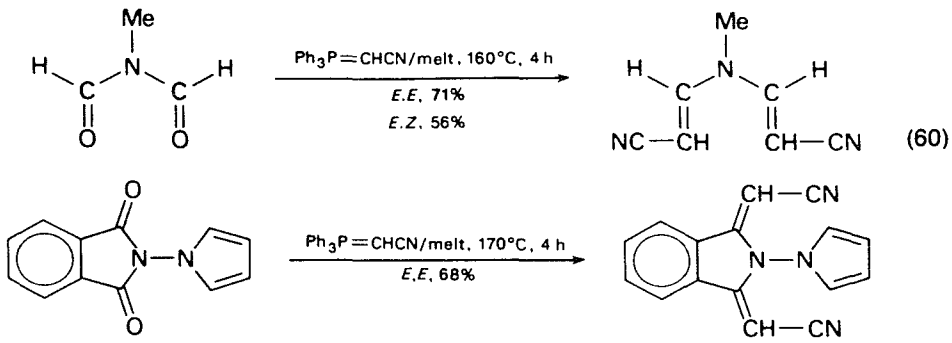


(54)

a. Mononitriles of muconic acid from o-benzoquinones, catechols and phenols. A new copper reagent 'CuO/NH_3' (equation 55) reacts with *o*-benzoquinones, catechols and phenols in the presence of oxygen to afford the corresponding *cis, cis*-mononitriles of muconic acid (equations 56–58, R = t-Bu; equations 57 and 58, R = H; 40–70% yield)[130]. The mononitrile of muconic acid can be converted into the industrially important ε-caprolactam (equation 59). The oxidative cleavage of *o*-benzoquinones and catechols can also be achieved in the absence of oxygen. 4-*t*-Butylcatechol yields a mixture of three isomeric muconic mononitriles. The formation of the nitrile may involve sequential two-electron processes[131].

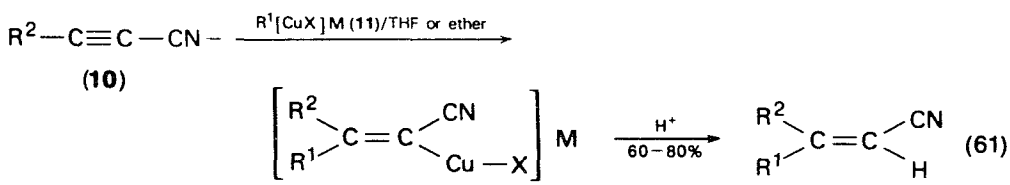
Certain acyclic and cyclic amides react stereospecifically with cyanomethylenetriphenylphosphorane (the Wittig reagent), to give either 2-alkenemononitrile or 2-dialkenedinitrile derivatives (equation 60)[132].





3. *Stereospecific synthesis of 2-alkenenitriles from 2-alkynenitriles*

A recent report[133] has described an efficient, stereospecific synthesis of *cis*-2-alkenenitriles from vinyl cuprates and suitable cyanide sources, e.g. cyanogen chloride, benzenesulphonyl cyanide or *p*-toluenesulphonyl cyanide. A similar, recent study[134] has shown that specifically substituted 2-alkenenitriles are also accessible by adding organocopper(I) compounds to 2-alkynenitriles: this addition proceeds in the *cis* manner. The required 2-alkynenitriles are obtained by *cis* addition of alkyl cuprates to 1-alkynes. Thus, 2-alkynenitriles, $R^2C{\equiv}CCN$ (**10**; R^2 = Me, Ph, etc,), readily react with organocuprates (**11**) in a stereospecific manner, with a formation of the 2-cyanovinyl cuprates (**12**) with groups R^2 and CN in the *cis* position, from which pure *E*(*trans*)- or *Z*(*cis*)-2-alkenenitriles (**13**) can be obtained in excellent yields (equation 61). 2-alkynenitriles (**10**) are useful starting compounds for *E*(*trans*)- as well *Z*(*cis*)-2-Alkenenitriles (**13**) as they readily react in the *cis* manner with various organocuprates; however, the reaction conditions must be carefully controlled[134]. The isomerization of the adduct **12** appears to be strongly dependent on the reaction temperature and the type of cuprate (**11**) used.



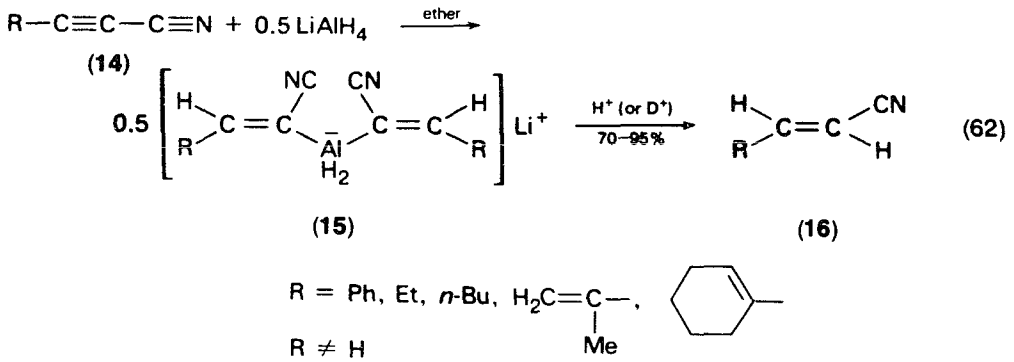
R^1, R^2 = alkyl, 1-alkenyl, Ph

X = Cl, Br, I, R^1

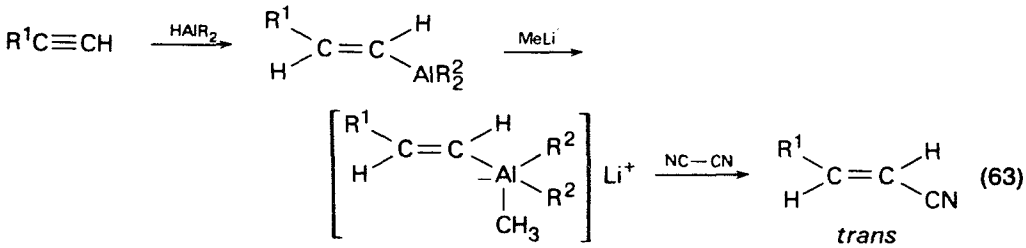
M = Li, MgCl, MgBr

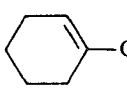
a. Lithium aluminium hydride reagent. In diethyl ether as the medium, lithium aluminium hydride is capable of adding in the *trans* manner to 2-alkynenitriles (**14**), to furnish the α-cyano-substituted vinyl alanates (**15**), from which the desired *trans*-2-alkenenitriles (**16**) are obtained on careful acidification (70–98% yield) (equation 62)[122].

b. Diisobutylaluminium hydride reagent. As shown by Zweifel and coworkers[135], isomerically pure α,β-unsaturated nitriles can be prepared directly from alkynes. Thus, in a hydrocarbon as the solvent, diisobutylaluminium hydride adds *cis* to an acetylenic

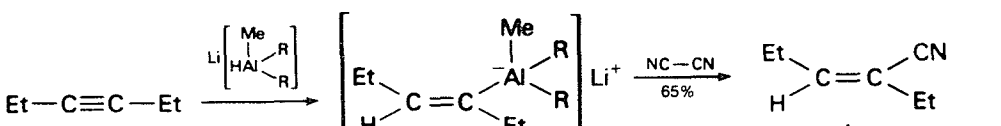


bond; the resultant *trans*-vinylalane may be converted into the *trans*-alanate with methyllithium in ether. Subsequent addition of cyanogen yields *trans*-α,β-unsaturated nitriles (equation 63). In diglyme as the solvent, lithium methyl diisobutylalanate,



Alkyne	Yield (%)
BuC≡CH	87
c-HexC≡CH	78
PhC≡CH	64
EtC≡CEt	76
	62

however, adds *trans* to the acetylenic bond. Subsequent addition of cyanogen affords *cis*-α,β-unsaturated nitriles (equation 64)[135].

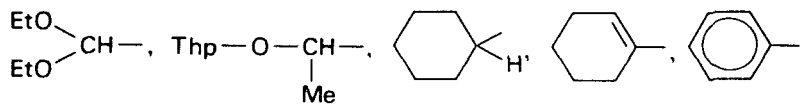


c. Phenyl cyanate reagent. Recently, Murray and Zweifel have reported[136] an improved procedure for the preparation of phenyl cyanate (PhOCN) by conducting the reaction in pentane–ether instead of acetone[137], to suppress the von Braun side-reaction (equation 65). The reagent can be utilized either for synthesis of important

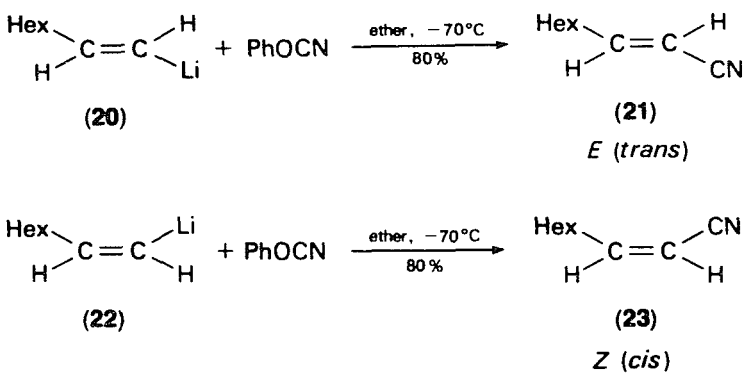
$$PhOH + BrCN + Et_3N \xrightarrow{n\text{-pentane/ether}} PhOC{\equiv}N + Et_3N \cdot HBr \qquad (65)$$

2-alkynenitriles or isomeric α,β-unsaturated nitriles. Treatment of lithium acetylides (**17**) with phenyl cyanate (**18**) at − 70°C produces the corresponding 2-alkynenitriles (**19**) (equation 66)[136]. The reagent has also successfully been

$$\underset{\textbf{(17)}}{RC{\equiv}CLi} + \underset{\textbf{(18)}}{PhOCN} \xrightarrow[70-95\%]{\text{ether, } -70°C} \underset{\textbf{(19)}}{RC{\equiv}CCN} \qquad (66)$$

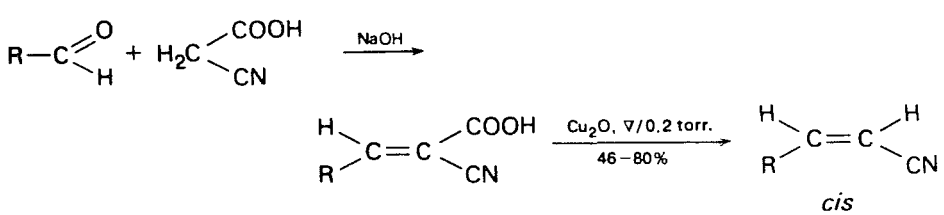
R = *n*-Hex, *t*-Bu, 

applied for cyanation of the *E*(*trans*)- and *Z*(*cis*)-1-lithio-1-octenes. Treatment of the (*E*)-vinyllithium compound (**20**) with phenyl cyanate at − 70°C affords an 80% (isolated) yield of isomerically pure (*E*)-2-nonenenitrile (**21**). Cyanation of the (*Z*) isomer (**22**) to the (*Z*) isomer (**23**) can be achieved by adding cold vinyllithium reagent (**22**) to phenyl cyanate at −70°C. This slight modification gives the (*Z*)-alkenenitrile (**23**) in 80% yield (equation 67)[136]. An alternative method for the preparation of phenyl cyanate has been reported[137].



(67)

d. Decarboxylation of α-cyanoacrylic acids. This method provides a convenient access to *cis*-α,β-unsaturated nitriles (equation 68)[138]. These are obtained thermally using copper(I) oxide as the catalyst and removing the *cis* isomer as fast as it is formed.

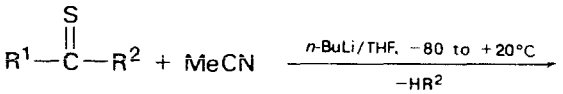


(68)

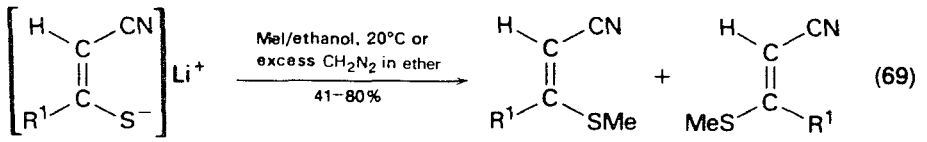
R = Ph, 2-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$

e. Cis-*and* trans-*3-methylthioacrylonitriles*. Thiocarboxylic *O*-esters (**24**; R^1 = Ph, R^2 = ester) and dithio- and trithio-carbonic esters undergo condensation with acetonitrile

in THF at −80°C in the presence of butyllithium to give the lithium salt (**25**). This can be methylated to give (*Z*) and (*E*) isomers of 3-substituted 3-methylthioacrylonitriles (**26**) in various ratios (separation of isomers by fractional distillation) (equation 69)[139].



(**24**)



(**25**) (*Z*)-(**26**) (*E*)-(**26**)

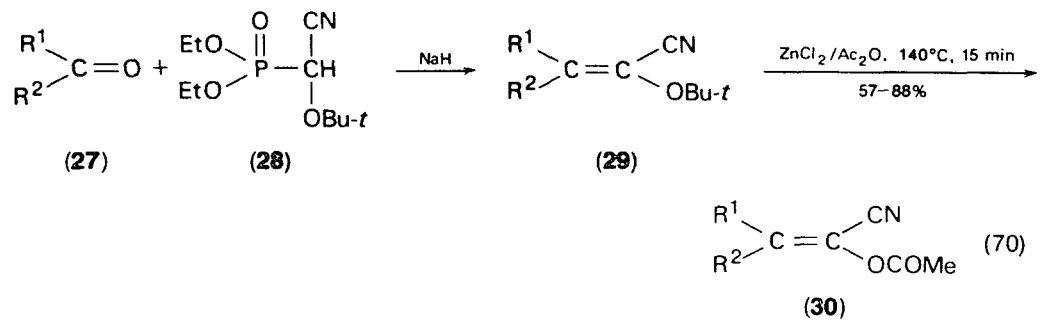
f. Chiral isocyanate reagent. A chiral isocyanate reagent, (*R*)-(−)-1-naphthylethyl isocyanate, is useful for chromatographic separation of diastereomers; the reagent has been used to resolve 5-cyano-2-pentene[140] and also for the preparation of the chiral 1,3-dialkylallenates and the synthesis of the chiral pheromone of the male bean-weevil[141].

E. Additional Syntheses of Unsaturated Nitriles

1. Conversion of carbonyl compounds

The direct conversion of carbonyl compounds into 2-alkenenitriles is of great interest, as the latter compounds serve as versatile intermediates in organic synthesis[1,142,143]. Several methods give good to excellent yields of nitriles from aromatic carbonyl compounds[124,127,144–149], but only a few methods are efficient with aliphatic aldehydes or ketones[124,145,147–149].

a. Carbon homologation of carbonyl compounds to unsaturated nitriles. The Wittig–Horner reaction of carbonyl compounds (**27**) using diethyl *t*-butoxycyanomethanephosphonate (**28**) gives α-*t*-butoxyacrylonitriles (**29**). Cleavage of the *t*-butyl ether bond in **29** by use of zinc chloride in refluxing acetic anhydride affords α-acetoxyacrylonitriles (**30**) in high yield (equation 70)[150]. The new homologation sequence is reasonably efficient for an array of structually diverse aldehydes and



(**27**) (**28**) (**29**) (**30**)

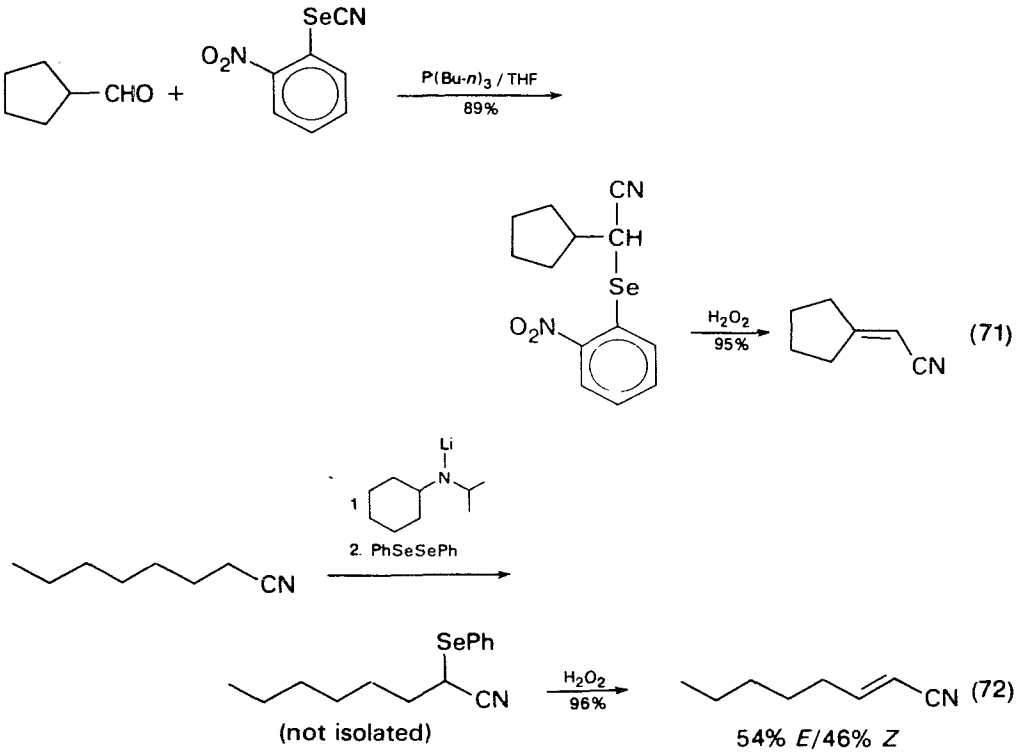
R^1, R^2 = $Ph(CH_2)_2$—, cholest-4-en-8-one or 5α-androstane-3,17-dione skeletons

ketones. The presence of carbon–carbon double bonds, aromatic rings, certain ketonic functions or another carboxylate group do not interfere with the reaction. The alkaline solvolysis of **30** can give acids, esters or amides[150,151].

α-Alkoxyacrylonitriles may also be obtained from metalated α-(trimethylsilyl) derivatives [e.g. $Me_3SiCH(R)CN$] with carbonyl compounds[152].

b. Unsaturated nitriles via α-selenonitrile intermediates. *o*-Nitrophenyl selenocyanate effects the facile cyanoselenylation of aldehydes. Subsequent oxidation (H_2O_2) of the intermediate α-selenonitrile affords the α,β-unsaturated nitrile in excellent yield (equation 71)[153].

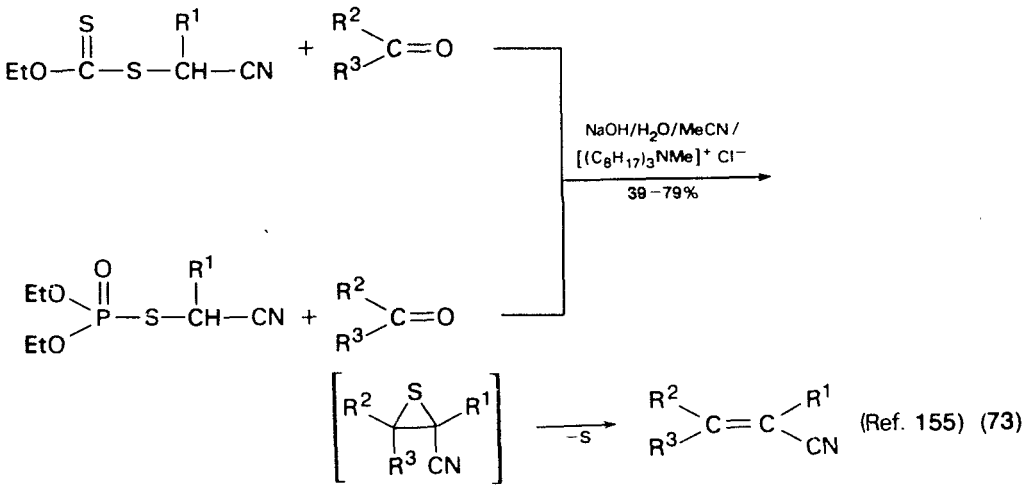
The conversion (96%) of the saturated nitrile into the α,β-unsaturated one involves similar oxidation of the intermediate α-phenylselenonitrile with hydrogen peroxide (equation 72)[154].



c. Additional methods. Additional, new methods for the synthesis of α-alkenenitriles from ketones or aldehydes involve application of either *O*-ethyl *S*-cyanomethyl dithiocarbonate or *S*-cyanomethyl diethyl phosphorothionate[155], the enolate from acetonitrile plus a carbonyl compound (two-carbon chain-elongation)[147,156], the Wittig reagent[147,157], oxalyl chloride[158], iodine–copper(I) cyanide[159], cyanomethylcopper(II)[160], flow pyrolysis of *N*,1-dichloroperfluoro-1,2-dihydro-2-naphthylideneamine[161], a Schiff base plus a phase-transfer catalyst[162], diethyl phosphonate cyanohydrin[163], the sodium salt of a 1-alkyl-1-cyanoacetate plus a 1-bromo-1-nitroalkane[164], potassium cyanide plus an aryl isothiocyanate[165], degradation of hydrazones[166], electrochemical reduction of dinitriles[167] and oxidation of α,β-diaminoacrylonitrile derivatives (to give di-*N*-substituted diaminomaleonitriles)[168]. The synthesis and reactions of diiminosuccinonitrile (DISN) and diaminomaleonitrile

(DAMN) have been reported[169,170]. Synthesis with the organomagnesium derivative of phenylacetonitrile leads to the formation of both the unsaturated nitrile and the hydroxynitrile (i.e. cyanohydrin)[171].

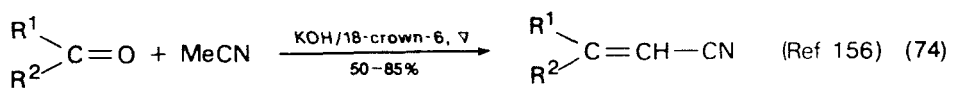
d. Special reactions. These include the preparation of acetylenenitriles[172], mixed acetylene–alkene-nitriles[173], 1-cyclobutenecarbonitrile (via dehydrocyanation of the dinitrile)[174], conjugated nitriles[175]; also unsaturated nitriles via base-catalysed elimination[176], acid-catalysed elimination[177], thermal degradation[178] and thermal rearrangement[179,180]; most of these transformations are shown below in equations (73)–(97).



(Ref. 155) (73)

R^1 = H; R^2 = R^3 = $-(CH_2)_n-$, n = 4, 5, 6

R^1 = Me; R^2 = R^3 = $-(CH_2)_n-$, n = 4, 5, 6

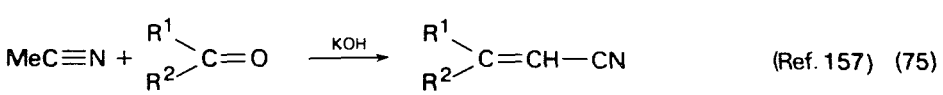


(Ref 156) (74)

R^1 = H, Me

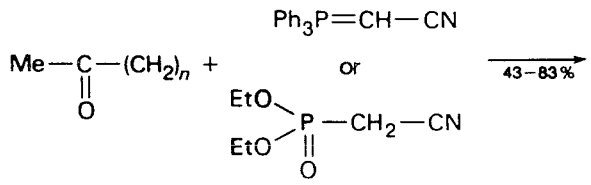
R^2 = Ph, Me–C6H4–, MeO–C6H4–, Cl–C6H4–, 3,4-(O2CH2)C6H3–

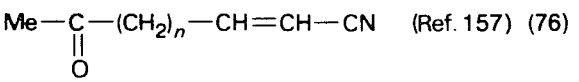
R^1R^2 = $-(CH_2)_5-$

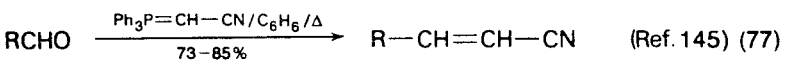


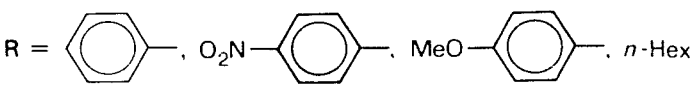
(Ref. 157) (75)

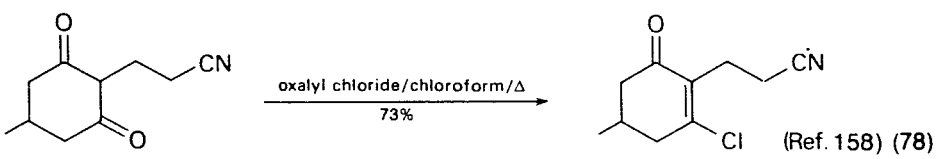
R^1R^2CO = cyclohexanones, cycloheptanone, cyclohexadecanone, diethyl ketone, etc.,

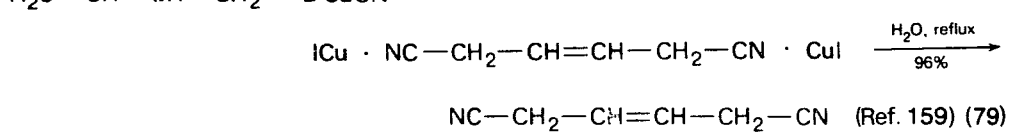

Ph3P=CH—CN
or
43–83%
EtO
EtO
P—CH2—CN
n = 3,4

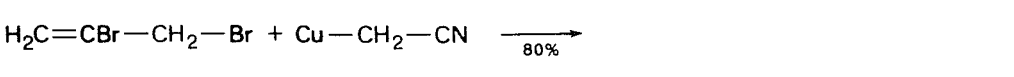

(Ref. 157) (76)

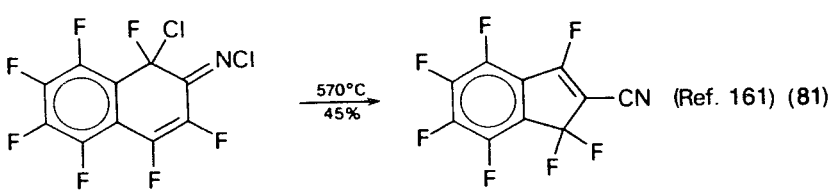

RCHO
Ph3P=CH—CN/C6H6/Δ
73–85%
R—CH=CH—CN
(Ref. 145) (77)

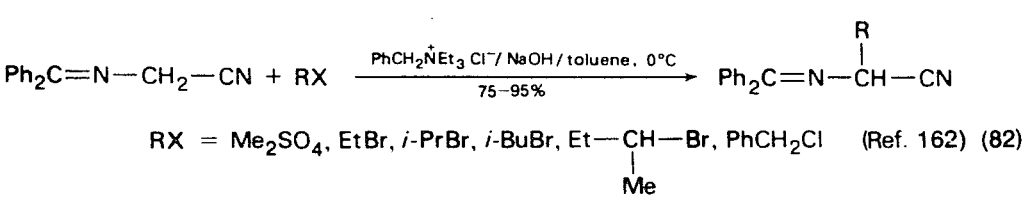

R =
O2N
MeO
n-Hex

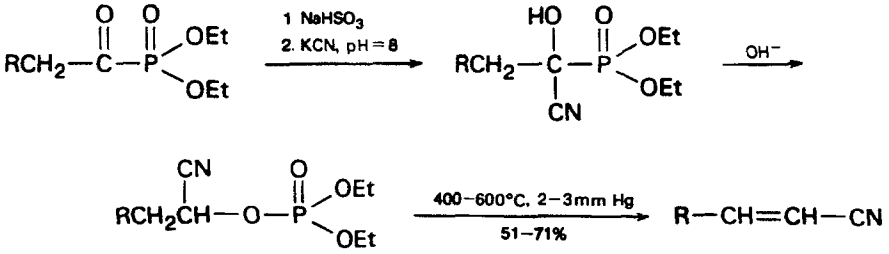

CN
O
oxalyl chloride/chloroform/Δ
73%
Cl
(Ref. 158) (78)


H2C=CH—CH=CH2 + 2 CuCN
I2/heptane, 85°C
ICu · NC—CH2—CH=CH—CH2—CN · CuI
H2O, reflux
96%
NC—CH2—CH=CH—CH2—CN
(Ref. 159) (79)


H2C=CBr—CH2—Br + Cu—CH2—CN
80%
H2C=CBr—CH2—CH2—CN
(Ref. 160) (80)

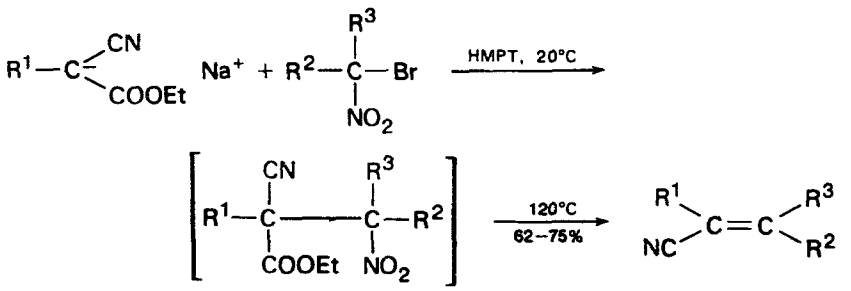

F
F
Cl
NCl
570°C
45%
CN
(Ref. 161) (81)


Ph2C=N—CH2—CN + RX
PhCH2N̂Et3 Cl⁻/ NaOH/ toluene, 0°C
75–95%
Ph2C=N—CH—CN
R
RX = Me2SO4, EtBr, i-PrBr, i-BuBr, Et—CH—Br, PhCH2Cl
Me
(Ref. 162) (82)



(Ref. 163) (83)

R = Me, Et, *n*-Bu, *n*-C_8H_{17}, *n*-$C_{10}H_{21}$

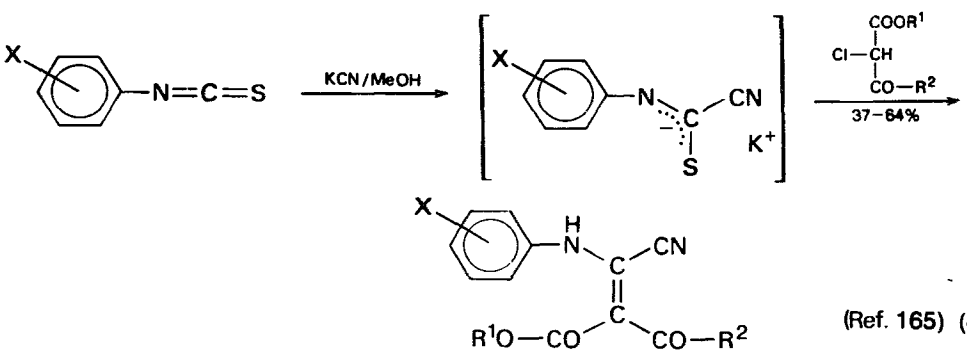


(Ref. 164) (84)

R^1 = *i*-Pr, *n*-Bu, *n*-C_8H_{17}, $PhCH_2$

R^2 = Me

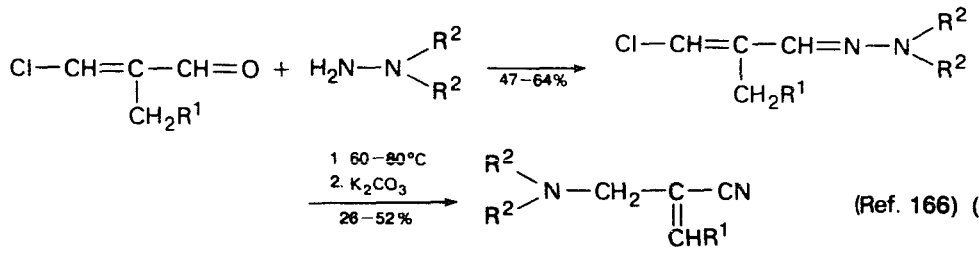
R^3 = Me, Et



(Ref. 165) (85)

R^1 = Et, R^2 = Me

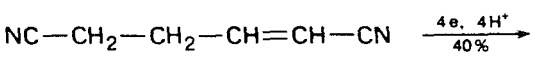
R^1 = Me, R^2 = MeO



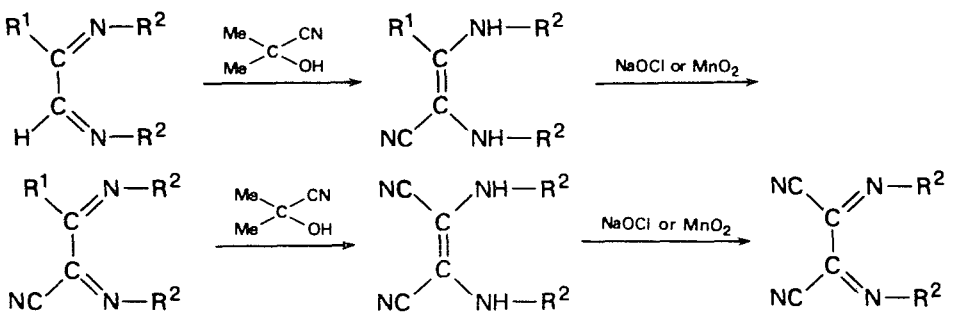
(Ref. 166) (86)

R^1 = H, Me

R^2 = Me, Et

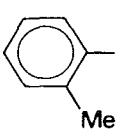


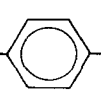
(Ref. 167) (87)

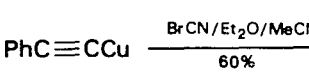


(Ref. 168) (88)

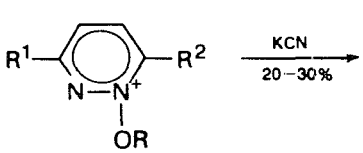
R^1 = H, R^2 = *t*-Bu

R^1 = H, R^2 = 

R^1 = O_2N—  , R^2 = *t*-Bu

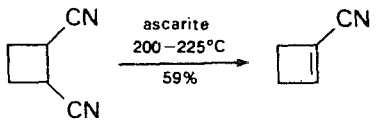


(Ref. 172) (89)

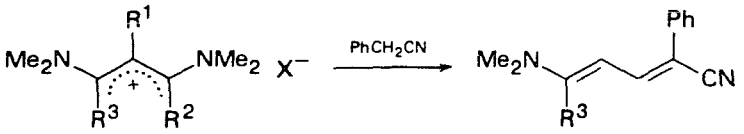


(Ref. 173) (90)

R = Me, PhCO



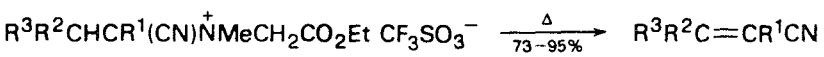
(Ref. 174) (91)



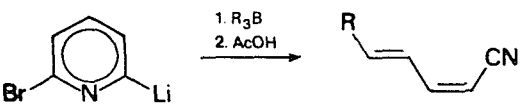
(Ref. 175) (92)

R^3 = CO_2R, COPh, $CH(OMe)_2$

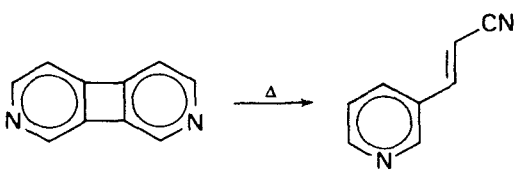
X^- = ClO_4^-



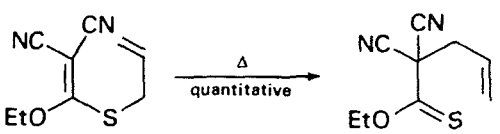
(Ref. 176) (93)



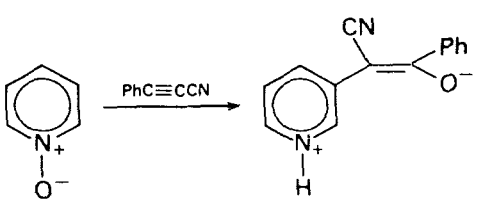
(Ref. 177) (94)



(Ref. 178) (95)



(Ref. 179) (96)



(Ref. 180) (97)

F. Synthesis of Aminonitriles, Enaminonitriles and Related Compounds

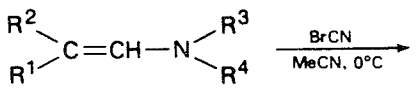
The synthesis, structure and reactions of enamines and aminonitriles have been surveyed[181–184]. A comprehensive account of enaminonitriles and *O*-aminonitriles has appeared[185].

1. α-Cyanoenamines

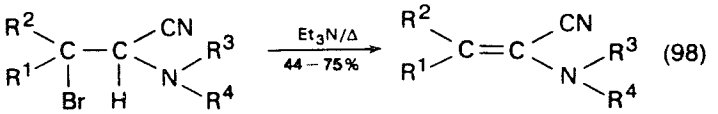
2-Amino-2-alkenenitriles (α-cyanoenamines) have in recent years received considerable attention as starting materials for the synthesis of a variety of compounds.

Tertiary α-cyanoenamines have been synthesized from 2-alkenals[186], α-chloroenamines[187], α-halo aldehydes[188,189], carboxyamides[190] and from the addition of cyanogen bromide to enamines[189]. Secondary α-cyanoenamines have hitherto been exclusively obtained from α-chloroaldimines and potassium cyanide in methanol[191a] The synthetic utility of α-cyanoenamines has been demonstrated by their conversion into α-diones[187], and by their intermediacy in the transformation of aldehydes into amides[191b]. The reaction of tertiary α-cyanoenamines with organolithium reagents provides possibilities (depending on the organometallic reagent used) for, e.g. selective deprotonations, additions to the nitrile group, or Michael additions[187–189], thus allowing carbon-chain elongations with the aid of electrophiles. It has been reported that the nitrogenous groups in tertiary α-cyanoenamines play a determinative role in these reactions[189]. Conversely, α-aminonitriles have been readily converted via a metalation–alkylation step (lithium diisopropylamide + RCH_2I, Br or Cl) either into carbonyl compounds (70–90% yield) or via dehydrocyanation (KOH + refluxing toluene) into enamines or dieneamines (48–93% yield)[192].

a. Tertiary α-cyanoenamines via cyanation of enamines with cyanogen bromide. A new synthesis of an α-cyanoenamine, **33**, involves as the first step reaction of an enamine (e.g. **31**) with cyanogen bromide to afford **32**, which on treatment with triethylamine eliminates hydrogen bromide to give **33** (equation 98)[189]. Tertiary α-cyanoenamines, e.g. **33** ($R^3 = R^4 \neq H$) are converted into *vic*-diketones on treatment with organolithium compounds[189].



(31)

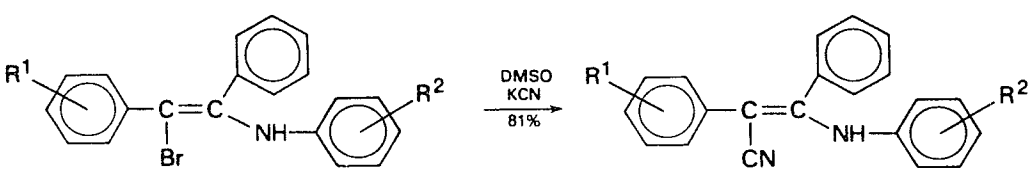


(98)

(32) **(33)**

R^1	R^2	R^3	R^4
Me	Me	Me	Me
Me	Me	$-(CH_2)_4-$	

b. Secondary α-cyanoenamines by nucleophilic substitution of halogen-substituted enamines. α,β-Disubstituted cinnamonitriles (**35**) can be prepared by treatment of bromoenamines (**34**) with potassium cyanide in dimethyl sulphoxide (equation 99)[193].

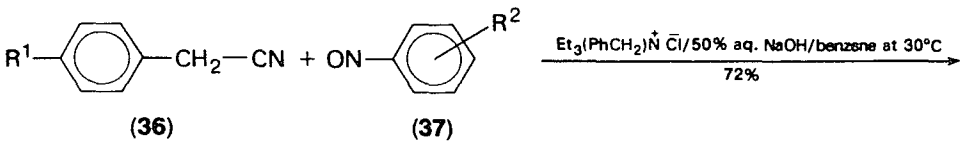


(cis + trans)

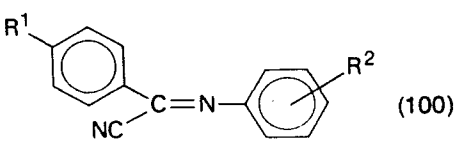
(34) **(35)**

(99)

Compounds of type **35** can also be prepared by using phase-transfer catalysis[194]. Thus, **39** has been conveniently obtained from an excess (2:1) of 4-substituted phenylacetonitriles **36** with a 3- or 4-substituted nitrosobenzene (**37**) as shown in equation (101). When equimolar amounts of **36** and **37** were used, the intermediate 2-phenyliminophenylacetonitrile (the Schiff base) (**38**, $R^1 = R^2 = H$) is isolated in 72% yield (equation 100). The electronic effect of substituents and of the reactant ratio on reactions of 4-substituted acetonitriles (**36**) with nitrosobenzenes (**37**) has been observed[194].

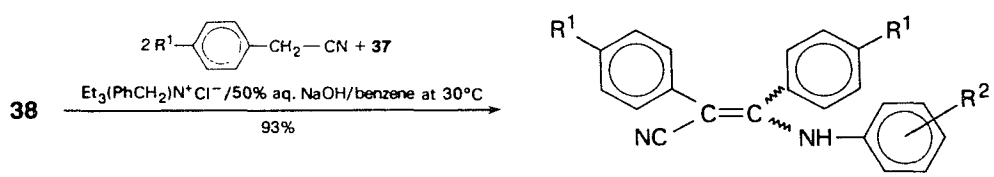


(**36**) (**37**)



(100)

(**38**)

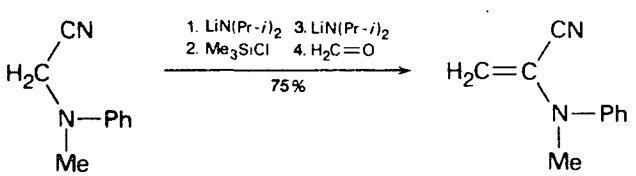


(**39**)

$R^1 = R^2 = H$

$R^1 = H$, $R^2 = 4\text{-Me}$ (101)

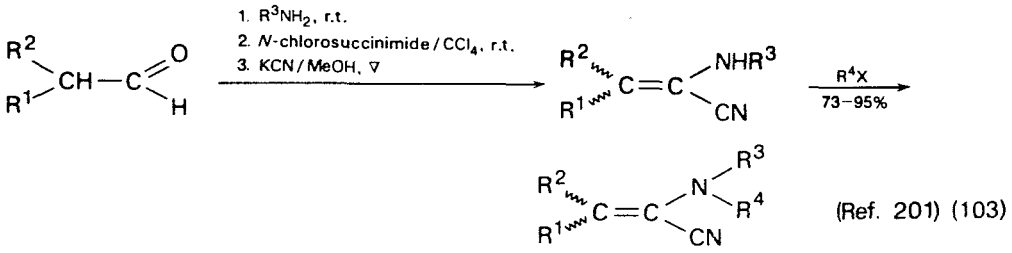
c. Cyanoenamines via deprotonation of α-aminonitriles. Deprotonation of α-aminonitriles, derived from aromatic aldehydes, with potassium amide in liquid ammonia[195], sodium hydride in *N,N*-dimethylformamide[196] or by phase-transfer catalysis[197], has been utilized synthetically[198,199]. Recently[192,200], the deprotonation of α-aminonitriles has been achieved with lithium diisopropylamide [$LiN(i\text{-}Pr)_2$] in tetrahydrofuran at −78°C. Thus, conversion of **40** into **41** [2-(*N*-methylanilino)acrylonitrile has been achieved via a sequence of reactions involving deprotonation, silylation and treatment with formaldehyde (equation 102). The latter has been utilized in the synthesis of compounds of the type $R^1CH_2COR^2$ [200].



(**40**) (**41**) (102)

2. *Additional preparations of aminonitriles*

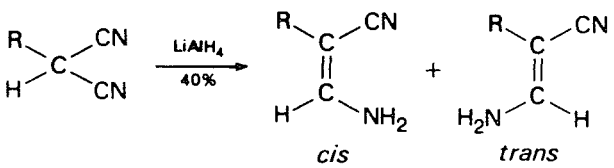
The syntheses of the following α-cyanoenamines, α-aminonitriles and related compounds have been reported: tertiary α-cyanoenamines having bulky substituents[201], enaminonitriles[202], α,β-unsaturated 3-amino-2-fluoronitriles[203], 2-cyanoenamines via transamination[204], α-aminonitriles via reaction of trimethylsilyl cyanide with a Schiff base or oxime[205], aryldicyandiamides[206], conjugated enamino nitriles[207], 3-cyanoazomethine imines[208,209], *N*-cyanoguanidine[210], 2-iminonitriles (imidoyl cyanides)[211], and also cyanoenamines via deprotonation of *trans*-3-(1-pyrrolidinyl)acrylonitrile with lithium diisopropylamide (LDA) at −105°C, followed by an electrophile E[212]. All these and other useful preparations are depicted in equations (103)–(122)[201–221].



(Ref. 201) (103)

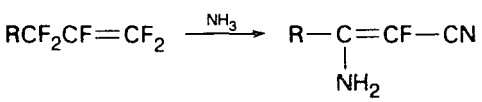
$R^1 = R^2 = Me$, $R^3 = t\text{-Bu}$

$R^4X = R^4OSO_2F$, $R^4OSO_2OR^4$; $Et_3O^+ BF_4^-$

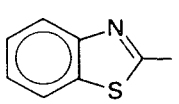


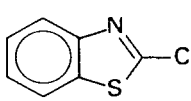
(Ref. 202) (104)

R = H, Me

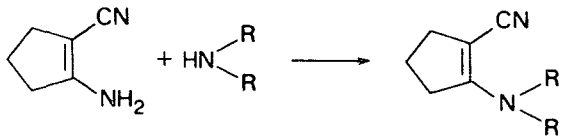


(Ref. 203) (105)

R =  , 93% yield

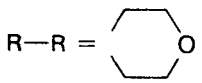
R =  , 77% yield

R = $HCF_2—CF_2—CF_2—$, 48% yield

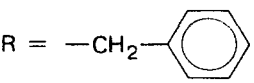


(Ref. 204) (106)

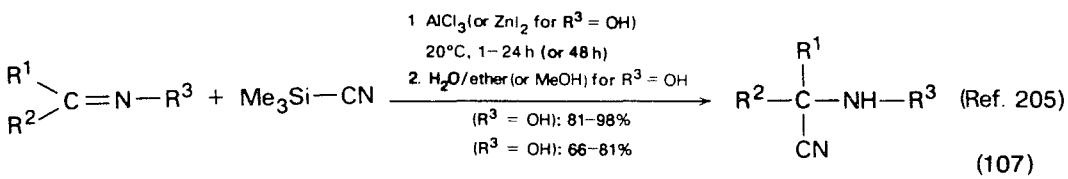
R = Me , 79% yield



, 44% yield



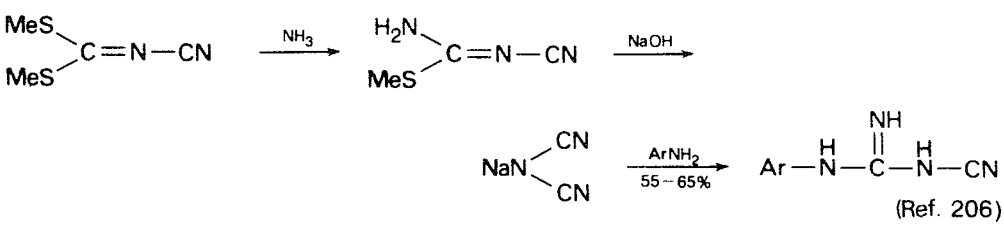
, 62% yield



(Ref. 205)

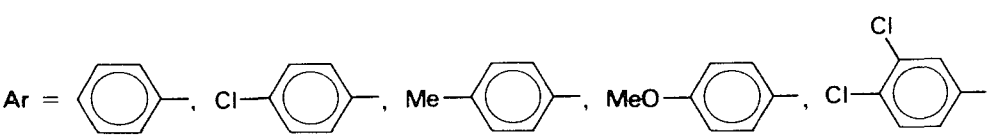
(107)

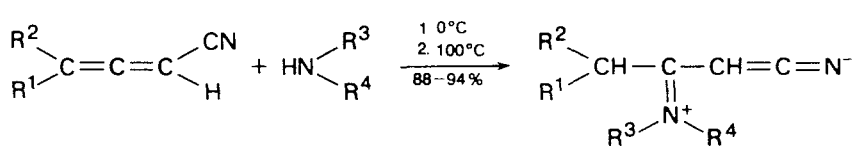
R^1, R^2, R^3 = H, Me, Pr, Ph, OH



(Ref. 206)

(108)

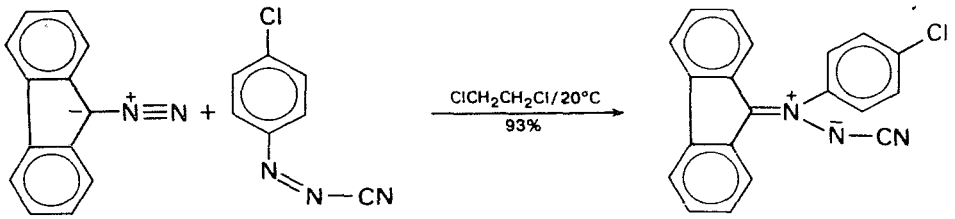




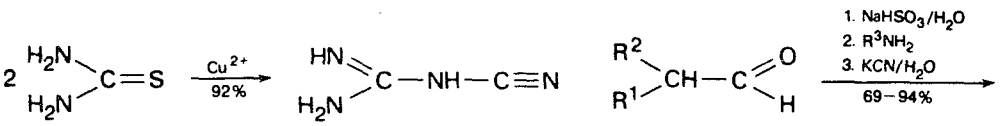
(Ref. 207)

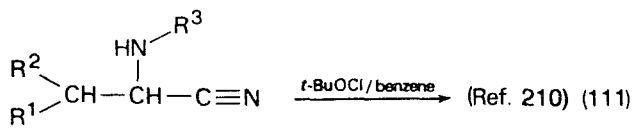
(109)

R^1, R^2, R^3, R^4 = H, D, Me, Et, Pr, Bu

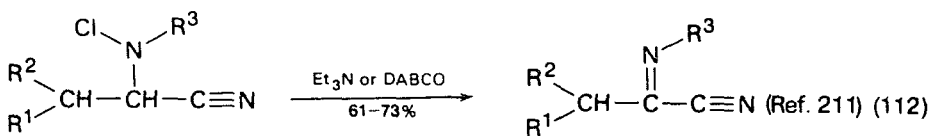


(Refs. 208 and 209) (110)



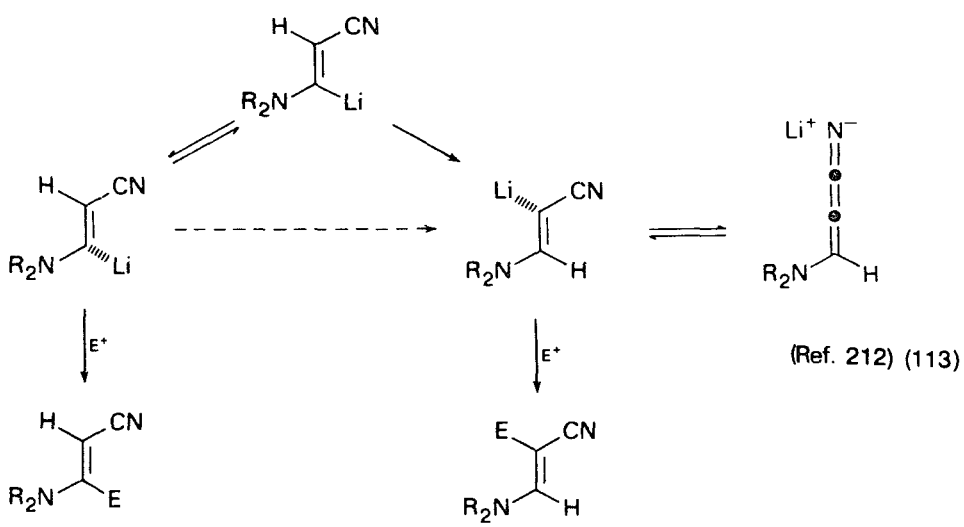


(Ref. 210) (111)

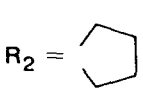


(Ref. 211) (112)

R^1, R^2, R^3 = H, Me, Pr

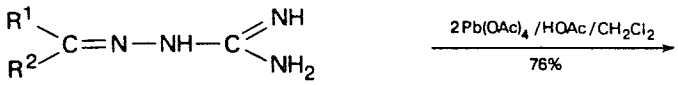


(Ref. 212) (113)

R_2 = 

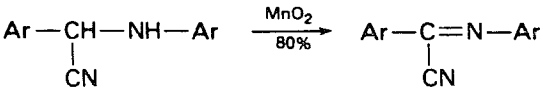
E = D, Me, Et, PhCHOH

Retention of stereochemistry is observed

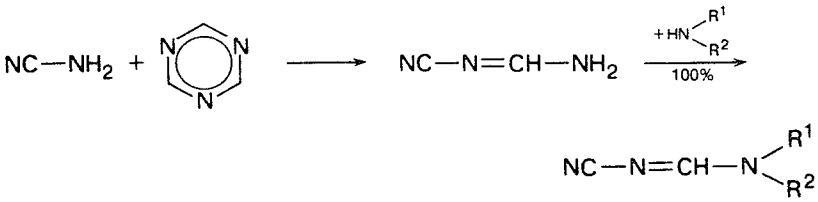


(Ref. 213) (114)

$R^1 = Ph, R^2 = Me$

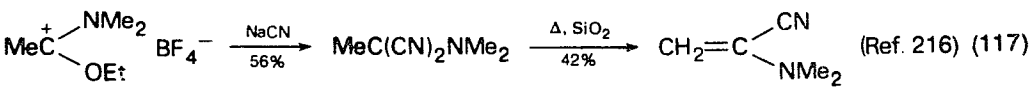


(Ref. 214) (115)

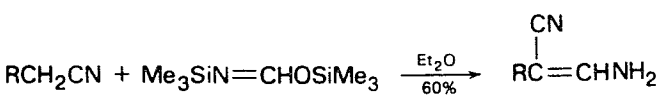


(Ref. 215) (116)

$R^1 = R^2 = Me$

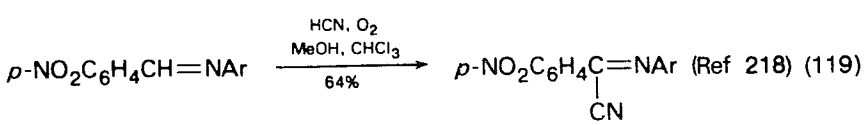


(Ref. 216) (117)



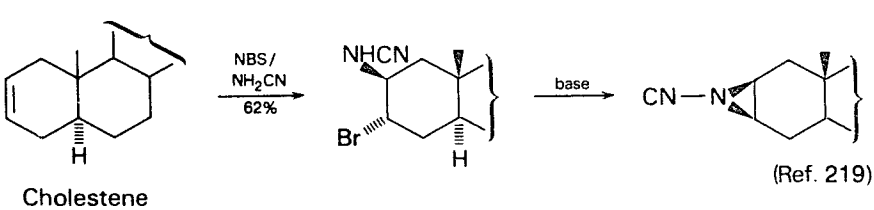
(Ref. 217) (118)

$R = CN$



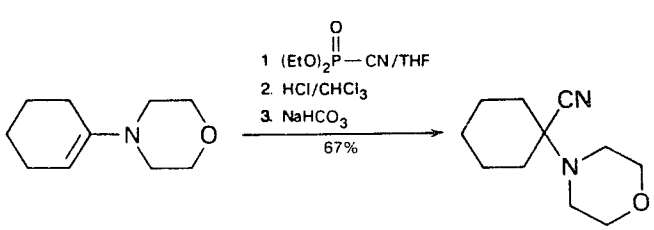
(Ref 218) (119)

$Ar = Ph$

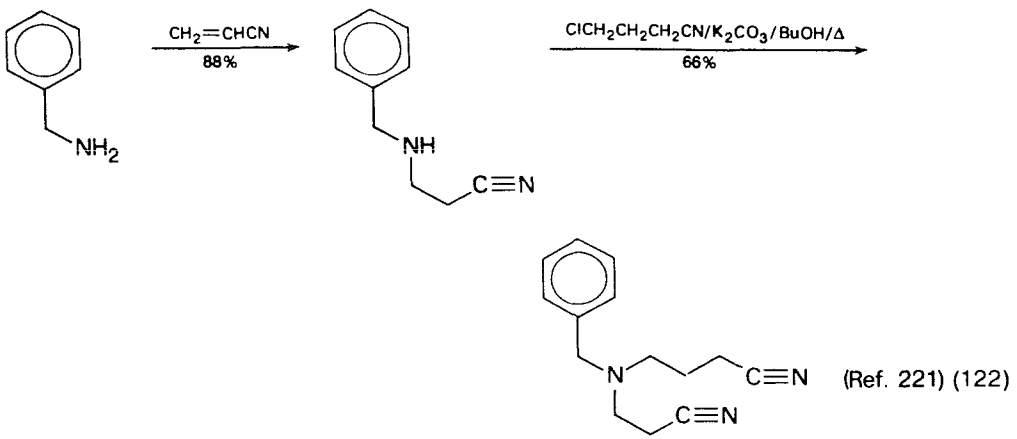


Cholestene

(Ref. 219) (120)



(Ref. 220) (121)



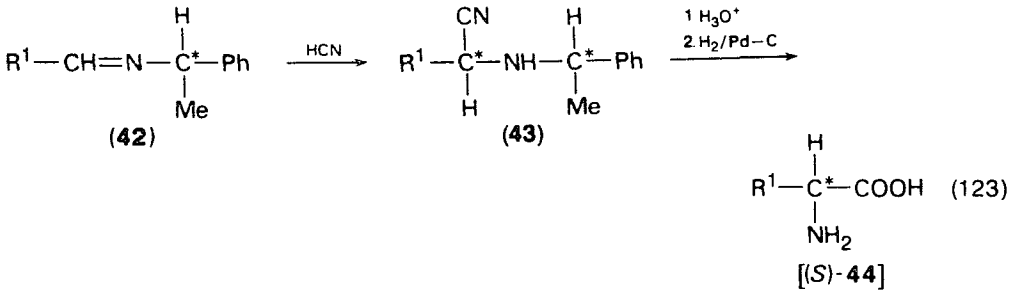
(Ref. 221) (122)

G. Asymmetric Synthesis of Amino Acids via Aminonitriles

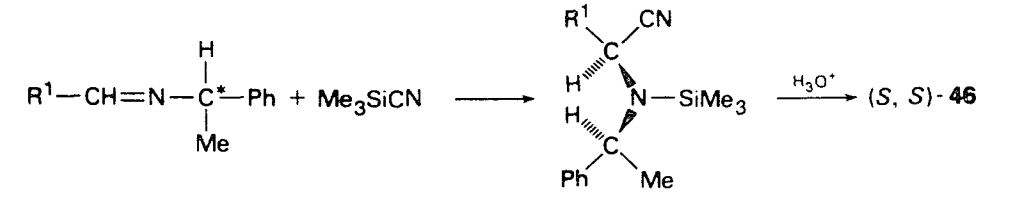
The application of asymmetric synthesis to the preparation of chiral organic molecules has been discussed in a book[222] and several recent reviews[223–228].

1. The Strecker synthesis

Chiral amines and amino acids have been prepared by addition of nucleophiles to imines. The most studied case is the Strecker synthesis in which cyanide is added to a chiral imine, such as **42**, selectively giving one diastereoisomer of the aminonitrile **43**. Nitrile hydrolysis, and reductive cleavage of the benzyl group, complete the synthesis of the amino acids (*S*)-**44** (equation 123)[222,229]. An early claim[230] that (*S*)-**44** having a 98% enantiomeric purity (i.e. an enantiomeric excess[225]) was obtainable in this way has been found to be incorrect[231,232]. Improved results [61–75% enantiomeric purity of (*S,S*)-**46**] are obtained in Lewis acid, e.g. zinc chloride-catalysed condensation of the imine (*S*)-**42** with trimethylsilyl cyanide, to give **45**, acid hydrolysis of which yields the aminonitrile (*S,S*)-**46** (equation 124)[233].

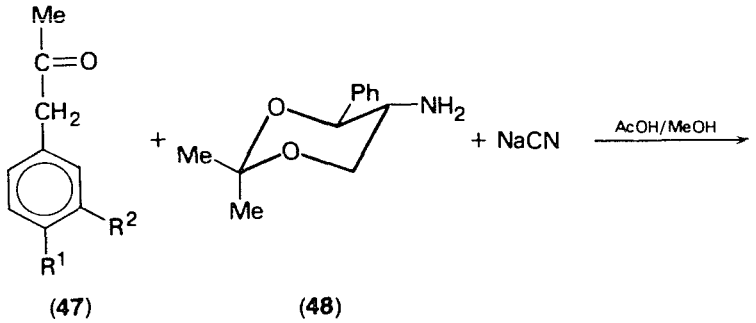


(42) (43) [(*S*)-**44**] (123)

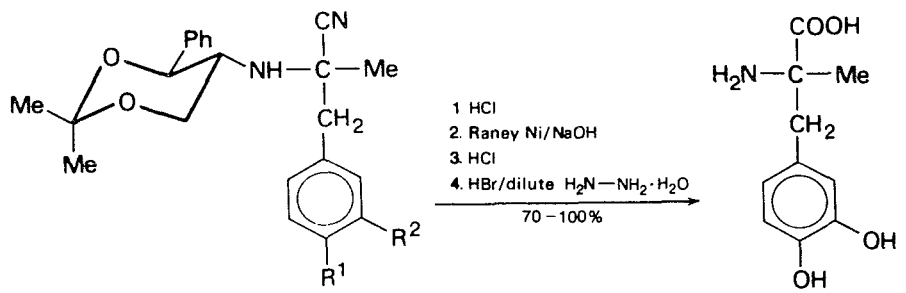


(42) (45) (124)

a. (S)- or (R)-α-Methylamino acids via external asymmetric Strecker synthesis. 1-aryl-2-propanone (**47**) with (4*S*:5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (chiral reagent **48**) and NaCN gives the chiral aminonitrile **49**, and through (*i*) hydrolysis of the nitrile group in (**49**), (*ii*) oxidative C—N cleavage and (*iii*) ether cleavage (HBr at 140°C), affords the chiral α-amino acid **50** (equation 125)[234]. A Strecker asym-



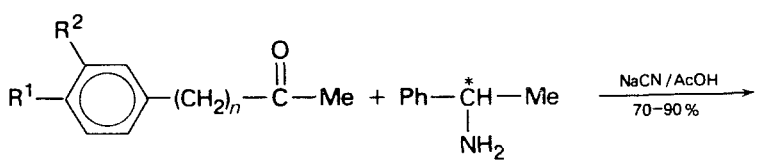
(**47**) (**48**)



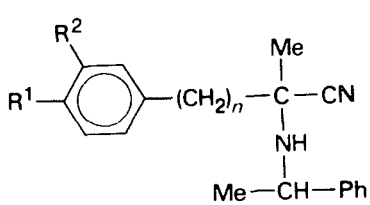
(125)

(**49**) (**50**)

R^1	R^2
OMe	OMe
OMe	H
H	H



(**51**) [(*S*)-(−)-**52**]



(126)

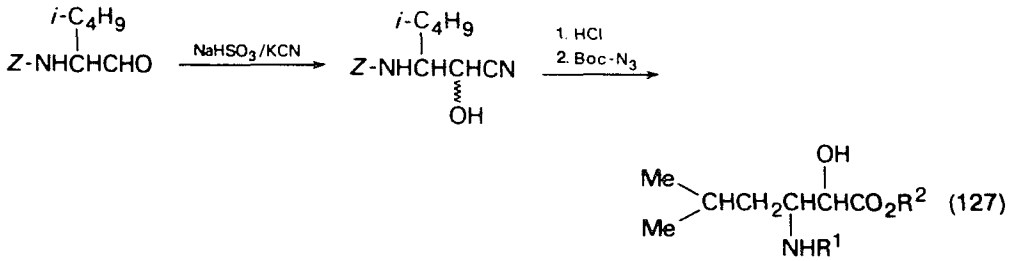
[(*R*)- or (*S*)-**53**]

R^1, R^2 = H, OMe

n = 1, 2

metric synthesis with (*S*)-(−)-1-phenylethylamine (**52**) as the chiral reagent and an arylalkyl methyl ketone (**51**), to give the chiral α-methyl-α-aminonitrile (**53**) in high yield, has been described[229] (equation 126), and other, analogous syntheses have been discussed[234,235]. Furthermore, interest in asymmetric induction has resulted in several efficient procedures for the synthesis of chiral 2-hydroxynitriles[236].

b. (2S,3R)-3-Amino acids via a cyanohydrin reaction. Recently Rich and coworkers (equation 127)[237] have described the synthesis of (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid and its derivatives. The first step is a conversion of the aldehyde into the cyanohydrin, hydrolysis of which gives the hydroxyamino acids as a mixture of diastereoisomers in 85–95% yield (separated by column chromatography over silica gel).



(127)

$R^1 = R^2 = H$ (2*S*, 3*R*)

H. Synthesis of Saturated Nitriles

Many procedures used for the preparation of unsaturated nitriles may also be applied for the synthesis of saturated nitriles. However, methods characteristic for the preparation of certain types of saturated nitriles are: a substitution reaction of alkyl or acyl halides with tetraethylammonium cyanide[238], a substitution reaction of alkyl halides with potassium cyanide and 18-crown-6[239], hydrocyanation of methacrylonitrile in the presence of 18-crown-6[239], reaction of acrylonitrile with cuprous trialkylmethylborate[240], hydrocyanation of an unsaturated steroid in the presence of 18-crown-6[241], the Friedel–Crafts reaction[242], hydrogenation of an unsaturated nitrile[243], decomposition of an unsaturated hydrazone[244] (equations 128–135). Dinitriles can be prepared from dicarboxylic acids by an exchange reaction[245], and via an ethyl cyanoacetate reagent[246] (equations 136 and 137). Syntheses of spirocyanocyclopropane, dispirodicyanocyclohexane and tetracyanocyclopropane are given in equations (138)–(140)[247–250].

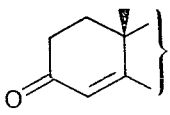
$$Et_4N^+ CN^- + RX \xrightarrow[50-85\%]{CH_2Cl_2/-15 \text{ to } 50^\circ C} RCN + Et_4N^+ X^- \quad \text{(Ref. 238)} \quad (128)$$

R = primary, secondary or tertiary group

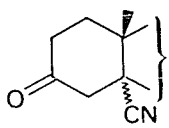
$$ClCH_2CH_2Cl \xrightarrow[97\%]{KCN/MeCN/18\text{-crown-}6} NCCH_2CH_2CN \quad \text{(Ref. 239)} \quad (129)$$

$$CH_2{=}C(CH_3){-}CN \xrightarrow[92\%]{KCN/MeCN/18\text{-crown-}6} CH_3CH(CN)CH_2CN \quad \text{(Ref. 239)} \quad (130)$$

$$[R_3BCH_3]Cu + CH_2{=}CH{-}CN \longrightarrow \xrightarrow[88-93\%]{H_2O} RCH_2CH_2CN \quad \text{(Ref. 240) (131)}$$

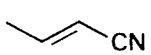


$$\xrightarrow[83-86\%]{Me_2C(OH)CN/KCN/18\text{-crown-}6/C_6H_6}$$

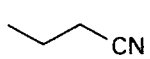


(Ref. 241) (132)

$$PhH + Cl(CH_2)_4CN \xrightarrow[98\%]{AlCl_3} Ph(CH_2)_4CN \quad \text{(Ref. 242) (133)}$$



$$\xrightarrow[100\%]{H_2 / Ni\ boride}$$



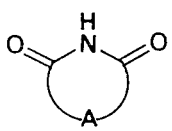
(Ref. 243) (134)

$$R^1R^2CHCH{=}NNMe_2 \xrightarrow[93\%]{1.\ Et_2NLi/PhH/HMPT,\ 2.\ R^3Br} R^1R^2R^3CCN \quad \text{(Ref 244) (135)}$$

$$R^1 = R^2 = R^3 = Et$$

$$HOOC{-}(CH_2)_n{-}COOH + NC{-}A{-}CN \xrightarrow[n = 10,\ 97\%]{H_3PO_4/150-300^\circ C,\ n = 7,\ 87\%}$$

$$NC{-}(CH_2)_n{-}CN +$$



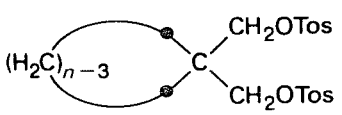
(Ref. 245) (136)

$$A = -(CH_2)_2-\underset{\displaystyle Me}{\underset{|}{CH}}-,\ -CH_2-CH_2-,\ -CH_2-CH_2-CH_2$$

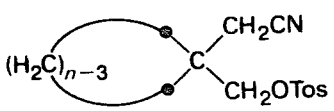
$$R^1{-}CH{=}O + H_2C\begin{matrix}COOR^2\\CN\end{matrix} + KCN \xrightarrow{DMSO} R^1{-}\underset{\displaystyle NC}{\underset{|}{CH}}{-}\overset{-}{C}\begin{matrix}COOR^2\\CN\end{matrix}\ K^+ \xrightarrow{R^3X}$$

$$R^1{-}\underset{\displaystyle CN}{\underset{|}{CH}}{-}\underset{\displaystyle CN}{\underset{|}{C}}\begin{matrix}COOR^2\\R^3\end{matrix} \xrightarrow[62\%]{H_2O,\ 145^\circ C} R^1{-}\underset{\displaystyle CN}{\underset{|}{CH}}{-}\underset{\displaystyle CN}{\underset{|}{CH}}{-}R^3 \quad \text{(Ref. 246) (137)}$$

$$R^1 = Et,\ R^3X = EtI$$

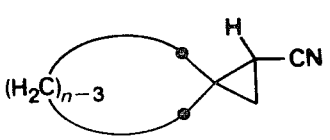


$$\xrightarrow[n = 6,\ 76\%]{NaCN}$$

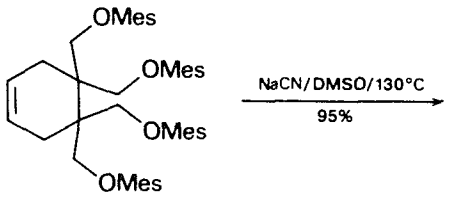


$$\longrightarrow$$

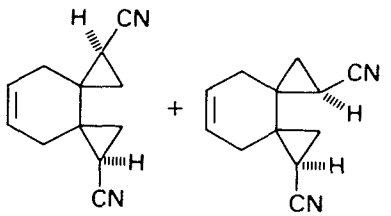
$n = 3-6$



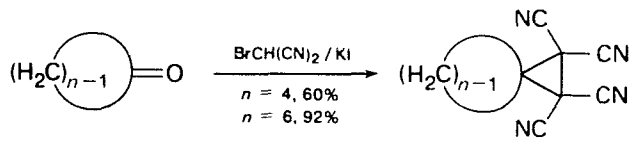
(Refs. 247–250) (138)



Mes = mesyl



(Refs. 247–250) (139)



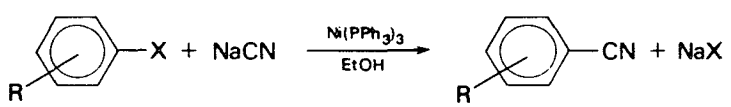
(Refs. 247–250) (140)

J. Synthesis of Aromatic Nitriles

The reaction of an organic halide with a metal cyanide remains one of the most convenient methods for the synthesis of nitriles. Conversion of aryl halides into the corresponding nitriles is usually effected by heating the halide with copper(I) cyanide at 150–250°C without a solvent, or in such solvents as pyridine, quinoline, DMF, DMSO or HMPT[17,251] Recently, new methods particulary suitable for the synthesis of aryl nitriles have been developed.

1. Nickel-catalysed cyanation of aromatic halides

In a new procedure[252,253] employing nickel(0) complexes as catalysts, the reaction temperature of the conversion of aryl halides into nitriles can be as low as 30°C, e.g. using sodium cyanide in the presence of tris(triphenylphosphine)nickel(0) (equation 141). The reaction can be conducted in methanol, ethanol or acetone, at 30–60°C, and the yields are high; for example, bromobenzene gives benzonitrile (97% yield) and 1-chloronaphthalene yields 1-naphthonitrile (90% yield).



(141)

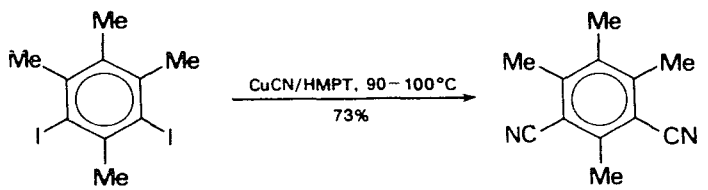
X = Cl, Br, I

Cyanation of bromobenzene with acetone cyanohydrin–triethylamine in the presence of *trans*-chlorobis(triphenylphosphine)nickel [i.e. $NiCl_2(PPh_3)_2$] catalyst is also effective (80% conversion)[253]. Similar conversion of chloro- or iodo-aryl compounds into aryl cyanides has been performed with potassium cyanide in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] catalyst in refluxing tetrahydrofuran; yields of aryl cyanides were 82–91%; however, the conversion of bromobenzene was only 12%[254].

2. Synthesis of polycyanobenzenes

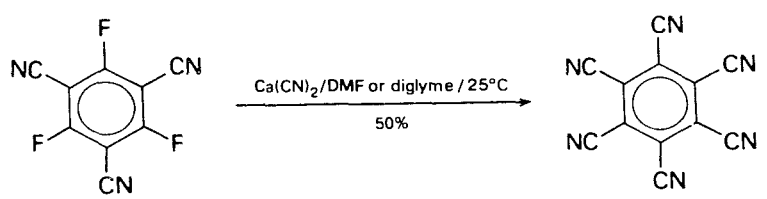
The conventional procedures for introducing several cyano groups into a benzene nucleus are the dehydration of benzenepoly(carboxamides) and the Sandmeyer reaction of appropriate aminocyano compounds. However, these direct methods often suffer from poor availability of the starting materials, and low yields due to extensive side-reactions. Multiple replacement of aryl halogen atoms by cyano groups can in some cases be effected by the action of copper(I) cyanide in aprotic solvents, preferably at elevated temperatures[17,251].

a. Conversion of polyiodobenzenes. Suzuki and coworkers[255] have found that heating of readily obtainable[256] polyiodobenzenes with copper(I) cyanide in HMPT at ~80–100°C for 1–2 h leads to complete replacement of iodine atoms by cyano groups. Catalysts are unnecessary. Thus, 4,6-diiodo-1,2,3,4-tetramethylbenzene is converted into 4,6-dicyano-1,2,3,5-tetramethylbenzene in 73% yield. The range of other conversions is 38–88% (equation 142)[255].

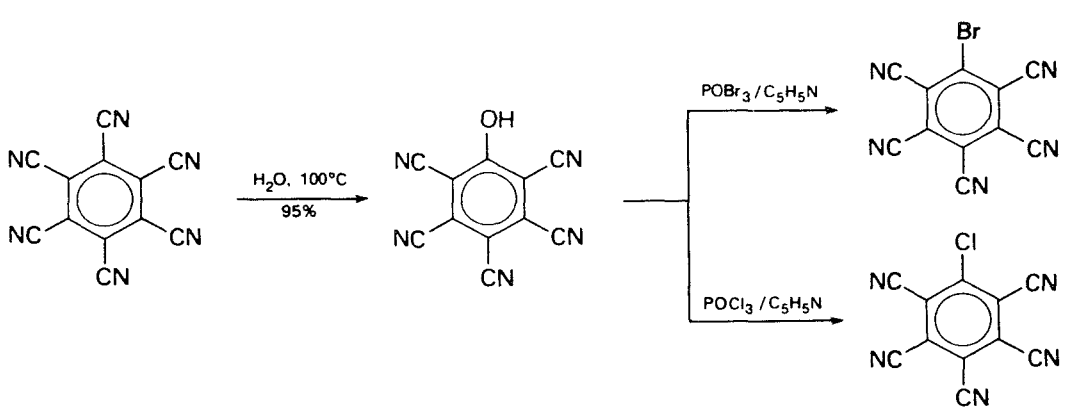


(142)

b. Conversion of 1,3,5-tricyano-2,4,6-trifluorobenzene. Hexacyanobenzene is prepared by reaction of 2,4,6-trichloro-1,3,5-tricyanobenzene with potassium fluoride in dimethyl sulphoxide, and reaction of the resultant 1,3,5-tricyano-2,4,6-trifluorobenzene with calcium cyanide (equation 143)[257a]. Hexacyanobenzene reacts with boiling water to give pentacyanophenol which can be converted to bromo- and chloro-pentacyanobenzene (equation 144)[257b].

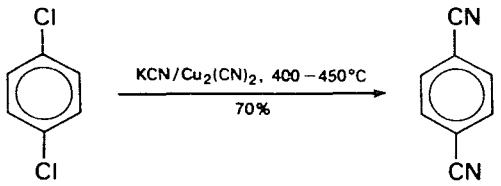


(143)



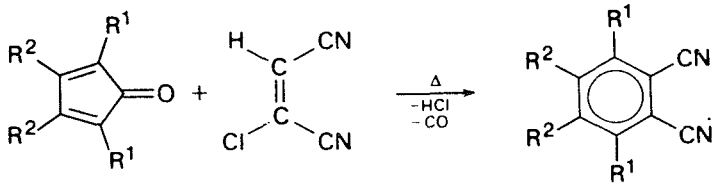
(144)

c. Conversion of p*-dichlorobenzene.* *p*-Dicyanobenzene can be prepared in good yield by the reaction of *p*-dichlorobenzene with molten eutectic of potassium cyanide and copper(I)cyanide in a Carius tube at 400–500°C (equation 145)[258].



(145)

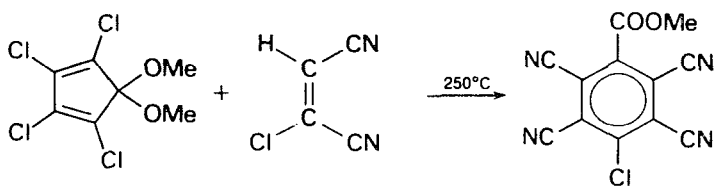
d. Di- and tetra-cyanobenzene derivatives via ring-enlargement and aromatization. Tetrasubstituted phthalodinitriles are conveniently obtained by refluxing tetrasubstituted cyclopentadienones with chloromaleodinitrile in bromobenzene (equation 146)[259]. The analogous reaction of tetrachlorocyclopentadienone dimethyl acetal with the reagent, without a solvent, at 250–260°C *in vacuo* takes a different course, giving rise to methyl 4-chloro-2,3,5,6-tetracyanobenzoate (equation 147)[259].



(146)

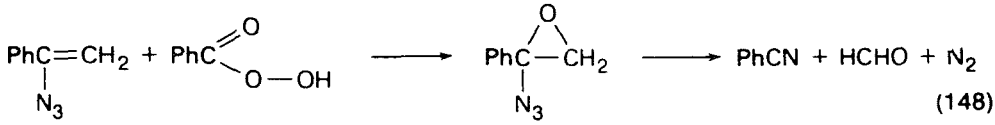
$R^1 = R^2 = R^3 = Ph$ (96%)

$R^1 = Pr$, $R^2 = R^3 = Ph$ (86%)

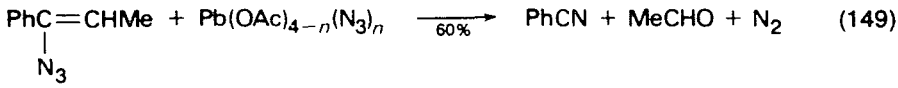


(147)

e. Aryl nitriles by oxidation of α-azidostyrenes. Benzonitrile can be prepared by cleavage of α-azidostyrene with peroxybenzoic acid, or of 1-azido-1-phenylpropene with lead tetraacetate–trimethylsilyl azide (equations 148 and 149)[260,261]. The fragmentation of the azido epoxide intermediate provides an isoelectronic, aza analogue of an extremely versatile reaction discovered by Eschenmoser and coworkers[262].

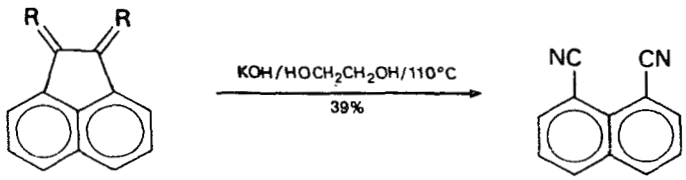


(148)



(149)

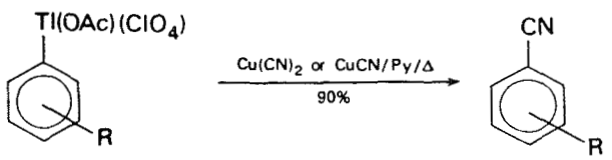
f. Aromatic nitriles from bis(tosylhydrazones). Thermal, potassium–hydroxide-induced, ring-opening of the bis (tosylhydrazone) of acetnapthenequinone affords 1,8-dicyanonaphthalene (equation 150)[263].



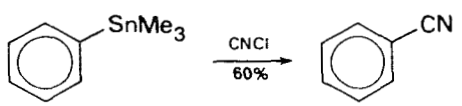
(150)

R = N—NHTs

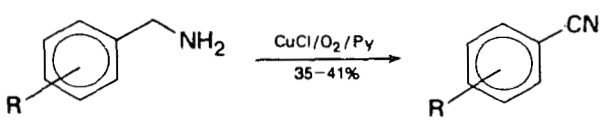
g. Additional methods. Aromatic cyano compounds may also be prepared from aromatic hydrocarbons[264,265], benzoic acid[266] and replacement of benzylic amino[267], bromo[268], hydroxyl[269] or hydroxylamino groups[270] with cyanide. Special methods for the synthesis of aromatic nitriles involve dehydrogenation[271], the Beckmann fragmentation[272] and anodic cyanation[273]. Also, as depicted, special methods involve the replacement of organometallic groups, e.g. thallium[274] or tin[275], oxidation[276], solid-absorbent[277], addition[278], cycloaddition[264,279], the Diels–Alder reaction of thiophene using dicyanoacetylene as the dienophile[280], the reaction of 2,3,4,5-tetramethylthiophene with dicyanoacetylene in the presence of aluminium chloride (to give thiepin), followed by thermal sulphur extrusion[281] or regiospecific reaction[282]; also, pyrolysis of 2-phenyl-Δ^2-thiazoline-4-carboxylic acid[283], of condensed, aromatic 1,2,5-thiadiazole 1,1-dioxide[284] or of *N,N*-dichloroperfluoro-*p*-toluidine at 550°C[284] (equations 151–162).



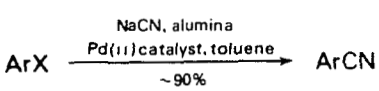
(Ref. 274) (151)



(Ref. 275) (152)



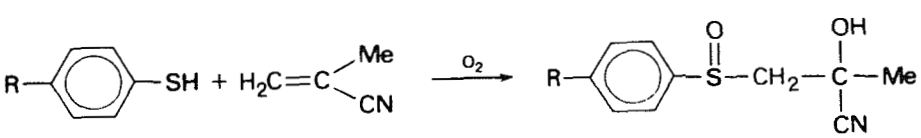
(Ref. 276) (153)



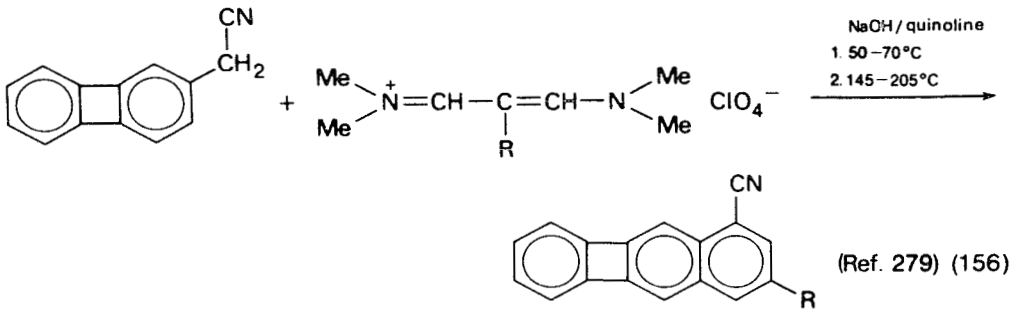
(Ref. 277) (154)

Ar = naphthyl, Ph

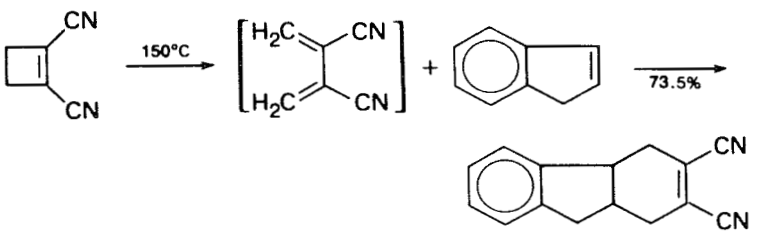
X = Br, I



(Ref. 278) (155)



(Ref. 279) (156)



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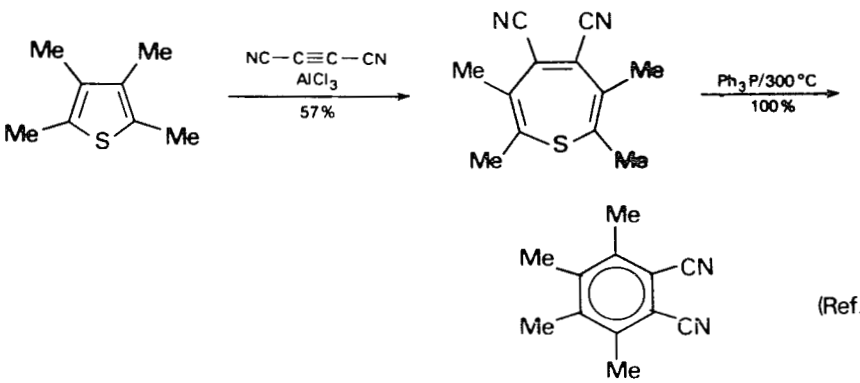
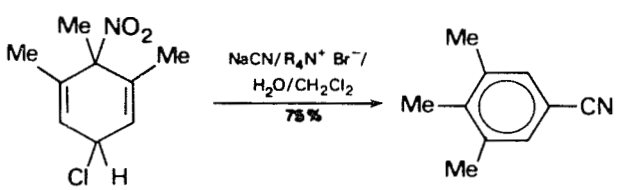
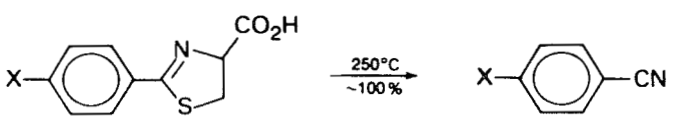


(Ref. 281) (158)

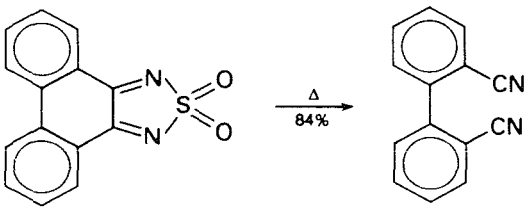


(Ref. 282) (159)

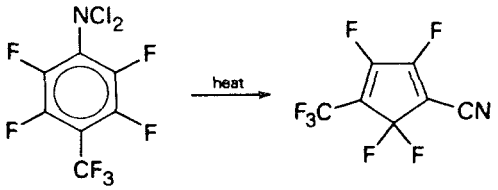


X = H, Cl

(Ref. 283) (160)



(Ref. 284) (161)



(Ref. 284) (162)

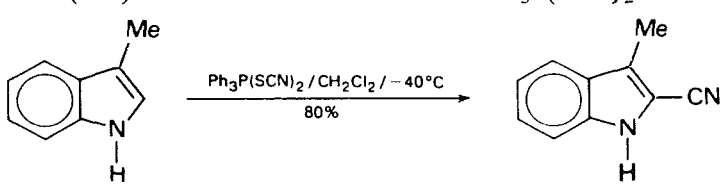
K. Synthesis of Heterocyclic Carbonitriles

Reactions of aromatic heterocycles that involve the catalytic action of the cyanide ion have been reviewed[285].

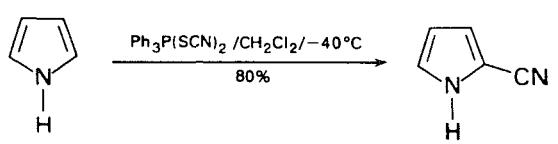
1. Cyanation of indoles, pyrroles and related heterocycles

Indole and pyrrole carbonitriles are very important intermediates in organic synthesis[286–288]. Among important reactions for cyanation involving cyano reagents are: (*i*) *N*-indolylmagnesium iodide with cyanogen chloride[289], (*ii*) pyrroles with aryl cyanates in the presence of hydrogen chloride[290], (*iii*) indole with trichloroacetonitrile[291], (*iv*) indole with chlorosulphonyl isocyanate[292,293] and (*v*) anodic cyanation of indoles and pyrroles[273,294]; the last method is unique, and the cyanation takes place predominantly at an unusual position of the pyrrole nucleus, namely C-3. Some recent methods for cyanation are discussed next.

a. Cyanation with triphenylphosphine–thiocyanogen, $Ph_3P(SCN)_2$. Treatment of indole and pyrrole with the combined reagent [$Ph_3P(SCN)_2$ in dry dichloromethane at − 40°C for several hours] gives high yields of the cyanated indole and pyrrole compounds (equations 163 and 164)[295]. If C-3 is substituted, the cyanation occurs at C-2 of the indole ring. For pyrrole, the cyanation occurs at C-2. No cyanation is observed with indoles having electron-withdrawing groups (e.g., ethoxycarbonyl or benzoyl) at N-1 or C-2 or with 2,3-dialkyl-substituted indoles. With hydroxyindoles, thiocyanation of the alcohol group occurs competitively with the cyanation of the indole nucleus. A possible route for the cyanation for indole is an addition of the electron-rich carbon atom (C-3) to the —N=C=S carbon of $Ph_3P(SCN)_2$[295].

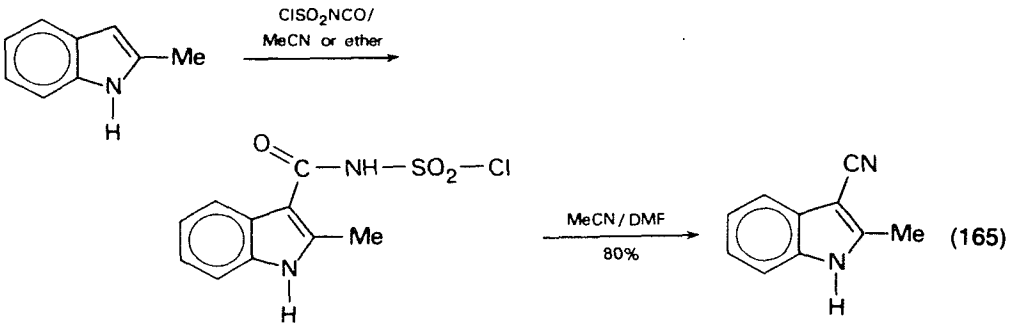


(163)



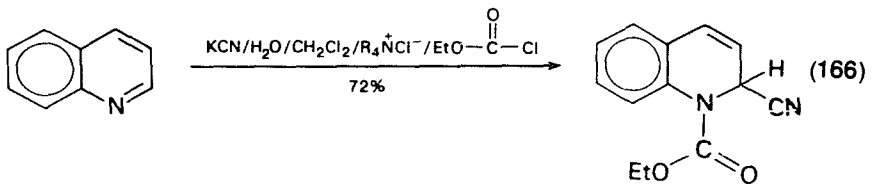
(164)

b. Cyanation with chlorosulphonyl isocyanate, $ClSO_2NCO$. Reaction of indoles with the powerful electrophile chlorosulphonyl isocyanate[288] offers a versatile route to 3-substituted indoles[293]. The reaction in dry ether or acetonitrile at 0–5°C furnishes the intermediate *N*-(chlorosulphonyl)indole-3-carboxamide, which in turn gives indole-3-carbonitrile in a one-flask manipulation (equation 165)[293].



(165)

c. Cyanation of quinoline and isoquinoline via phase-transfer catalysis. A new method for improving the yields of Reissert reactions[296] by using a phase-transfer catalyst has been described[297]. Thus, addition of an acyl chloride to a mixture of quinoline (or isoquinoline) with potassium cyanide in dichloromethane–water in the presence of benzyltriethylammonium chloride (the phase-transfer catalyst) yields Reissert products in good yields (equations 166 and 167)[297].



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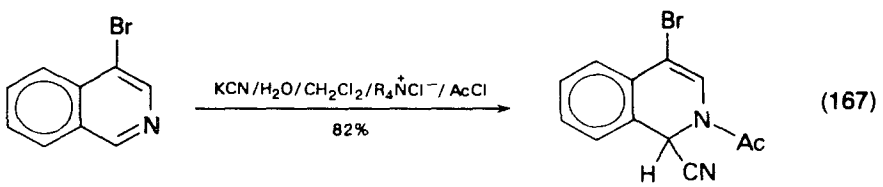
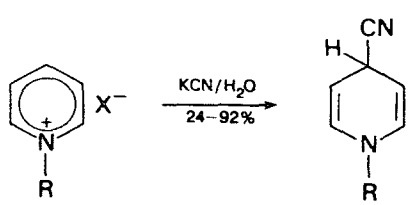


(167)

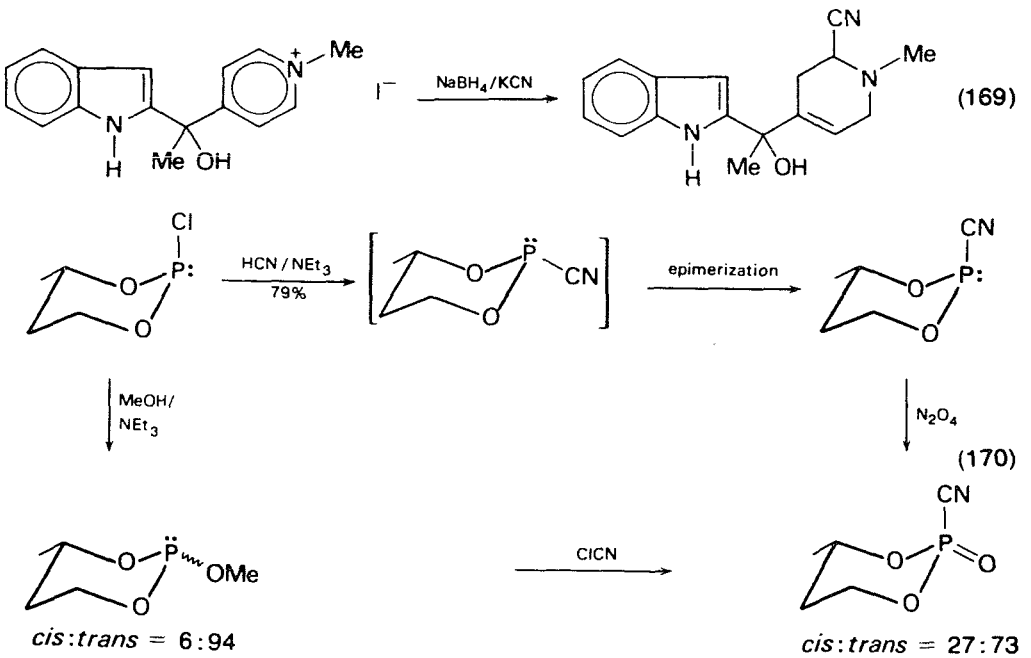
d. Additional methods. Additional, special methods for the cyanation of heterocycles include the preparation of 4-cyano-1,4-dihydropyridines (equation 168)[298], a 2-cyano-1,2,3,4-tetrahydropyridine derivative (equation 169)[299], cyanation of the 1,2,3-dioxaphosphorinane ring (equation 170)[300] and cyanation of *N*-1-methylthymine[301a]. A new preparation of 4-cyanopyridine has recently been described[301b].



(168)

R = 4-pyridyl, 2,4-$(O_2N)_2C_6H_3$, $MeOCH_2$, PhCH=CH,

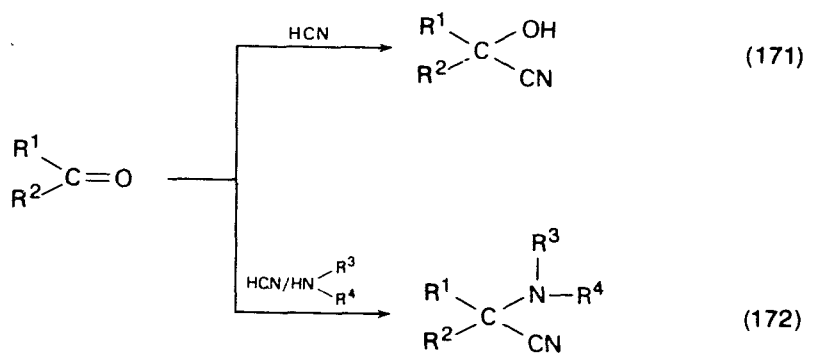
X = Br, Cl



L. Cyanohydrins

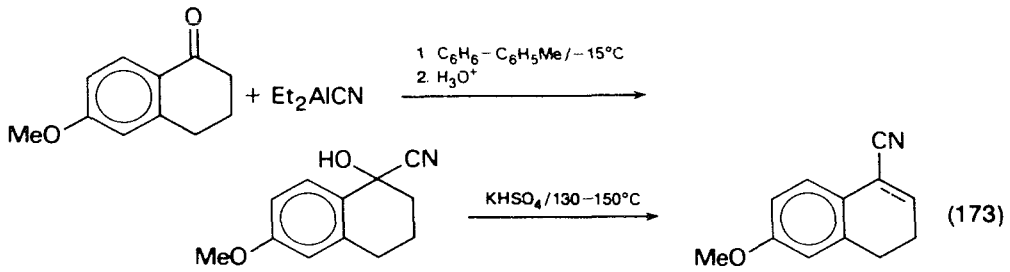
1. *Synthesis and transformations of cyanohydrins*

The preparation and reactions of cyanohydrins have been reviewed[7,16]. Of the numerous classical methods for the nucleophilic carboxylation of carbonyl compounds to α-hydroxy carboxylic acids or related compounds, one of the most important entails the addition of hydrogen cyanide to aldehydes and ketones, resulting in the formation of cyanohydrins (equation 171)[142]; these are also useful intermediates for the preparation of α-hydroxy aldehydes, amino alcohols, nitriles, ketones and lactones. If amines are present, the α-aminonitriles, useful precursors of α-amino acids, are obtained (e.g. the Steecker synthesis or the Bücherer reaction) (equation 172). Recent improve-

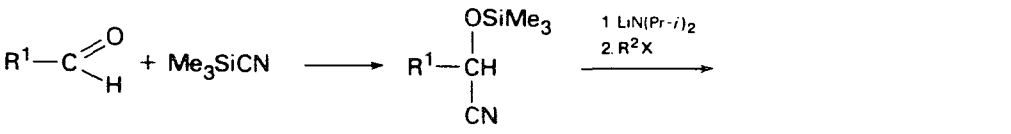


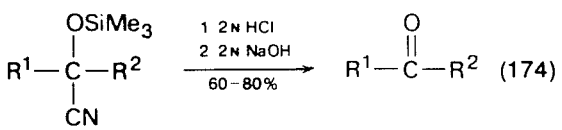
ments in the standard synthetic procedures, using hydrogen cyanide alone , have featured the use of diethylaluminium cyanide (equation 173)[302] (or trialkylaluminium and hydrogen cyanide, the Nagata reagent[302–305]) or trimethylsilyl cyanide (equation

174)[306] in the presence of a Lewis acid (particularly zinc iodide[307]) or other catalyst[308,309]. Subsequent acid-catalysed cleavage of the *O*-(trimethylsilyl)cyanohydrins obtained with the latter reagents allows isolation of ketone cyanohydrins in good overall yield (equation 175)[308].



(173)





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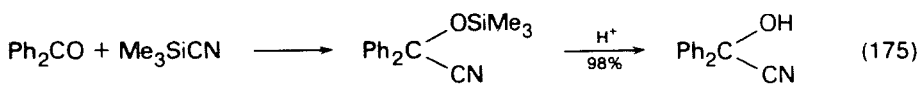
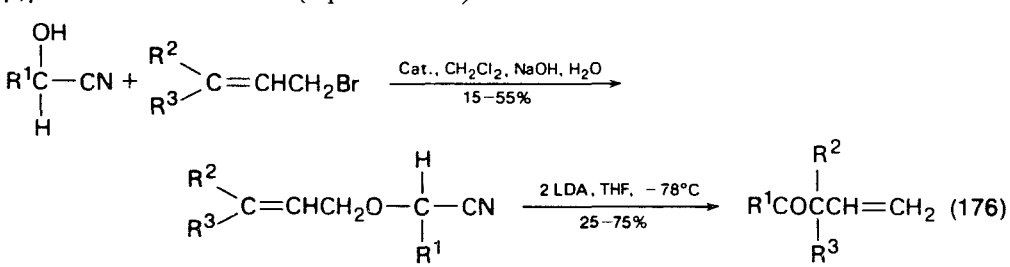


(175)

a. Aromatic cyanohydrins. Aromatic cyanohydrins can be prepared by starting with the treatment of an aromatic aldehyde with sodium hydrogen sulphite in water. The mixture is cooled to 0°C, and ether is added, followed by a solution of sodium cyanide in water. The cyanohydrin is isolated by extraction with ether[310a]. Recently, a similar procedure was used for the preparation of cyanohydrin nonanal[310b].

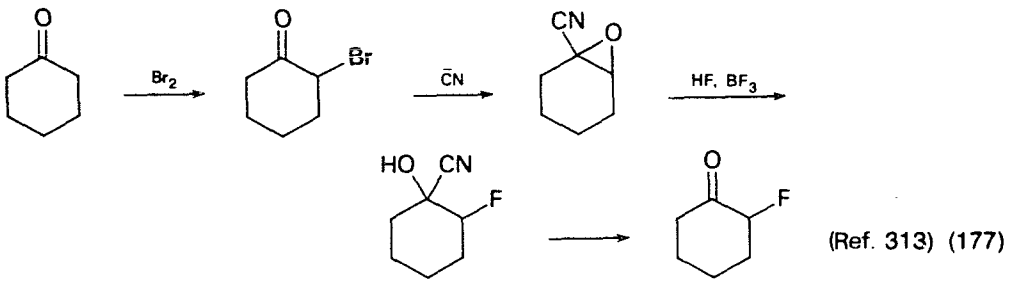
b. Aryl ketone cyanohydrins. Cyanohydrins of aromatic aldehydes readily add to vinyl ethers to give stable mixed acetals. These can be alkylated, in the presence of aqueous sodium hydroxide, with tetramethylammonium chloride as the phase-transfer catalyst. These acetals are not isolated, but are hydrolysed by dilute hydrochloric acid to aryl ketone cyanohydrins which are then hydrolysed to ketones by methanolic potassium carbonate[311].

c. β,γ-*Unsaturated ketones via cyanohydrins*. Under phase-transfer conditions (Aliquat 336), cyanohydrins of aliphatic aldehydes react with allylic bromides to afford β,γ-unsaturated ethers. On treatment with lithium diisopropylamide (LDA) the latter undergo a [2,3]sigmatropic rearrangement and elimination of lithium cyanide to give β,γ-unsaturated ketones (equation 176)[312].

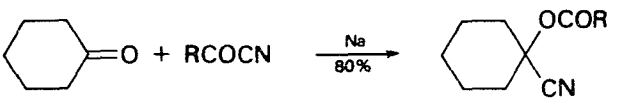


(176)

d. Selected preparation of cyanohydrins, and their reactions. A few methods for the preparation of cyanohydrins, and some of their transformations, are shown[313–321] (equations 177–186).

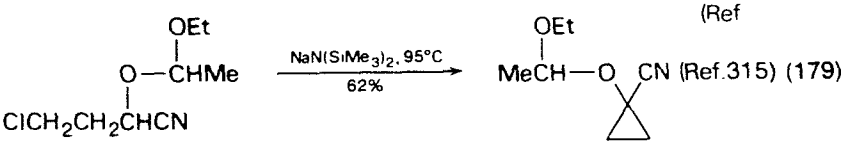


(Ref. 313) (177)

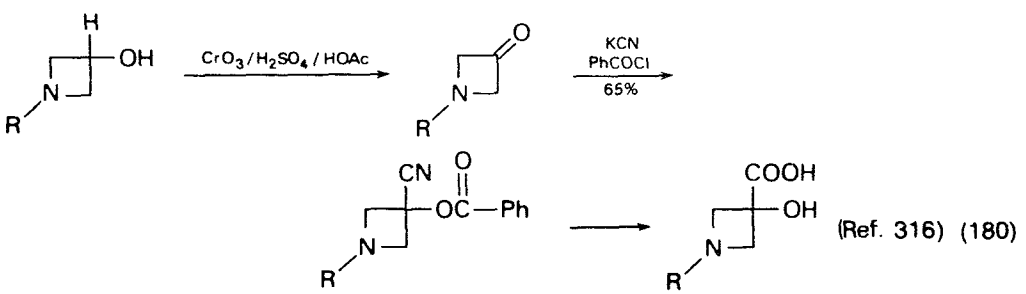


(Ref. 314) (178)

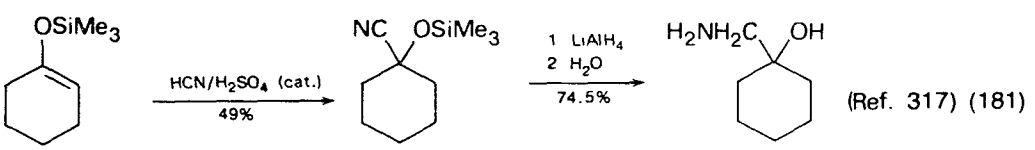
R = Ph



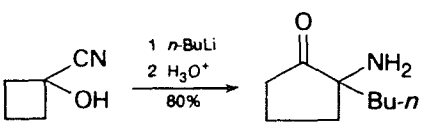
(Ref.315) (179)



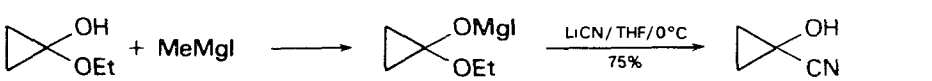
(Ref. 316) (180)



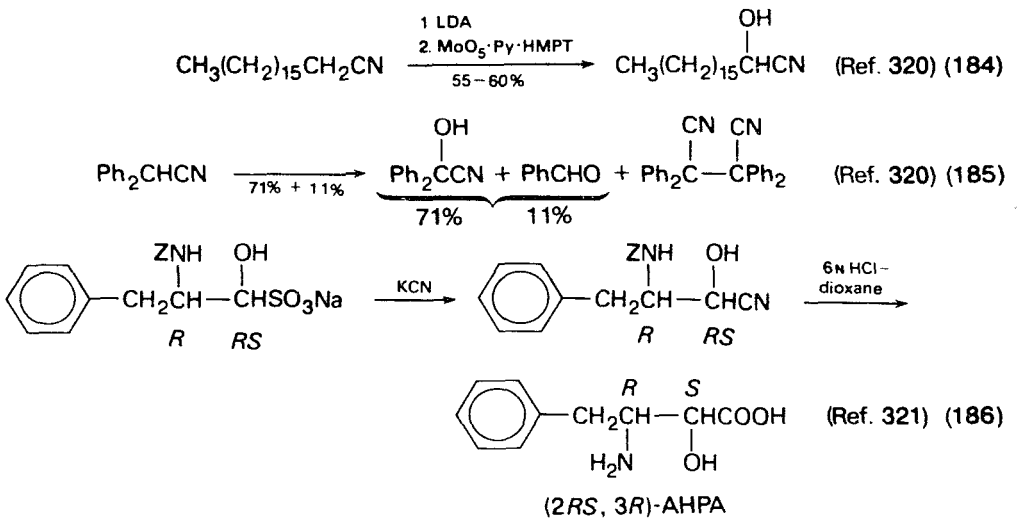
(Ref. 317) (181)



(Ref. 318) (182)



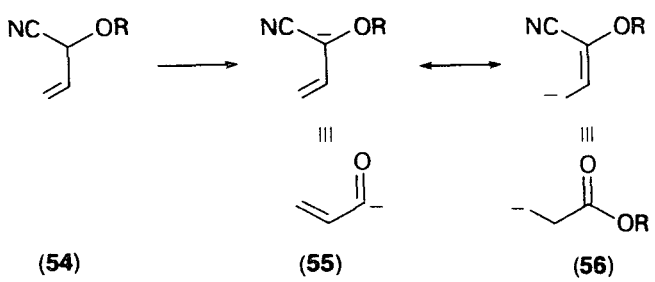
(Ref. 319) (183)



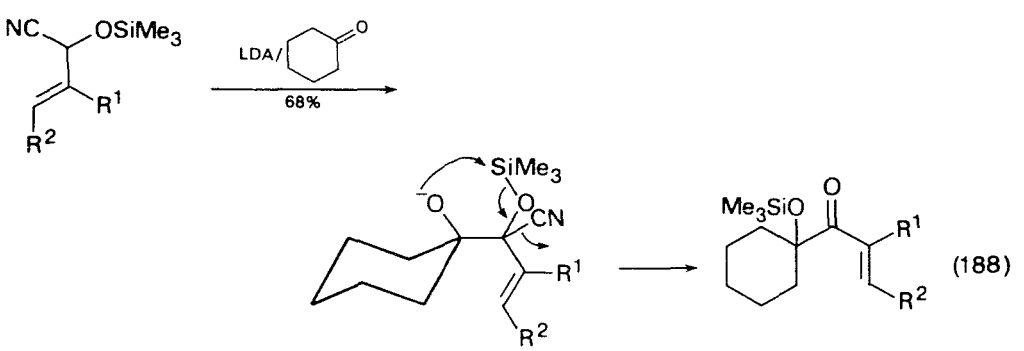
2. *Protected cyanohydrins*

The use of such protected cyanohydrins as 2-(dialkylamino)acetonitriles[322,323] and the *O*-protected cyanohydrins[324–327] as acyl anion equivalents[142,328] has been studied by Stork[323,327] and Hünig[306,325,326], and has found wide applicability in chemical synthesis.

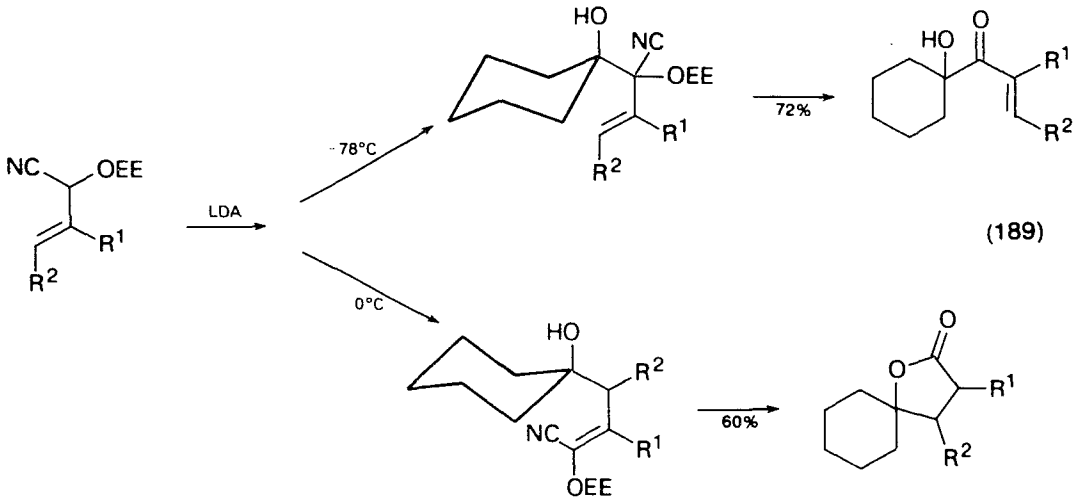
a. Regiocontrolled reactivity of (trimethylsilyl)- and (ethoxyethyl)-protected cyanohydrins. A recent study by Jacobson and coworkers[324] has shown that the protected cyanohydrins (**54**) might serve as acyl anion equivalents[328] (**55**) or homoenolate equivalents[329,330] (**56**) (equation 187). It has been found[324] that on metalation with



(187)



lithium diisopropylamide (LDA) trimethylsilyl-protected cyanohydrins display exclusively α reactivity with aldehydes and ketones at − 78°C; for example, they form with cyclohexanone the α adduct in 68% yield, via acyl anion equivalent addition (equation 188). The metalated ethoxyethyl(EE)- protected cyanohydrin also reacts with cyclohexanone to give the α adduct at −78°C (72% yield); however, at 0°C, the product is γ-lactone (60% yield) formed via homoenolate equivalent addition (equation 189). Thus, temperature control allows for complete regiocontrol in the metalated, ethoxyethyl-protected cyanohydrin addition to ketones and aldehydes[324].

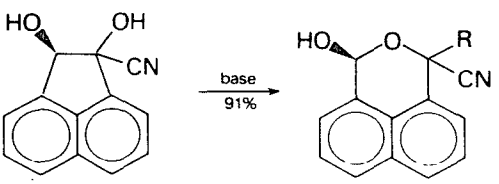


(189)

EE = ethoxyethyl

3. *Acenaphthenone cyanohydrin rearrangement*

Cyclic, unsaturated ketol homologues of 2-hydroxyacenaphthenone undergo a facile, frequently quantitative, carbon-to-oxygen, acyl rearrangment[331]. An example[332] is that observed for acenaphthenone cyanohydrin which readily rearranges to 3-cyanonaphthalide at pH 7 or higher (equation 190). The mechanism involves a cyclic, aromatic transition-state, not an acyclic hydroxy acid intermediate.



(190)

4. *Carbohydrate cyanohydrins*

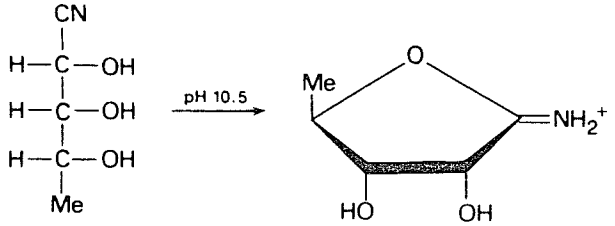
The condensation of cyanide with an aldose in aqueous solution to produce the 2-epimeric aldonitriles (cyanohydrins) was first reported by Kiliani[333] in 1885. The cyanohydrins were hydrolysed *in situ* to the 2-epimeric aldonic salts (aldonates). Kiliani also found that aldonic acids could lose water to form aldonolactones.

The utility of the Kiliani reaction was extended when Fischer[334] showed that aldonolactones could be reduced with sodium amalgam to aldoses, providing a con-

venient route for the preparation of aldoses from parent aldoses having one carbon atom less.

During the preparation of ^{14}C-labelled aldoses, Isbell and coworkers[335] observed that the ratio of epimeric aldonates depends on the reaction conditions. For example, cyanide with *D*-arabinose at pH 11 yields 73% of *D*-gluconate whereas, at pH < 9, 70% of *D*-mannonate is formed[335a]. The mechanisms of formation and hydrolysis of aldose cyanohydrins have been studied[336,337].

Recently, Barker and coworkers[338a] reexamined the Kiliani reaction using ^{13}C-cyanide, ^{13}C-enriched aldoses and ^{13}C-NMR spectroscopy. The study[338a] has demonstrated that an equilibrium exists between the parent aldose, the cyanide and the 2-epimeric nitriles; these are, in turn, in equilibrium with imido-1,4-lactones that, on further hydrolysis, yield aldonates. As an example, a specially synthesized aldononitrile can be readily converted into the protonated imido-1,4-lactone at pH 10.5 (equation 191).



(191)

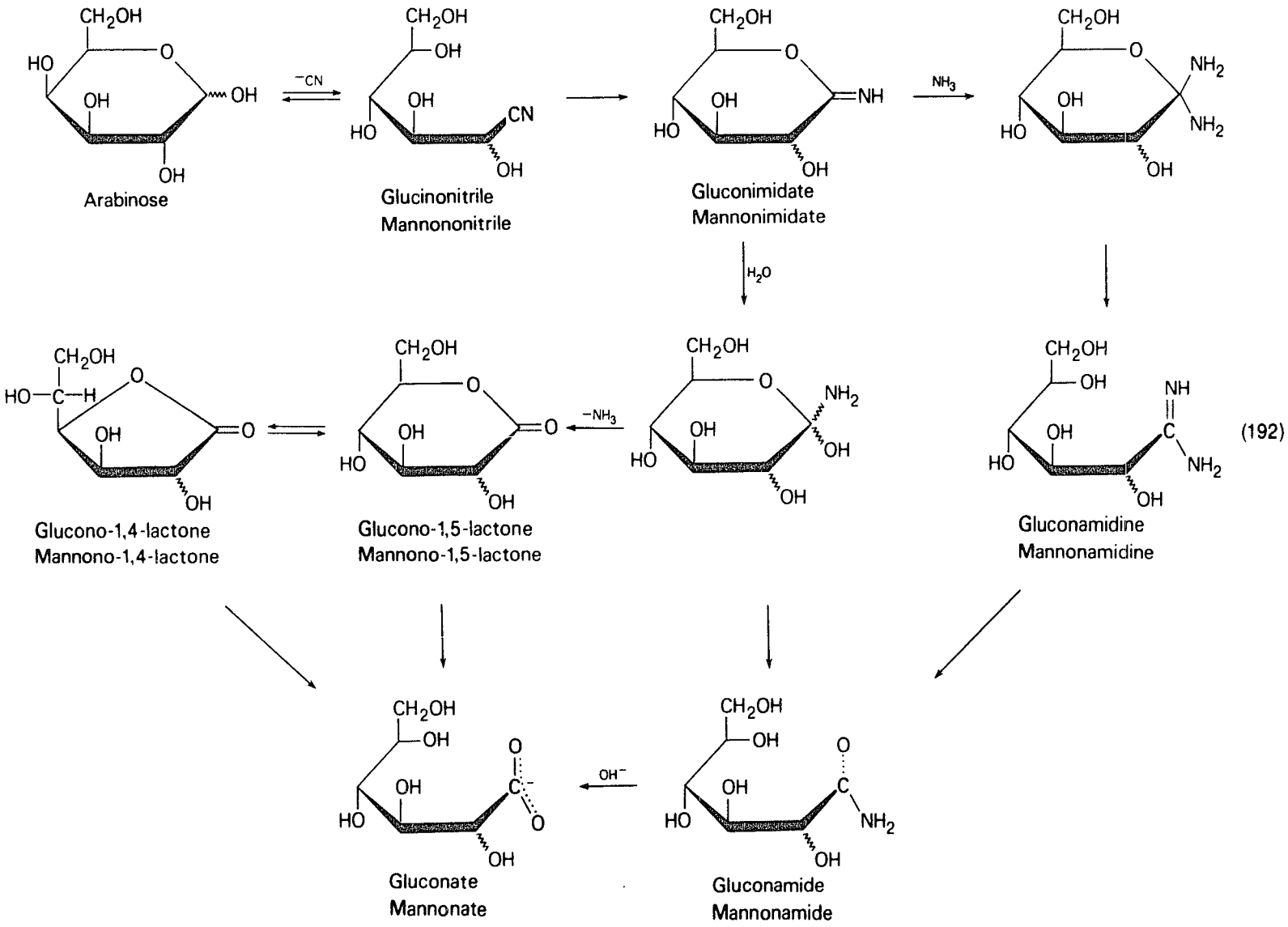
Recently, Blazer and Whaley[338b] have reexamined the Kiliani reaction of D-arabinose with sodium ^{13}C-cyanide or $^{13}C^{15}N$-cyanide by ^{13}C-NMR spectroscopy; the identified intermediates include cyanohydrins, amides, lactones, amidines and an imidate (equation 192). This has confirmed the work by Isbell and coworkers[335] on the Kiliani–Fischer synthesis of C(1)-labelled glucose and mannose. Isbell was able to vary the ratio of mannonate to gluconate from 70:30 to 27:73 by altering reaction conditions (e.g. pH); however, no explanation was proposed for the cause of the variation in epimer ratios. Thus, the cause of the pH dependence of the mannonate-to-gluconate ratio remains unknown from the original and the present study. The authors[338b] suggest, however, that since the cyanohydrin formation occurs via attack of cyanide on D-*aldehydo*-arabinose, the conformational equilibria influenced by the pH might determine which face of the aldehydo group is preferentially attacked.

5. *Specific reduction of cyanohydrins*

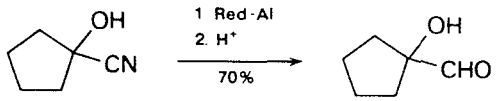
Sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) is a useful alternative to $LiAlH_4$. While its reactivity is similar to that of $LiAlH_4$, it is easier to handle, has a greater solubility in a wide range of solvents including aromatic hydrocarbons, and is stable at temperatures[339] up to 200°C. The reagent has proved to be specific for the reduction of cyanohydrins. Thus, it is effective for the conversion of cyanohydrins to α-hydroxy aldehydes[340] in good yield (equation 193), and offers a new approach to the synthesis of branched-chain sugars, or cross linked polysaccharides, from mono- or di-saccharide aldose cyanohydrins, respectively.

6. *Thio and seleno analogues of cyanohydrins*

The preparation and some of the reactions of thio analogues of cyanohydrins, e.g. thiocarbonyl cyanide[341], and cyanoselenenylation of aldehydes[342a] (equation 194) have recently been reported. The dissociation constants of cyanohydrins of some substituted thian-4-ones have been determined[342b].


Arabinose
Glucinonitrile
Mannononitrile
Gluconimidate
Mannonimidate
Gluconamidine
Mannonamidine
Glucono-1,4-lactone
Mannono-1,4-lactone
Glucono-1,5-lactone
Mannono-1,5-lactone
Gluconate
Mannonate
Gluconamide
Mannonamide
−CN
NH3
H2O
−NH3
OH−

(192)



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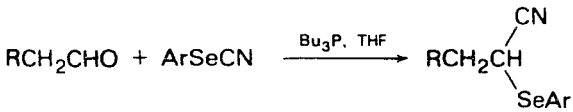


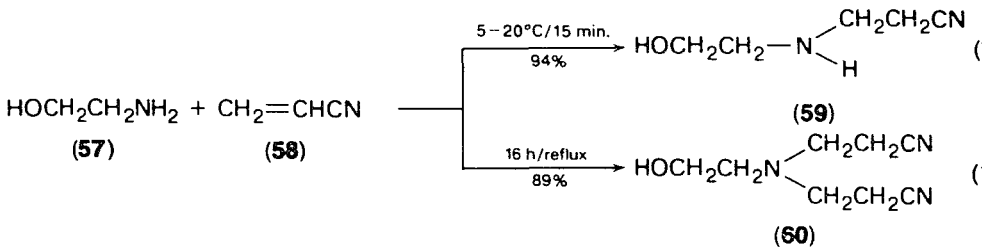
(194)

M. Cyanoethylation

1. Cyanoethylation via acrylonitrile

The chemistry of acrylonitrile and its derivatives is still a topic of interest to academic and industrial chemists. Recent reviews on the subject include the chloro derivatives of acrylonitrile[14], 2-acetoxy- or 2-chloro-acrylonitriles as ketene equivalents[343] and cyanoethylation of organic compounds via acrylonitrile[6].

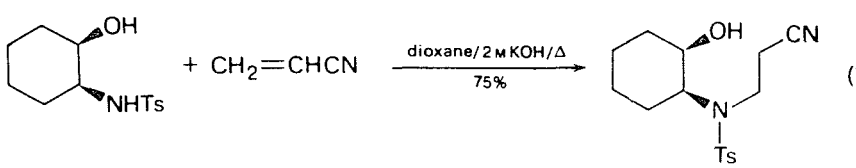
a. Cyanoethylation of alkanolamines. Compounds possessing labile hydrogen atoms may add to acrylonitrile, forming molecules containing a cyanoethyl group[6,344]. Hydrogen donors may be amines, alcohols or compounds in which hydrogen atoms are activated by electron-withdrawing groups. Thus, cyanoethylation[345] of ethanolamine (**57**) with acrylonitrile (**58**) at 5–20°C gives (**59**) (equation 195), while under reflux it yields the *N,N*-bis(cyanoethyl) compound (**60**) (equation 196). *N,N*-Bis(2-cyanoethyl)



(195)

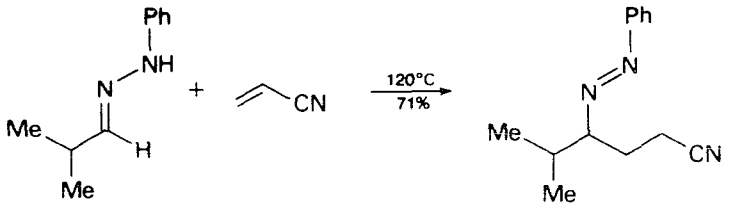
(196)

derivatives have been obtained from alkanolamines in which the amino group is attached to the methylene group. Alkyl groups on the α-carbon atom lower the reactivity: thus, $HOCH_2CH(CH_3)NH_2$ yields a mixture of mono- and bis-cyanoethyl derivatives (under reflux); the disubstituted $HOCH_2C(CH_3)_2NH_2$ gives only the monocyanoethyl derivative (reflux, 98% yield)[345a]. However, the base-catalysed conjugate addition to acrylonitrile gives a monocyanoethyl derivative as the only product[345b] (equation 197).



(197)

b. Reaction of phenylhydrazones with acrylonitrile. Reaction of phenylhydrazones of aliphatic aldehydes with acrylonitrile gives phenylazoalkanes by an ene reaction. Thus treatment of isobutyraldehyde phenylhydrazone (**61**) with acrylonitrile gives the phenylazolkane (**62**) as a 9:1 *trans–cis* mixture (equation 198)[346,347]. With more electron-deficient alkenes, e.g. methyl vinyl ketone, a Michael reaction occurs at

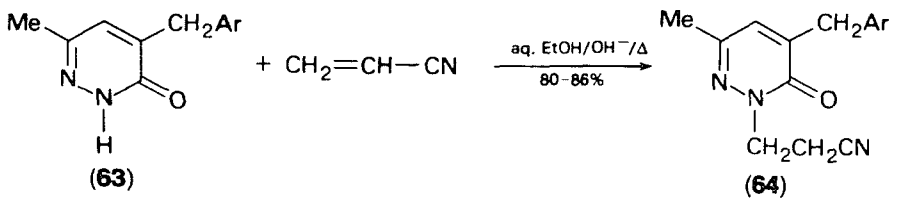


(198)

(61) (62)

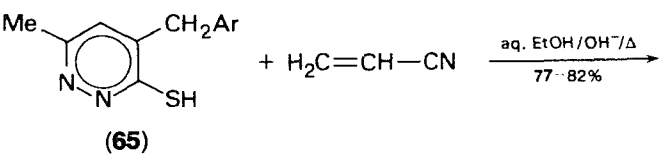
nitrogen, followed by cyclization to give pyrazolidines. The reactions of phenylhydrazone monoanions with acrylonitrile take a variety of pathways, depending on the counterion (e.g. cuprous lithium or diethylaluminium salt)[346,347].

c. N- and S-cyanoethylation of pyridazines. Treatment of 4-arylmethyl-6-methylpyridazin-3(2*H*)-one (**63**) with acrylonitrile in refluxing, aqueous ethanol containing some sodium hydroxide gives the *N*-cyanoethyl derivative (**64**) (equation 199). When 4-arylmethyl-3-mercapto-6-methylpyridazine (**65**) is allowed to react with acrylonitrile under similar conditions, the reaction gives the *S*-cyanoethyl derivatives (**66**) (equation 200)[348].

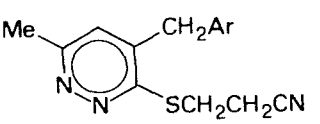


(199)

(63) (64)

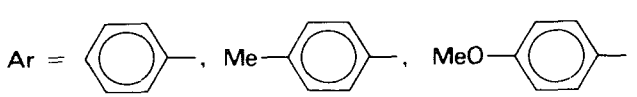


(65)



(200)

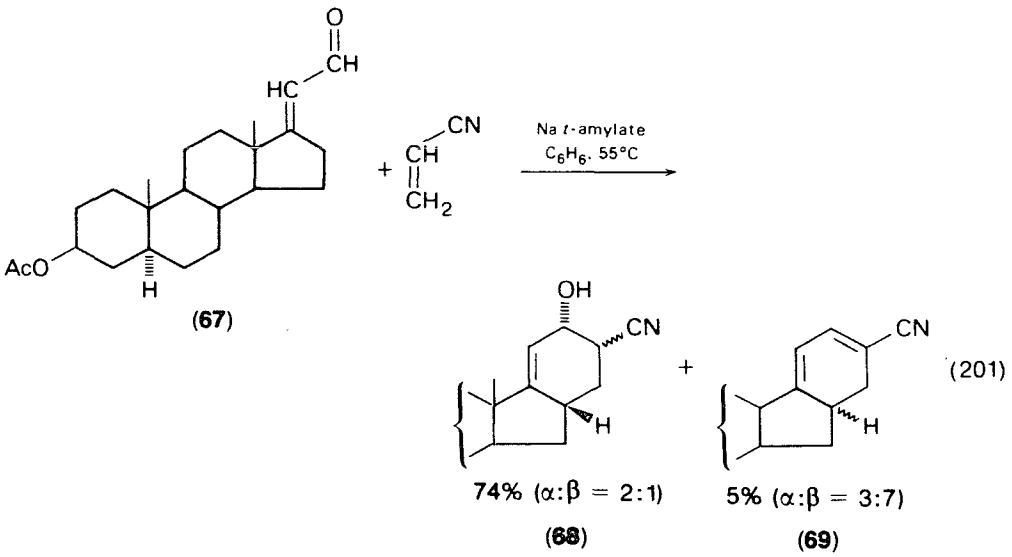
(66)



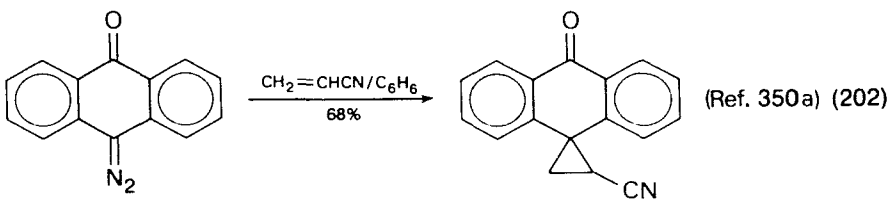
d. γ-Cyanoethylation of steroid α,β-unsaturated aldehydes. Cyanoethylation of 3β-acetoxy-5α-pregn-17-en-21-al (**67**) with a slight excess of acrylonitrile in benzene in the presence of a base leads to the cyclization products **68** and **69** (equation 201). This is the first example of a γ-cyanoethylation that is followed by an aldol addition (formation of **68**) or a crotonization (formation of **69**)[349].

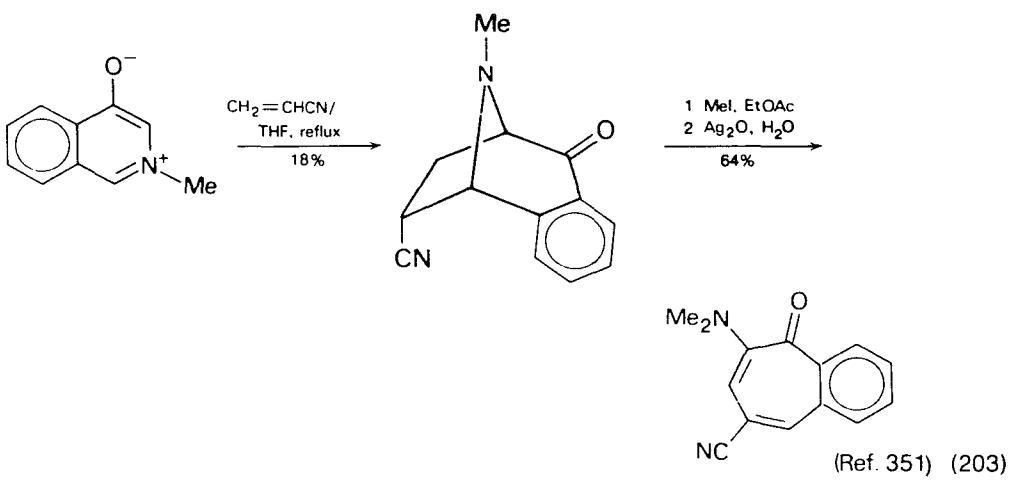
2. *Selected synthesis of carbocyclic compounds via cyanoethylation*

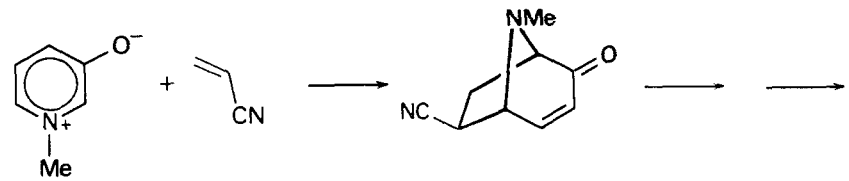
Cyanoethylation is a useful method for synthesis of carbocyclic and heterocyclic molecules. The formation of adducts or ring-systems via acrylonitrile may proceed by various pathways; the mechanism may involve annelation, the Diels–Alder cycloaddi-

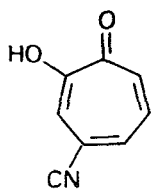


tion or a dipolar cycloaddition. Thus, the nitrile may be referred to as the dienophile in the Diels–Alder reactions, or as the dipolarophile in the 1,3-dipolar cycloaddition reactions. Dipolar cycloadditions are important as a means of synthesis of heterocyclic molecules. Some synthetic applications of acrylonitrile in the acyclic and carbocyclic fields are shown in equations (202)–(218)[350–364]; the synthesis of heterocyclic molecules via acrylonitrile has been discussed[343,364], e.g. the preparation of 2-oxopyridine derivatives from 2-cyanoacrylates[350b].

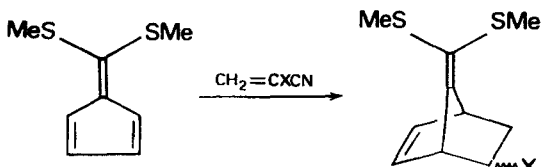








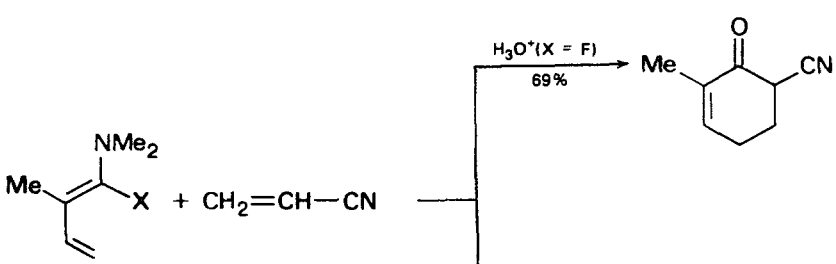
(Ref. 352) (204)



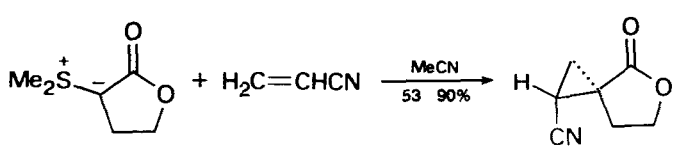
X = Cl, 59%

X = OAc, 64%

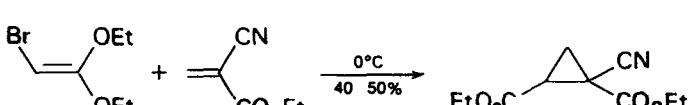
(Ref. 353) (205)



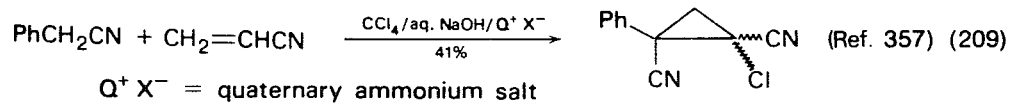
(Ref. 354) (206)



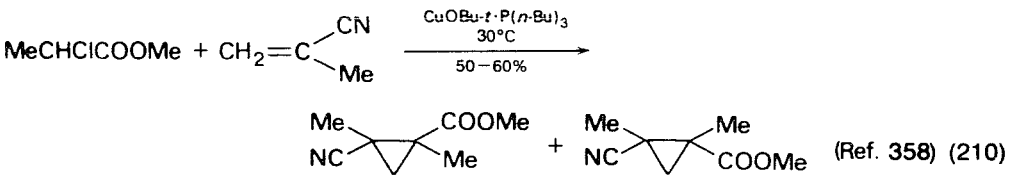
(Ref. 355) (207)



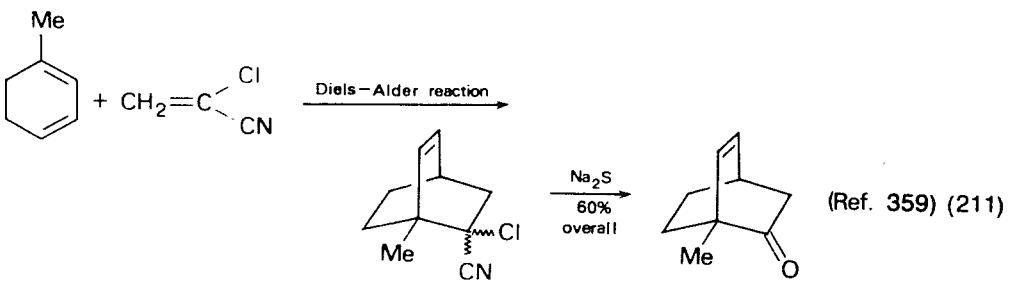
(Ref. 356) (208)



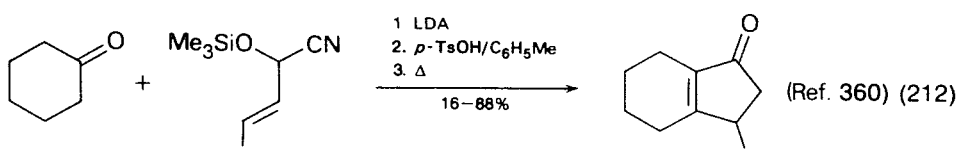
(Ref. 357) (209)



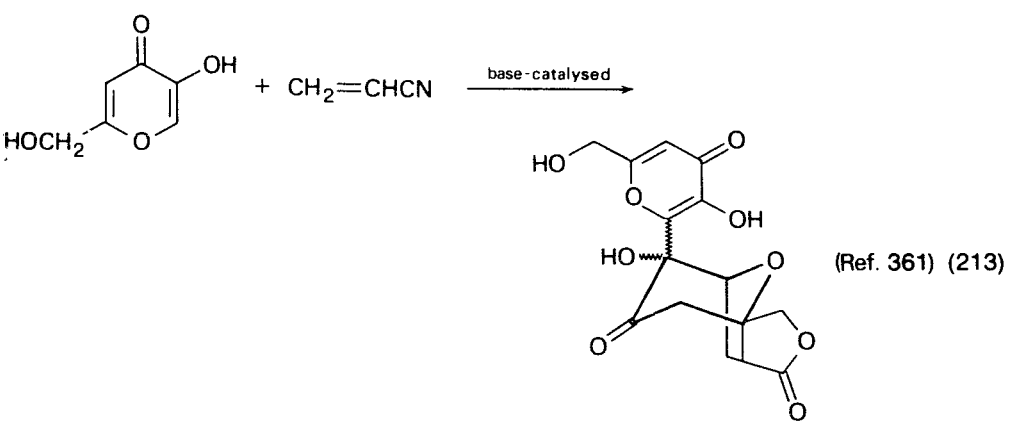
(Ref. 358) (210)



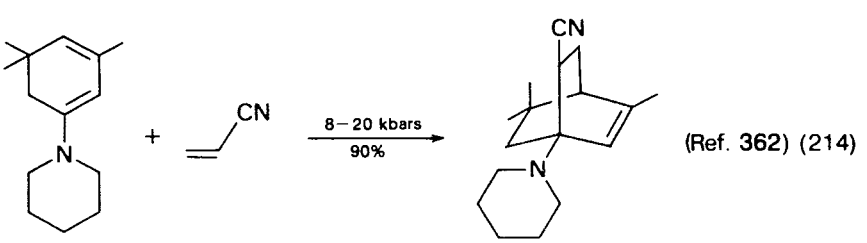
(Ref. 359) (211)



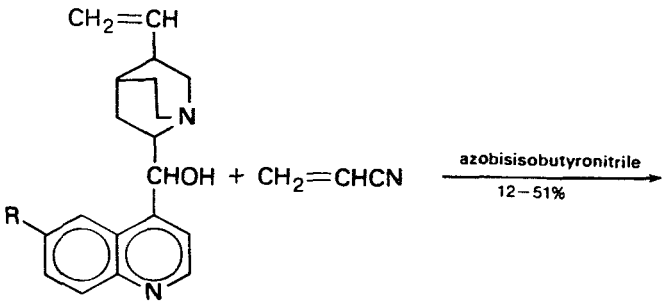
(Ref. 360) (212)



(Ref. 361) (213)

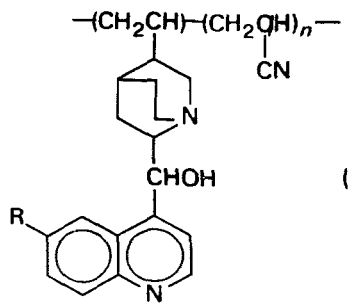


(Ref. 362) (214)



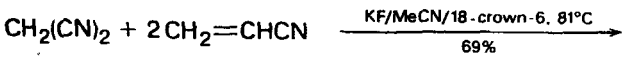
Quinine, quinidine; R = MeO

Cinchonine, cinchonidine; R = H

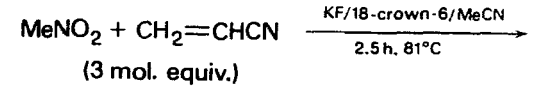


Polymeric alkaloid

(Ref. 363) (215)

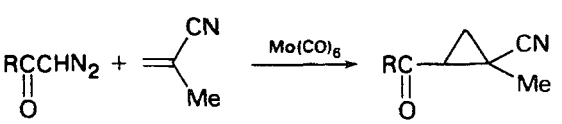


$(NC)_2C(CH_2CH_2CN)_2$ (Ref. 364a) (216)



$O_2NC(CH_2CH_2CN)_3$ (Ref. 364a) (217)

72%

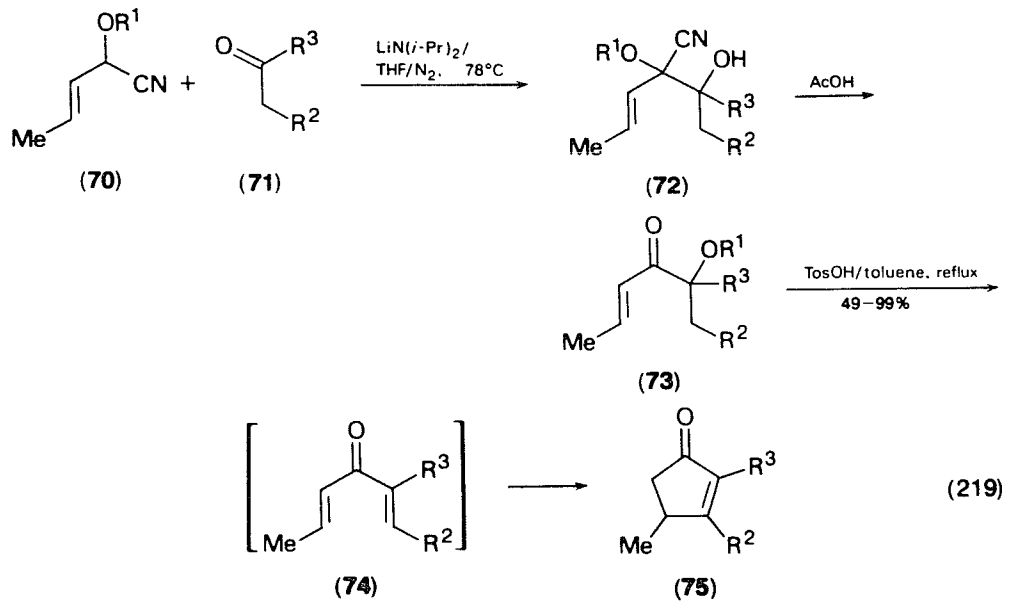


(Ref. 364b) (218)

a. Three-carbon annelation via the Nazarov cyclization. By regioselective addition of ketones (**71**) to the α carbon atom of protected, α,β-unsaturated cyanohydrins (**70**), the adducts **72** are obtained. In the case of the trimethylsilyl protecting group in (**70**), loss of cyanide takes place immediately, to give the enone (**73**); dehydration of (**73**) via the intermediate dienone (**74**) proceeds by Nazarov cyclization to cyclopentenone derivatives (**75**) (48–99%) (equation 219)[360].

3. *Ketene adducts with 2-acetoxy- and 2-chloro-acrylonitriles as ketene equivalents*

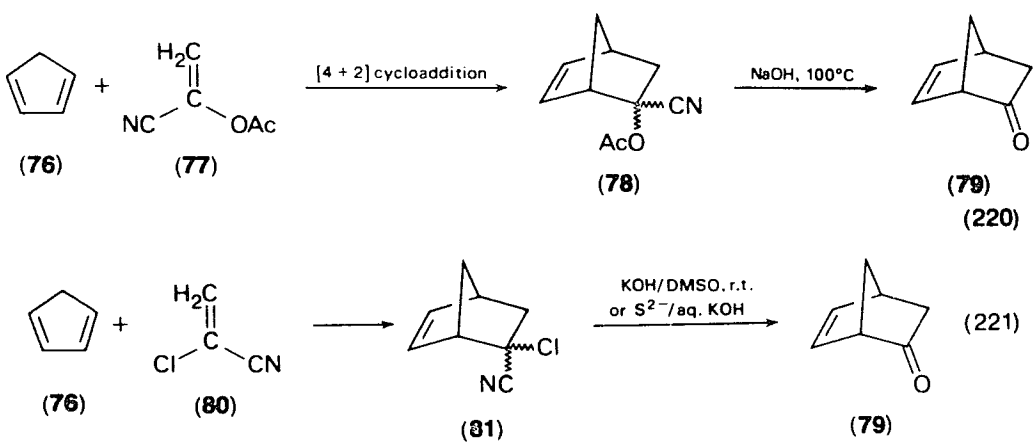
Reactions of ketene equivalents aptly illustrate the highly creative activity in organic chemistry that endeavours to bring about reactions that cannot be accomplished in a direct manner[343]. Since the direct route to norbonenones (e.g. **79**) by [4 + 2]addition of cyclopentadiene with ketene itself is not possible, a variety of synthons of the type

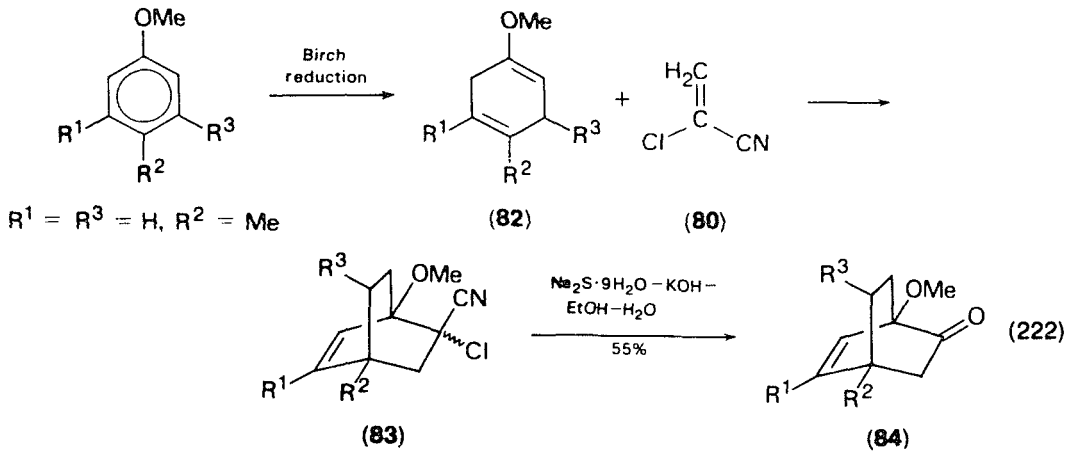


R^1 = $SiMe_3$, EtO—CH=CH—; R^2 = Me;
R^3 = Ph; R^4 = H, $SiMe_3$

$H_2C{=}C(X)(X')$ have been created which permit the allowed [4 + 2]addition reaction. One such synthon is acrylonitrile as a ketene equivalent. Bartlett[365] found that 2-acetoxyacrylonitrile (**77**) indeed forms a [4 + 2]adduct (**78**) with cyclopentadiene (**76**), which can be transformed into the norbornenone **79** by hydrolysis; this reaction may be regarded as the first example of a ketene equivalent (equation 220). The reagent **77** was then successfully applied to other diene systems[366–368].

It was soon realized[359,369–373] that the synthon 2-chloroacrylonitrile (**80**) was even more convenient; the [4 + 2]adduct (**81**) could be readily prepared, and could be transformed into the ketones (**79**) under milder conditions (equation 221). 2-Chloroacrylonitrile (**80**) has been used widely as a ketene equivalent for the synthesis of difficultly accessible ketones[343], as demonstrated in a recent preparation of

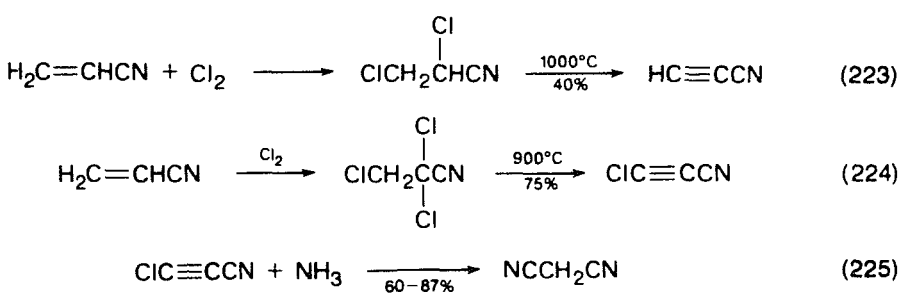




1-methoxybicyclo[2.2.2]oct-5-enone (**84**) by hydrolysis of the adduct (**83**) derived from the dehydroanisole derivative (**82**) and (**80**) (equation 222)[374].

4. *Cyanoacetylene and chlorocyanoacetylene from acrylonitrile*

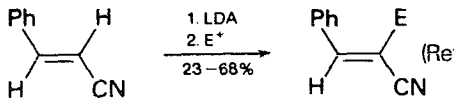
A general review of the chemistry of α-cyanoacetylenes has been published[375]. Chlorination of acrylonitrile, and pyrolysis of the resultant intermediates affords[376] cyanoacetylene (equation 223) or chlorocyanoacetylene (equation 224). Passing gaseous ammonia through a dilute solution of chlorocyanoacetylene in dichloromethane at 30°C leads to the formation of malononitrile in 60–87% yield (equation 225)[376]. Pyrolysis of a mixture of carbon tetrachloride and an excess of acrylonitrile in a quartz tube at 800–1000°C produces 3,3-dichloroacrylonitrile (50–60%); this reacts with a variety of nucleophiles, such as aliphatic alcohols, phenol, mercaptans and amines in the presence of a base, to give the corresponding 3,3-disubstituted acrylonitriles (42–83% yield)[377].



5. *α-Metalated nitriles in organic synthesis. Reactions of allylic nitrile anions*

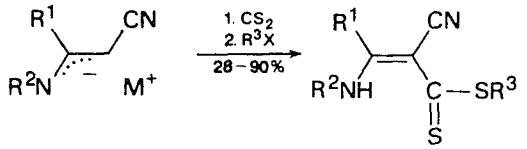
Metalation (deprotonation) of α,β-unsaturated nitriles can be accomplished with the strong bases frequently employed in carbanion chemistry, such as butyllithium or lithium hydride; however, the most effective and seemingly most popular reagent is lithium diisopropylamide (LDA). The α-metalated, unsaturated nitriles are usually not isolated, but subjected to reaction in the same vessel; hence, deprotonation with a strong base gives a carbanion that allows the formation of bonds by alkylation, acylation and condensation[378]. Thus, 2-lithioacrylonitriles[377,379] and similar cyanovinyl

anions[380–386], or primary nitrile anions[387], are important synthetic intermediates, particularly in reactions with electrophiles (e.g., alkyl halides, aldehydes and ketones). The examples below shown in equations (226)–(230) illustrate the scope of this use-

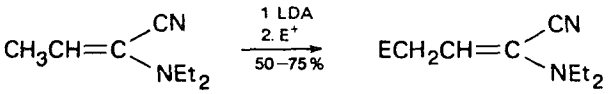


(Refs. 381 and 382) (226)

E = R (from RX), E = CH(OH)R from RCHO (in products)

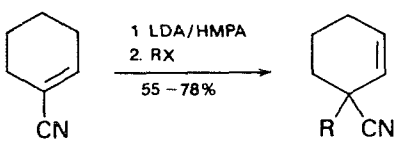


(Ref. 383) (227)

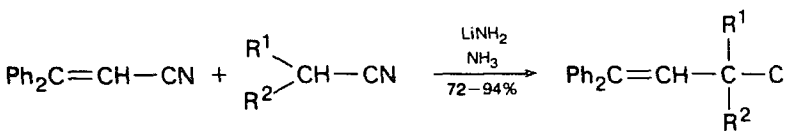


(Ref. 384) (228)

E = R from alkyl halides, epoxides, α,β-unsaturated ketones and Me_3SiCl (in products

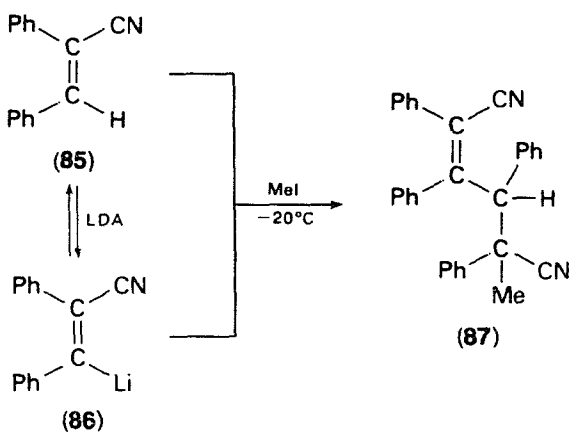


(Ref. 385) (229)



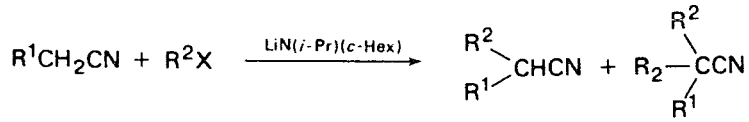
(Ref. 386) (230)

ful, synthetic method. In an interesting example[381], treatment of 2,3-diphenylacrylonitrile (**85**), at first with LDA at − 65°C (to give the salt **86**) and then with methyl iodide gives, surprisingly, the 2-methyl Michael adduct (**87**), and not the methylation product expected from the 2-lithio derivative (**86**) (equation 231).



(231)

a. Alkylation of primary nitriles. Use of lithium *N*-cyclohexyl-*N*-isopropylamide as the strong base for the alkylation of primary nitriles (i.e. their anions) with alkyl halides mainly gives secondary nitriles, together with some tertiary nitriles (equation 232)[387].

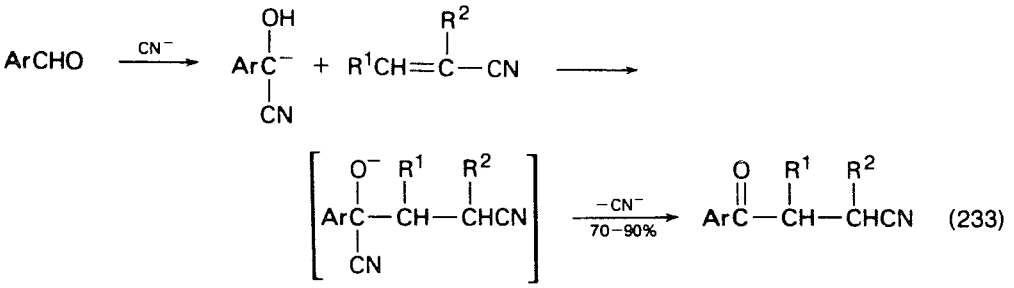


(232)

$R^1 = R^2$ = alkyl, arylalkyl, aryl

X = Cl, Br, I

b. Addition of aldehydes to acrylonitriles. One of the longest known reactions of organic chemistry is the benzoin condensation[388a] in which aromatic[388b] or heteroaromatic[388c] aldehydes are transferred into acyloins (α-hydroxy ketones) in a CN^--catalysed process. The mechanism involves the formation of a carbanion, facilitated by the use of aprotic solvents. The benzoin-type reaction has been extended to include a catalysed addition of aldehydes to α,β-unsaturated nitriles. Thus, 4-ketonitriles may be obtained by addition of aromatic and heterocyclic aldehydes to α,β-unsaturated nitriles (e.g. acrylonitrile) under catalysis by cyanide ions in dimethyl sulphoxide (equation 233)[388b].

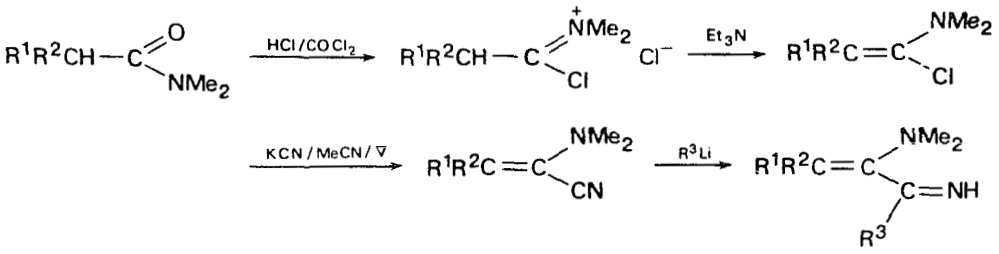


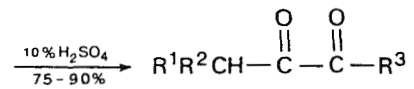
(233)

6. Useful synthetic transformations of unsaturated nitriles

a. Conversion of amide → α-cyanoenamine → α-diketone. The utility of α-cyanoenamines as reactive intermediates for the synthesis of α-diketones has been recognised[187]. Indeed, starting with amides and proceeding via an α-cyanoenamine intermediate, the synthesis of α-diketones has been achieved (equation 234)[187].

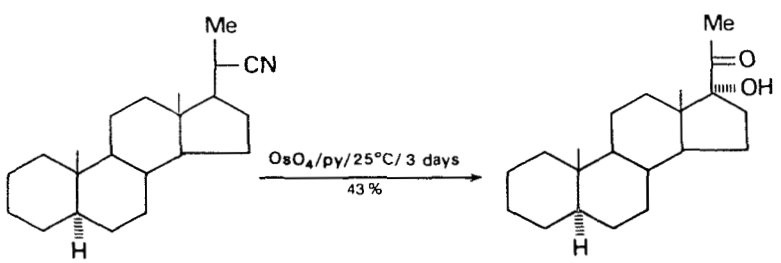
b. Hydroxylation of α,β-unsaturated nitrile steroids with osmium tetraoxide. Watt and coworkers[389] have found that the hydroxylation of α,β-unsaturated nitriles in various steroid systems, using stoichiometric amounts of osmium tetraoxide, furnishes α-hydroxy ketones or aldehydes in moderate yields (range 10–69%) (equations 235–237). The hydroxylation of α,β-unsaturated nitrile steroids with osmium tetraoxide has been compared with that of potassium permanganate, and differences pointed out.



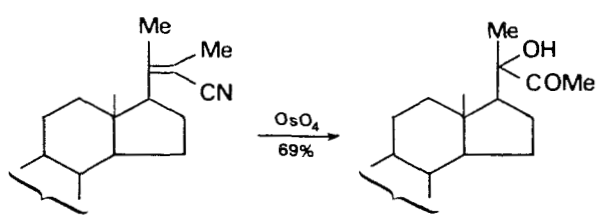


(234)

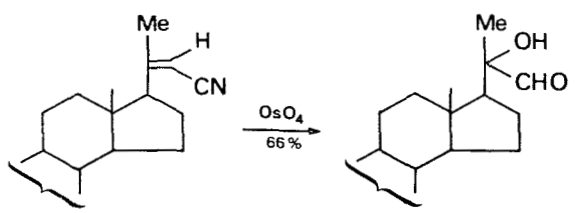
$R^1 = R^2 = Me$; $R^1 = Et$, $R^2 = Ph$;
$R^1 = Me$, $R^2 = Cl$; $R^1 = Me$, $R^2 = H$;
$R^1 = Ph$, $R^2 = H$



(235)



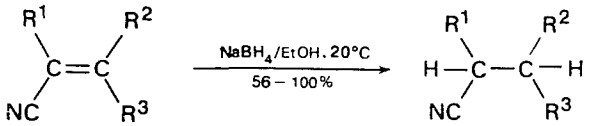
(236)



(237)

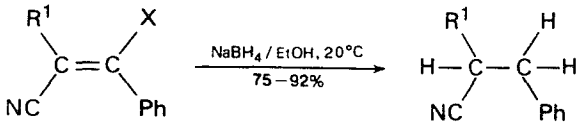
7. α,β-*Reduction of conjugated nitriles*

Catalytic hydrogenation of nitriles[390] may give rise to a number of products, which include alcohols, aldehydes, amides, primary, secondary and tertiary amines, hydrocarbons and imines. In several methods α,β-unsaturated nitriles may be converted into saturated nitriles without affecting the cyano group, e.g. by adding sodium borohydride to a solution of either cyanoalkene (equations 238,239; 241 and 242) or cyanoalkyne (equation 240) in ethanol. With cyanoalkenes (equation 239), reduction



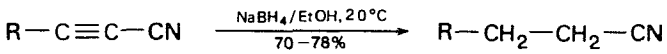
(238)

R^1 = Ph, 4-$O_2NC_6H_4$
R^2 = H, Ph, CN
R^3 = H, Ph



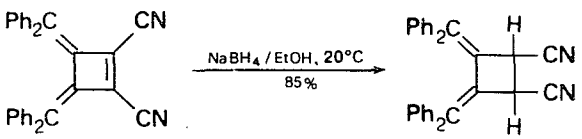
(239)

X = NO_2, MeO

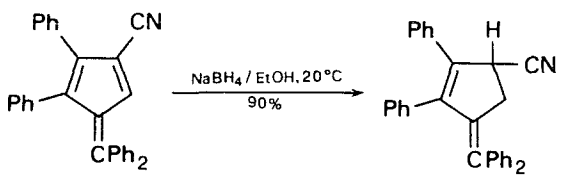


(240)

R = Ph, 2-phenanthryl

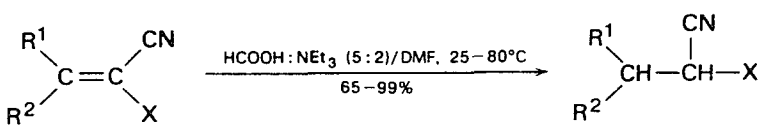


(241)



(242)

is accompanied by substitution with hydrogen of the nitro and methoxyl groups which are bound to the olefinic carbon atom (in contrast to the $NaBH_4$ reduction of a nitroalkene to a nitroalkane)[391]. Recently[392] it has been reported that an azeotrope composed of 2:5 triethylamine–formic acid, with *N,N*-dimethylformamide as the solvent, is suitable for selective reduction of carbon–carbon double bonds conjugated with two cyano, or other electron-withdrawing groups. Thus α,β-unsaturated nitriles can be selectively reduced to give the saturated nitriles (equation 243)[392].



(243)

R^1 = Et, Ph
R^2 = H, Me, Et, $PhCH_2$
R^1 R^2 = —$(CH_2)_5$—
X = CN, COOEt, SO_2Ph

a. Reductive addition via copper(I) trialkylmethylborates. By treatment of copper(I) trialkylmethylborates (**88**) with acrylonitrile, saturated alkyl cyanides (**89**) are obtained (equation 244)[393].

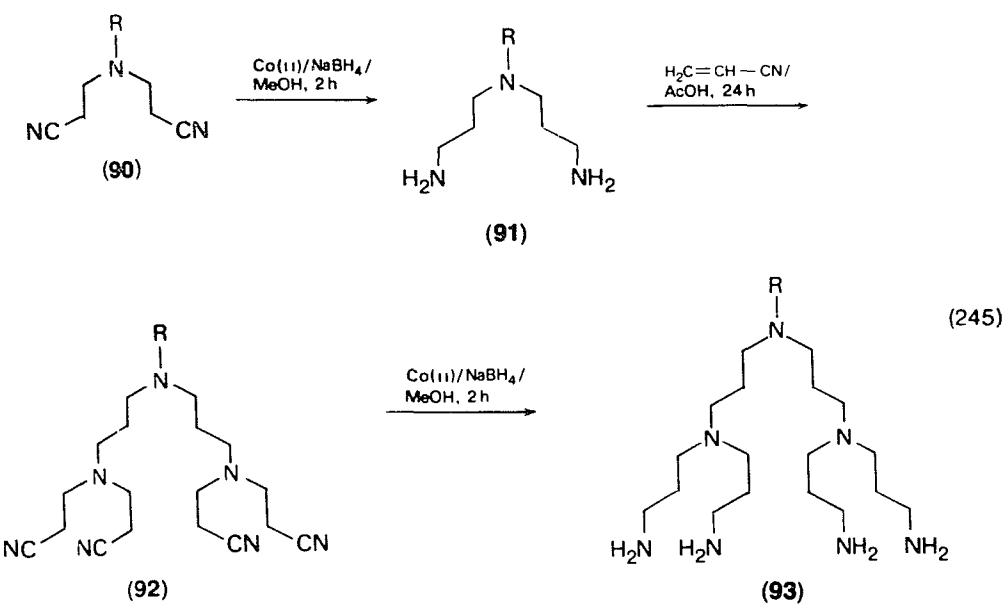
$$R_3B + MeLi + CuX \xrightarrow{THF,\ 0°C} \underset{(88)}{[R_3B{-}Me]Cu} \xrightarrow[19-93\%]{\substack{1\ H_2C{=}CH{-}CN \\ 2.\ NaOH/H_2O_2}} \underset{(89)}{RCH_2CH_2CN} \qquad (244)$$

R = alkyl

b. Reduction of the cyano group. Synthesis of novel 'cascade' molecules. For the construction of *large* molecular cavities and pseudo cavities that are capable of binding ionic guests or molecules (as complex or inclusion compounds) in a host–guest interaction[394], synthetic pathways allowing frequent repetition of similar steps would be advantageous.

Recently, Buhleier, Wehner and Vögtle[395] made use of this 'repeating-step' principle in the synthesis of 'cascade-like' structures, and, furthermore, in the synthesis of cyclic, polyaza compounds having a cavity of an appreciable size.

Reaction of monoamines (or diamines) in refluxing glacial acetic acid with acrylonitrile leads, via cyanoethylation, to the annexation of a pair of 'arms' per amino group (to give the oligonitrile **90** (equation 245). After reducing the nitrile groups[396] to amine groups (**91**), repetition of the acrylonitrile addition yields the lengthened 'cascade' molecule (**92**) which, on reduction to polyamines (**93**), or hydrolysis to polycarboxylic acids, should give novel complexons. By reacting monocycles of type (**94**) with acrylonitrile (or glycolonitrile) to form dinitriles, followed by reduction, and reaction of the product with dicarboxylic acid dichloride under high dilution, a new bicyclic compound (**97**) is obtained via intermediates (**95**) and (**96**); repetition of the synthetic sequence yields a tricyclic system (**98**) (equation 246)[395].



(245)

(94) (95) $n = 1, 2$ (96) (97) (246) (98)

c. Pyrolysis of poly(acrylonitrile). Thermal degradation of poly(acrylonitrile) $[-CH_2CH(CN)-]_n$, produced by addition polymerization of acrylonitrile to polymeric carbon has been studied and reviewed by Fitzer[397a].

N. Cyanomethylation via Acetonitrile

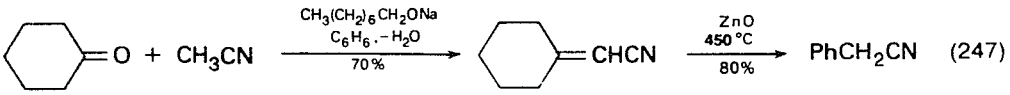
Cyanomethylation consists of a series of reactions leading to the extension of the carbon chain by two carbon atoms, or by such groups as $-CH_2CN$, $=CHCN$, or $\equiv CCN$. The procedures for the conversion of carbonyl compounds into higher derivatives by chain extension with one, two or more carbon atoms is an important, organic methodology today[1,142].

The synthetic application of polymetalated nitriles, e.g. *gem*-dianions from acetonitrile or arylacetonitrile, with regard to acylation reactions, has been reviewed by Kaiser and coworkers[397b]. Monolithiated acetonitrile (H_2LiCCN) is found, from *ab initio* calculations, to have three different structures[397c].

1. Nitriles by two-carbon elongation via an acetonitrile anion, e.g. $\bar{C}H_2CN$

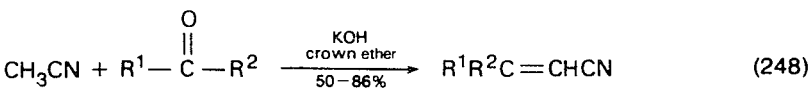
By two-carbon elongation nitriles may be prepared via acetonitrile or α-substituted acetonitrile anions; indirect procedures involving displacement or substitution may also be used. When the enolate of acetonitrile, e.g. the carbanion $\bar{C}H_2CN$ or $R^1R^2\bar{C}CN$[398] is generated by bases, amid bases (LDA or lithium hexamethyldisilazide) or naphthalene radical anions, it adds, via an aldol reaction to a wide variety of aldehydes and ketones, to give saturated or unsaturated nitriles containing two more carbon atoms. This reaction supplements cyanoethylation via acrylonitrile; however, the mechanism of C—C coupling in the two reactions may be different[7,142]. Reactions of tertiary carbanions [e.g. $(CH_3)_2\bar{C}CN$], generated by LDA in tetrahydrofuran below 0°C, have been reported[399].

a. Cyclohexylideneacetonitrile. This can be prepared in cyclohexanone and acetonitrile by azeotropic distillation of water from the mixture at ~80°C, if sodium octoxide is used as the catalyst. Benzyl cyanide can be obtained from the product by aromatization catalysed by zinc oxide (equation 247)[400a].



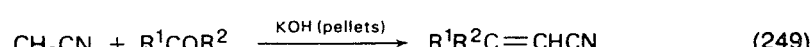
(247)

b. α,β-*Unsaturated nitriles.* Unsaturated nitriles may be obtained by condensation of aromatic or aliphatic aldehydes or ketones with acetonitrile in the presence of powdered potassium hydroxide and 18-crown-6 ether (equation 248)[156], or in the presence of potassium hydroxide alone (equation 249)[147].



(248)

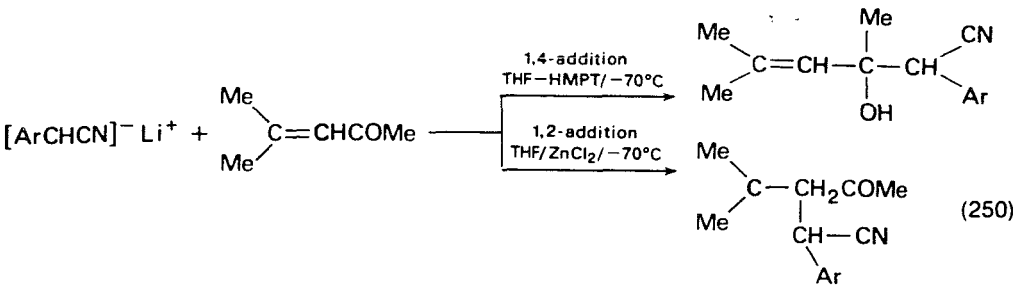
R^1 R^2 = alkyl, aryl, H



(249)

R^1 = alkyl, aryl
R^2 = alkyl

c. Selective 1,2- or 1,4-addition of arylacetonitrile anions to mesityl oxide. Lithiated arylacetonitriles react with some α-enones to give mixtures of 1,2- and 1,4-addition products in THF, but only 1,4-addition products in THF–HMPT (equation 250)[400b].

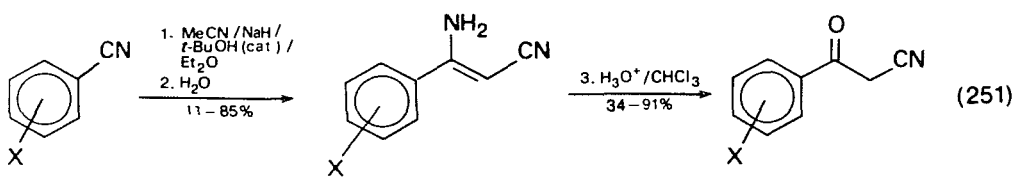


(250)

Ar = Ph, *p*-$MeOC_6H_4$, *m*-ClC_6H_4

Lithiated arylacetonitriles and mesityl oxide at −70°C in THF yield the 1,4-adducts[400c]. However, in the presence of zinc chloride, the allylic alcohols resulting from 1,2-addition are formed exclusively. Electronic effects of substituents on reaction products are observed, some contrary to Hünig and Wehner's findings[400b] who have studied similar addition reactions.

d. Benzoylacetonitrile. An improved procedure for the preparation of benzoylacetonitrile from benzonitriles involves cyanomethylation via acetonitrile; the intermediate 3-aminocinnamonitrile is then hydrolysed to the product (equation 252)[401].



(251)

e. Tritylation of weak carbon acids. The tritylation of molecules containing weakly activated hydrogen atoms has been effected by using the trityl cation in the presence of a sterically hindered base lacking nucleophilic properties, e.g., 2,4,6-collidine. This method permits, for the first time, direct tritylation of such weakly acidic compounds as acetonitrile or acetone (p*K* 20–25) in high yield (equation 252)[402].

$$Ph_3C^+ PF_6^- + CH_3CN \xrightarrow[91\%]{2,4,6\text{-collidine}} Ph_3C{-}CH_2CN \qquad (252)$$

f. Addition of acetonitrile to unsaturated nitro compounds. Acetonitrile, in the presence of a fluoride ion as the catalyst, adds across a conjugated system (a Michael addition) to produce a saturated acetonitrile derivative (equation 253)[403].

$$F^- + CH_3CN \rightleftharpoons {}^-CH_2CN + HF$$

$$^-CH_2CN + Ph_2C{=}CHNO_2 \xrightarrow{H^+} Ph_2C(CH_2CN)CH_2NO_2 \qquad (253)$$

45%

g. Addition of acetonitrile via electrolysis. In the presence of triethylammonium iodide as supporting electrolyte and a platinum electrode, acetonitrile adds to trialkylborons to yield alkylacetonitriles in good yield (equation 254)[404b].

h. Vilsmeier formylation of acetonitrile. Acetonitrile reacts with the Vilsmeier complex to give 2-cyano-3-dimethylaminoacrolein (equation 255)[404b].

$$R_3B + CH_3CN \xrightarrow[>50\%]{\text{electrolysis } Et_3N^+ I^-, Pt-Pt} RCH_2CN \qquad (254)$$

$$H_3C-CN \xrightarrow[32\%]{1.\ +\ 2\,[Me_2N{=}CH-Cl]^+\ PO_2Cl_2^-;\ 2.\ +\ H_2O} \begin{matrix} Me \\ \diagdown \\ N-CH=C(CN)-CH=O \\ \diagup \\ Me \end{matrix} \qquad (255)$$

i. Novel silylation of acetonitrile. Trimethylsilyl trifluoromethanesulphonate reagent converts acetonitrile into tris(trimethylsilyl)acetonitrile and *N*,2,2-tris(trimethylsilyl)keteneimine (equation 256)[404c].

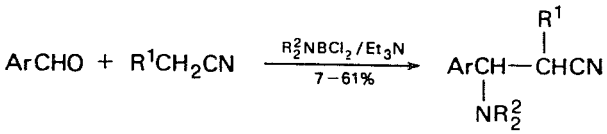
$$H_3C-C\equiv N \xrightarrow[Et_3N/\text{ether},\ 5^\circ C]{F_3CSO_2OSiMe_3} \underset{56\%}{Me_3Si-C(SiMe_3)_2-C\equiv N} + \underset{44\%}{(Me_3Si)_2C=C=N-SiMe_3} \qquad (256)$$

2. Reactions of substituted acetonitriles

a. Vicarious replacement of hydrogen by various α-substituted acetonitriles. Recently, Makosza and Winiarsky[405] have developed a new procedure by which a vicarious replacement of hydrogen in aromatic nitro compounds by acetonitrile derivatives can be achieved (equation 257). The product may be a mixture of *ortho* and *para*

$$XCH_2CN + \underset{X = PhS\ +\ \text{many others}}{\text{nitrobenzene}} \xrightarrow[2.\ HCl, H_2O]{1.\ NaOH/Me_2SO} \underset{50\%}{\text{2-nitrophenylacetonitrile}} + \underset{18\%}{\text{4-nitrophenylacetonitrile}} \qquad (257)$$

isomers; however, the preponderance of one isomer over the other may be controlled by various α substituents on the acetonitrile. Products containing a cyanomethyl group *ortho* to the nitro group cannot be readily prepared in other ways. The utility of these compounds as versatile starting materials in the sythesis of heterocycles is well established[406]. Other α-substituted acetonitriles have been found effective in two-carbon elongation reactions e.g. alkylacetonitrile (equation 258)[407], methoxyacetonitrile (equation 259)[408], methylthioacetonitrile (equation 260)[409], ethyl cyanoacetate (equation 261)[410], phenylacetonitrile (equation 262)[400] and cyanomethylcopper (equation 263)[411].



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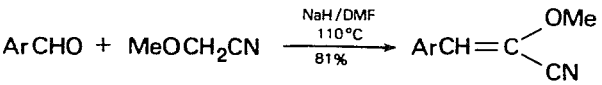

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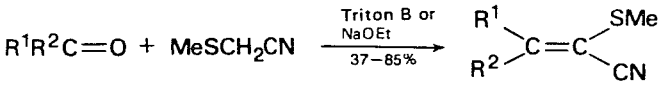
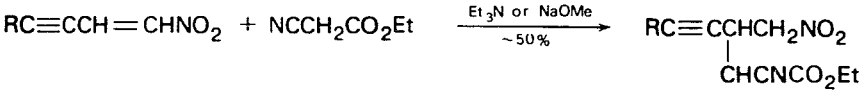
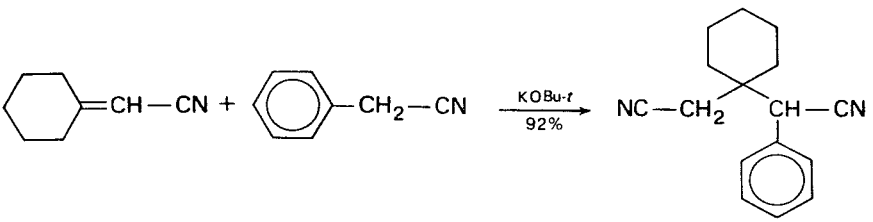


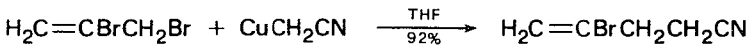
(260)



(261)

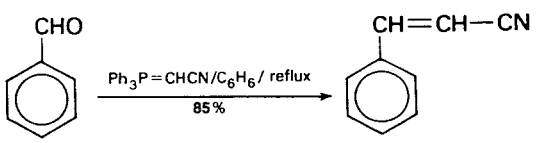


(262)

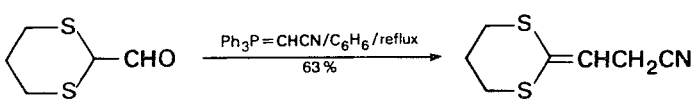


(263)

b. Additional methods. Additional methods for the introduction of the cyanomethylene group into an organic molecule involve reaction via cyanomethylenetriphenylphosphorane reagent (equations 264–266)[412–414], diethyl cyanomethylphosphonate reagent (equation 267)[415], phase-transfer catalysis (equation 268)[416] or a substitution reaction (equation 269)[417].



(264)



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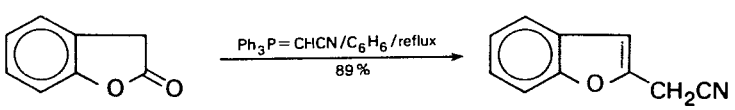
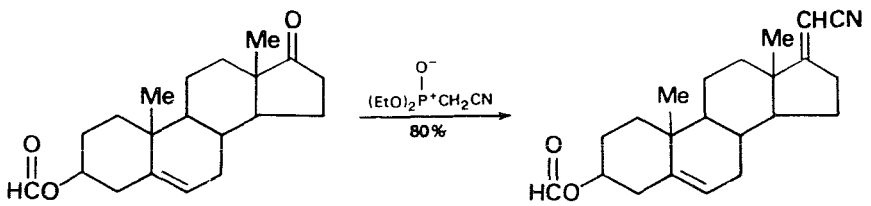
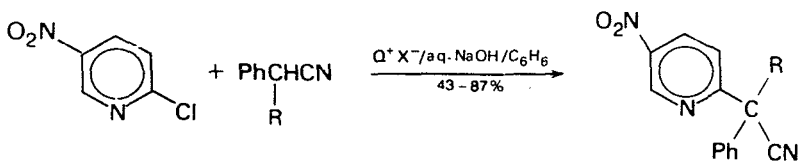


(266)

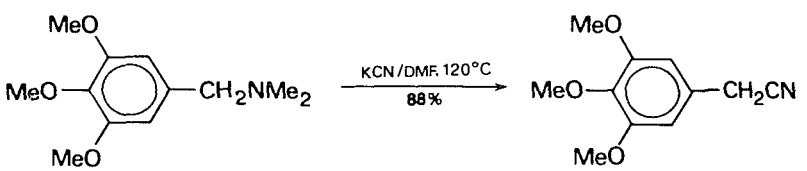


(267)



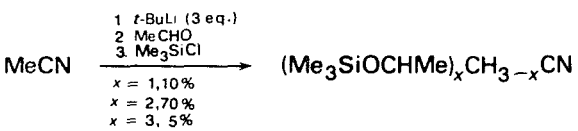
(268)

Q^+X^- = (−) Benzylcinchonidinium chloride

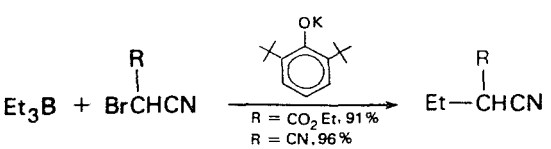


(269)

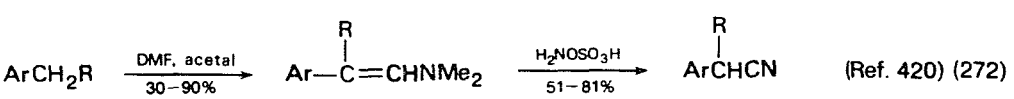
c. Special methods. Some special synthetic methods leading to useful cyanomethylene intermediates are shown in equations (270)–(274)[418–422].



(270)



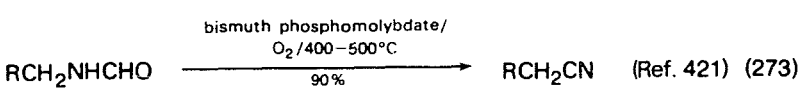
(Ref. 419) (271)



(Ref. 420) (272)

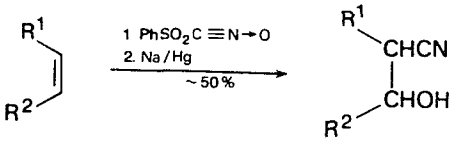
Ar = 4-pyridyl, subst. Ph

R = H, Me, alkyl, COOEt



(Ref. 421) (273)

R = Me

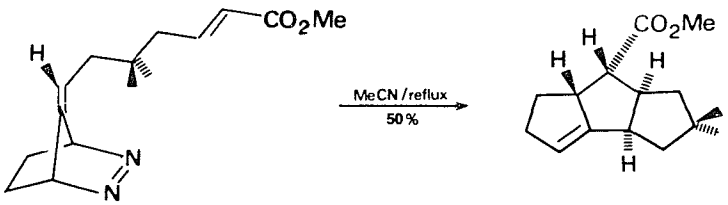


(Ref. 422) (274)

R^1, R^2 = alkyl, Ph, cyclic

d. Acetonitrile in thermal reactions. Warm acetonitrile[423] is a good medium for certain thermal, nitrogen-extrusion reactions (deazatizations)[424], leading to novel, skeletal rearrangements. For example, refluxing acetonitrile has been used for generation of the 1,3-diyl intermediate from a bicyclo azo compound; so using an intramolecular, diyl-trapping reaction, a regiospecific and stereospecific synthesis of a linearly fused tricyclopentanoid (antitumour agent) has been achieved (equation 275)[425]. Similar nitrogen extrusion with rearrangement has recently been reported for 7-isopropylidene-2,3-diazabicyclo[2.2.1]hept-2-ene in warm acetonitrile[426].

A homoallylic rearrangement of 19-iodocholesterol is observed in the presence of warm acetonitrile (equation 276)[427a]. Conversion of acids into nitriles by reaction with acetonitrile at high temperatures (150–300°C) has been reported in the patent literature[427b].



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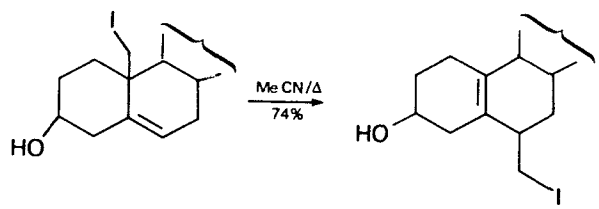


(276)

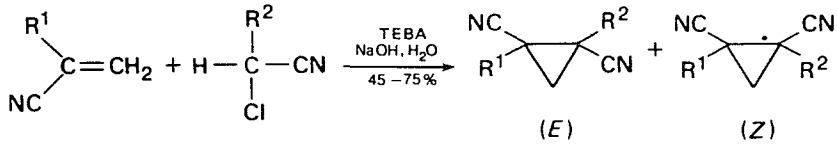
O. Synthesis and Alkylation of Nitriles under Phase-transfer Catalysis

1. Synthesis of nitriles

Among modern methods for the synthesis and alkylation of nitriles, methods employing phase-transfer conditions are of the utmost importance; considerable progress in this direction is attributable to results obtained by Makosza[428–430]. The general topic of phase-transfer catalysis has been thoroughly reviewed[428–434].

a. Catalytic synthesis of cyclopropanes. Cyclopropanes are formed by condensation of α-halocarbanions with electrophilic alkenes (e.g. acrylonitrile), e.g. in 50% sodium hydroxide with a catalytic amount of benzyltriethylammonium chloride (TEBA) (equation 277). Two isomeric cyclopropanes are formed, but the (*E*) (*trans*) isomer preponderates[435]. By addition of benzene[436], to afford an emulsion, hydrolysis in the aqueous alkaline solution is suppressed.

The same system[435] has also been used for the generation of carbanions from α-halonitriles in a modified Darzens reaction for the preparation of, for example,



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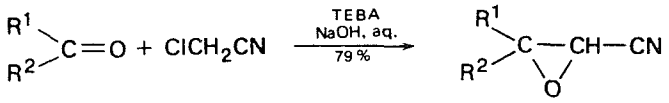
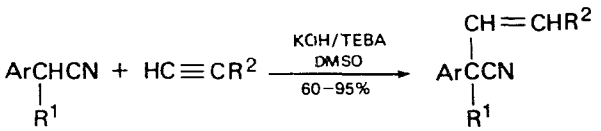


(278)

α-cyanoepoxides (equation 278)[437]; these are important intermediates for the synthesis of quinoxalines.

b. Synthesis of α-vinylnitriles. The anion of a nitrile generated with solid potassium hydroxide adds to acetylenic bonds with TEBA in dimethyl sulphoxide to afford 2-vinylnitriles in 60–95% yield (equation 279)[438a].

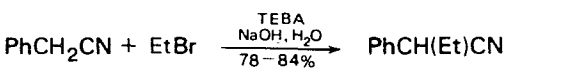


(279)

c. Phase-transfer photochemistry. Photochemical nucleophilic substitution of CN^- takes place using 18-crown-6 ether to dissolve KCN in anhydrous acetonitrile (e.g. biphenyl → 4-cyanobiphenyl, 50%). The photocyanation of aromatic compounds can also be carried out with another phase-transfer agent, tetrabutylammonium cyanide[438b].

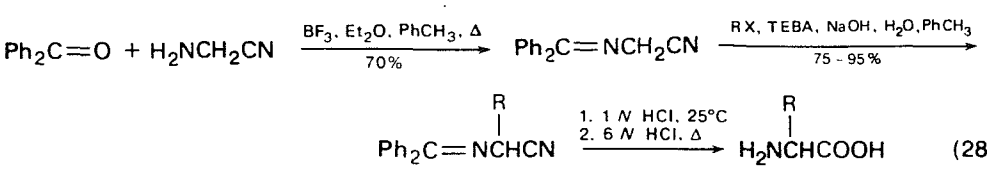
2. Alkylation of nitriles

A kinetic study[439] of the ethylation of phenylacetonitrile under phase-transfer conditions in the presence of tetrabutylammonium bromide (TEBA) has given results consistent with an interfacial type of process wherein the quaternary ammonium salt functions as a transfer agent that resides primarily in the organic phase. A general method for the alkylation of active methylene groups has been described in detail (equation 280)[440].



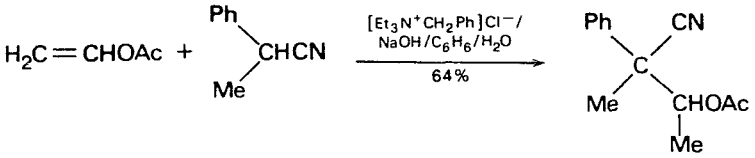
(280)

a. Indirect alkylation of amino acids. The indirect alkylation of glycine first involves the preparation of a Schiff base (equation 281), which is an active methylene compound. This imine can then be alkylated under the usual phase-transfer conditions to give an enaminonitrile intermediate; which is hydrolysed to the alkylated glycine[441].



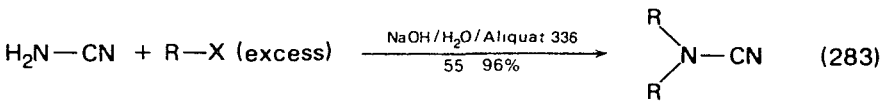
(281)

b. The Michael reaction. Certain Michael-type reactions of enol esters with 2-phenylpropionitrile may be conducted in a two-phase system containing TEBA (equation 282)[442a].



(282)

c. Catalytic two-phase alkylation of cyanamide. Cyanamide can be effectively alkylated with mono- and di-haloalkanes in the presence of 50% aqueous sodium hydroxide and a catalytic amount of Aliquat 336 [the so-called, catalytic, two-phase (CTP) system[435,436]]. Thus, cyanamide with an excess of alkyl halides yields dialkylcyanamides (equation 283). The use of 1,ω-dihaloalkanes or *o*-bis(bromomethyl)benzene constitutes a particularly useful method for the synthesis of such cyclic cyanamide derivatives as 1-cyanopyrrolidine, 1-cyanopiperidine, 1-cyanohexahydroazepine and 2-cyano-1,3-dihydroisoindole (equation 284)[442b].



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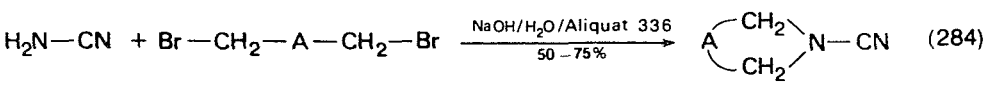
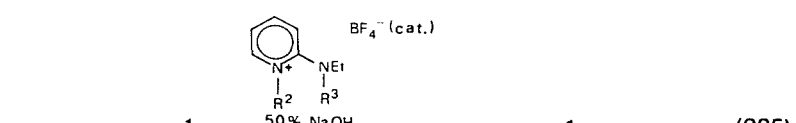


(284)

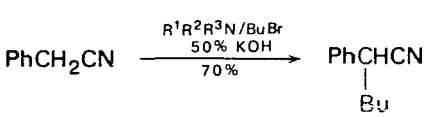
A = $-(CH_2)_n-$ ($n = 2-4$)

d. Additional phase-transfer reactions. A two-phase system for the *N*-alkylation of 2,6-dicyano-1,4-dihydropyridines with benzyldodecyldimethylammonium bromide[443], or alkylation reactions with two-phase catalysts, namely, 2-dialkylaminopyridinium salts (equation 285)[444], has been reported; also, similar alkylations of various primary, secondary and tertiary amines (equation 286)[445]. Additional pertinent reactions are shown in equations (287)–(293)[446–450].

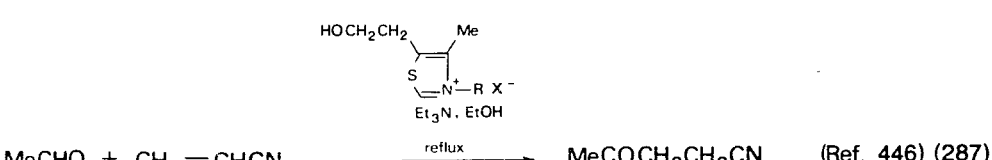


(285)

R^1 = Et



(286)



(Ref. 446) (287)

$$NCCH_2SePh \xrightarrow[81-96\%]{RCH_2X,\ TBA} NCCH(SePh)CH_2R \qquad \text{(Ref. 447) (288)}$$

R = Me, primary alkyl, allyl or benzyl

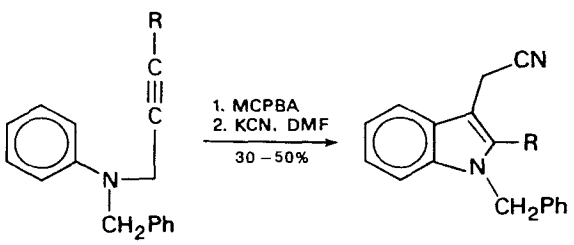
$$Ph_2C{=}NCH_2CN + RX \xrightarrow[50\%\ NaOH,\ toluene]{TEBA} Ph_2C{=}NCHCN \xrightarrow[75-95\%]{H_3O^+} H_2NCHCOOH$$

(Ref. 448) (289)

R = primary or secondary alkyl, Bz

$$NCCH_2CN + Br(CH_2)_nBr \xrightarrow[n = 4,\ 60\%]{DBU/DMF} (CH_2)_n C(CN)_2 \qquad \text{(Ref. 449) (290)}$$

DBU = 1,5-diazabicyclo[5.4.0] undecene-5



(Ref. 450a) (291)

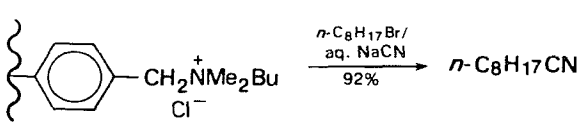
R = H, Me
MCPBA = *m*-chloroperbenzoic acid

$$RCHO \xrightarrow[44-71\%]{KCN/Ac_2O,\ H_2O/CH_2Cl_2,\ Q^+X^-} R{-}\overset{+}{C}H(OAc)(CN) \qquad \text{(Ref. 450b) (292)}$$

Q^+X^- = (–) Benzylcinchonidinium chloride

$$n\text{-}C_8H_{17}Br \xrightarrow[95\%]{CN^-,\ \text{Ⓟ}{-}(CH_2)_3{-}\overset{+}{P}Bu_3Br^-} n\text{-}C_8H_{17}CN \qquad \text{(Ref. 450c) (293)}$$

e. Three-phase catalytic reactions. Three-phase, catalytic *C*-alkylation of nitriles has been discussed[451]. The use of a solid-phase catalyst (e.g. polystyrene resin) involves a triphase reaction system (equation 294)[452].



(294)

Polystyrene resin

P. Synthesis of Cyano Compounds having such Functional Groups as O=C—CN, C=N—CN and S=C—CN

1. *Cyano compounds having as O=C—CN, O=C—CH_2CN and O=C—CH_2CH_2CN groups*

There are but few satisfactory procedures for the synthesis of 2-ketonitriles (acyl cyanides). The methods most preferred[453] consist in the addition of copper(I) cyanide to an acid chloride either in refluxing acetonitrile or benzonitrile, or in ether at 10°C in the presence of lithium iodide (equation 295).

$$R-\overset{\overset{O}{\|}}{C}-Cl + CuCN \xrightarrow[50-77\%]{\text{A: boiling acetonitrile or benzonitrile; B: ether/LiI 10°C}} R-\overset{\overset{O}{\|}}{C}-CN \qquad (295)$$

a. Aroyl cyanides. These can be readily prepared by reaction of the chlorides with sodium cyanide in dichloromethane–water, by use of a phase-transfer catalyst (equation 296)[454]. Both the acid chloride and the product are present in the organic phase, and thus protected from hydrolysis.

$$ArCOCl + NaCN \xrightarrow[\sim 60\%]{Bu_4N^+, Br^-,\ CH_2Cl_2, H_2O} ArC(=O)CN + NaCl \qquad (296)$$

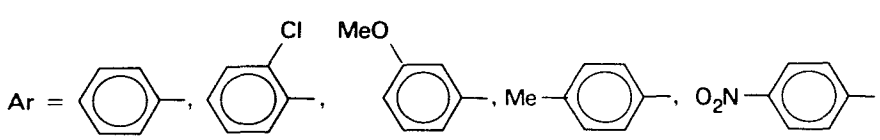
Anhydrous thallium(I) cyanide has been used for the preparation of α-ketonitriles (e.g. benzoyl cyanide), cyanoformates and trimethylsilyl cyanide (equations 297–299)[455]. Aromatic aldehydes can readily be converted, via their *S,S*-acetals, into benzyl cyanides; this involves treatment with mercury(II) cyanide and iodine, followed by bromination, and oxidative hydrolysis with dimethyl sulphoxide (equation 300)[456a]. A recent report[456b] has described a convenient one-step synthesis of aroyl cyanides from arylglycoxals or phenacyl bromides in 70–97% yields.

$$PhCOCl + TlCN \xrightarrow[74\%]{\text{ether}} PhCOCN \qquad (297)$$

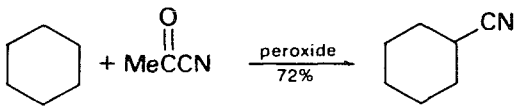
$$ClCOOMe + TlCN \xrightarrow[66\%]{MeCOOC_2H_5} NCCOOMe \qquad (298)$$

$$Me_3SiCl + TlCN \xrightarrow[84\%]{} Me_3SiCN \qquad (299)$$

$$Ar-\underset{\underset{SEt}{|}}{\overset{\overset{SEt}{|}}{CH}} \xrightarrow[68-93\%]{I_2/Hg(CN)_2/MeCN} Ar-\underset{\underset{SEt}{|}}{CH}-CN \xrightarrow[\sim 100\%]{Br_2/CCl_4,\ 40°C} \left[Ar-\underset{\underset{SEt}{|}}{\overset{\overset{Br}{|}}{C}}-CN \right] \xrightarrow[70-90\%]{DMSO,\ 20-55°C} Ar-\overset{\overset{O}{\|}}{C}-CN \qquad (300)$$

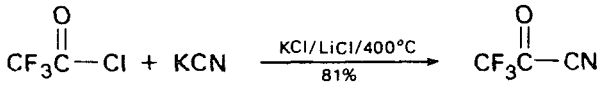
Ar = 

b. Benzoyl cyanide as an acylating agent. This has been used for the selective benzoylation of carbohydrates[457], and of steroid alcohols[458], allowing the selective derivatization, and separation, of epimeric hydroxy steroids[459]. Acetyl cyanide has been used as a special cyanating reagent for saturated hydrocarbons, e.g. cyclohexane (equation) 301)[460].

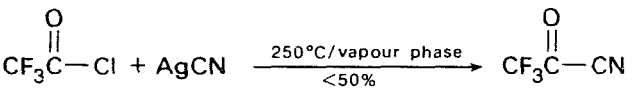


(301)

c. Trifluoroacetyl cyanide. This is obtained from trifluoroacetyl chloride (equations 302[461] and 303[462a]).

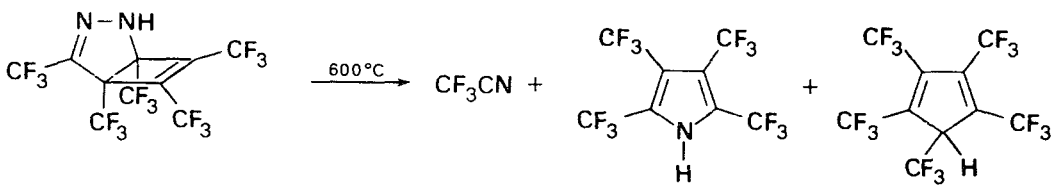


(302)



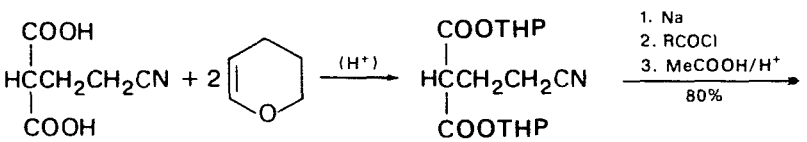
(303)

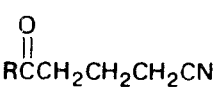
d. Trifluoroacetonitrile. As depicted, pyrolysis (600°C) transforms a perfluoropyrazoline derivative into a mixture whose dominant components are trifluoroacetonitrile and trifluorotetramethylpyrrole; the mixture also contains a 5*H*-perfluoropentamethylcyclopentadiene, a very strong fluorocarbon acid (equation 304)[462b]. 304)[462b].



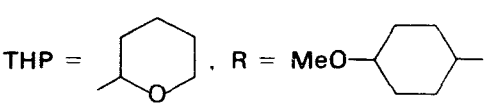
(304)

e. 4-Ketonitriles. 4-Acylbutanonitriles can be obtained by condensation of ethyl malonate with acrylonitrile, followed by the sequence of reactions shown in equation (305)[463].

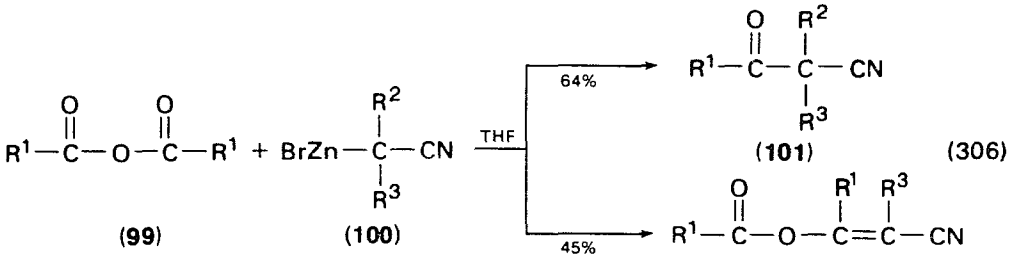




(305)



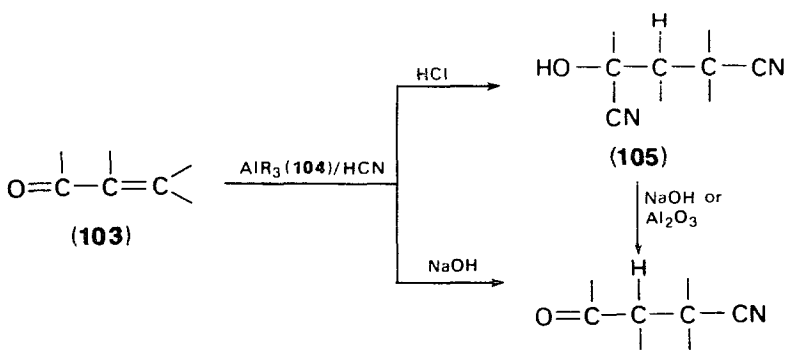
f. 3-Ketonitriles from carboxylic anhydrides. Carboxylic anhydrides (**99**) (R^1 = Me, Et) with the organozinc compound **100**, give rise either to a 3-ketonitrile (**101**), or to the enol ester, depending on the substitution of **100**. With $R^2 = R^3$ = Me the product is **101** and with R^2 = H, R^3 = *i*-Pr the product is the enol ester (**102**) (equation 306)[464].



(306)

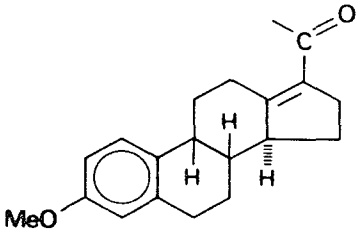
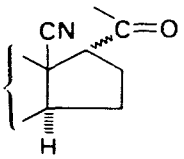
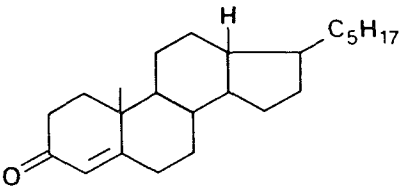
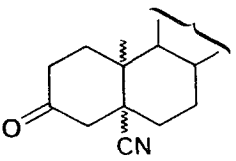
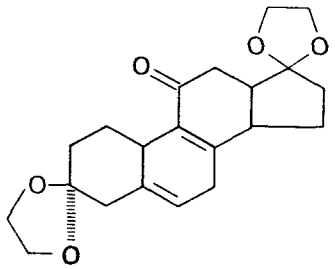
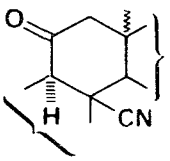
g. 3-Ketonitriles from α,β-unsaturated ketones via the Nagata reagent. α,β-Unsaturated ketones (**103**) (especially those derived from steroids) react with a hydrocyanation reagent prepared *in situ* from hydrogen cyanide and alkylaluminium compounds (**104**) [e.g. $AlEt_3$, $Al(i\text{-}Pr)_3$, $AlEt_2Cl$]. Processing with aqueous hydrochloric acid results in the formation of 1,3-dinitriles (**105**), whereas aqueous sodium hydroxide yields the β-kenotriles (**106**) directly (equation 307)[465].

h. 1,3-Diketonitriles via an ene reaction. In the ene synthesis, a variety of carbonyl compounds have been employed as enophiles[466], while only in a few examples does the carbonyl compound react as the ene component. For example, the formation of adducts in the reaction of β-oxo-*s*-triazine with acrylonitrile has been explained by an ene-synthesis mechanism involving hydrogen transfer from the enol of 3-oxo-*s*-triazine to a carbon atom of the enophile[467]. The same enol hydrogen transfer has also been found in the the thermal cyclization of unsaturated ketones[468]. A new example of the ene synthesis[469], in which enolizable 1,3-dicarbonyl compounds (e.g. **107**) act as ene components, is the reaction with carbonyl cyanide (**108**), a highly reactive enophile[466], to give the labile ene adduct **109**, which is isolated in the form of the etherate (equation

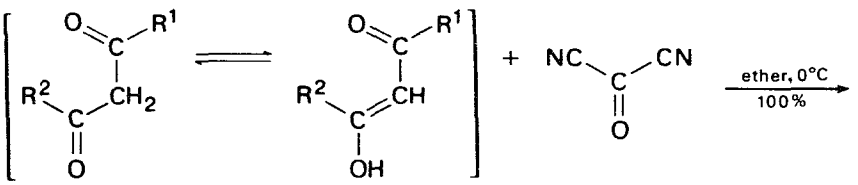


(307)

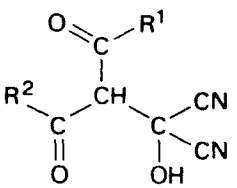
AlR_3 = $AlMe_3$, $AlEt_3$, $Al(i\text{-}Pr)_3$, $Al(i\text{-}Bu)_3$, $AlEt_2Cl$, $AlEtCl_2$

103	106	Yield (%) of 106
		>70
		100
		74

308). The reaction of a monoketone (as the ene component) with **108** has also been reported[470]. Other pertinent cyano preparations are shown in equations (309)–(312)[471–474].



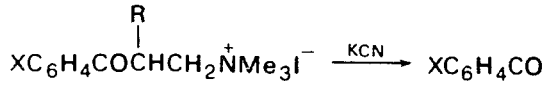
(107) (108)



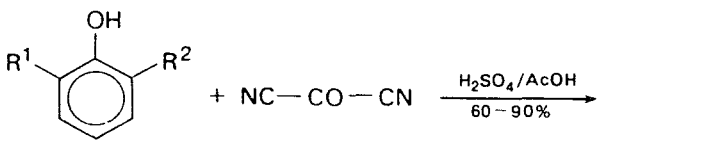
(109)

(308)

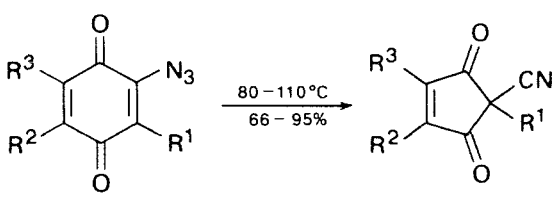
R^1	R^2
Ph	Ph
2,4,6-$Cl_3C_6H_2$	2,4,6-$Cl_3C_6H_2$
Me	Ph
CF_3	Ph
Me	Me
OEt	OEt



(Ref. 471) (309)

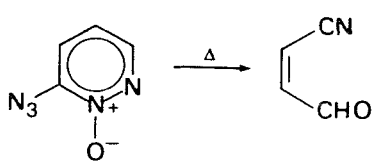


(Ref. 472) (310)



(Ref. 473) (311)

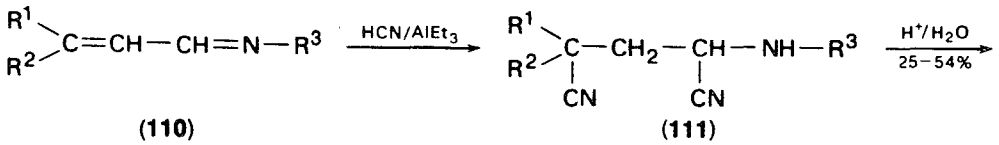
$R^1 = R^2$, R^3 = H or alkyl



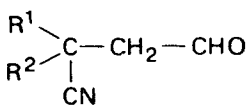
(Ref. 474) (312)

i. 3-Cyano aldehydes via hydrocyanation of alkylideneamines. 3-cyano aldehydes (**112**) cannot be prepared by hydrocyanation of α,β-unsaturated aldehydes using conventional methods. However, hydrocyanation of allylideneamine (**110**) with hydrogen cyanide–triethylaluminium (the Nagata reagent), followed by hydrolysis of the 1-amino-1,3-dicyanoalkanes **111** with aqueous oxalic acid, affords 3-cyano aldehydes (**112**) (equation 313)[475].

j. Cyanoformates from chloroformates. Primary and secondary alkyl, phenyl and benzyl cyanoformates (**114**) can be prepared in good yield by the crown-ether-catalysed reaction of solid potassium cyanide with the corresponding chloroformates (**113**) (equation 314)[476].

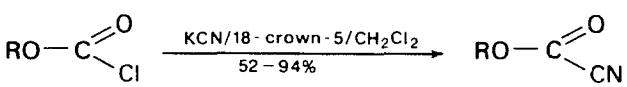


(110) (111)



(112) (313)

R^1	R^2	R^3	Yield of **112** (%)
H	Ph	*t*-Bu	25
H	Et	*t*-Bu	54
$-(CH_2)_5-$		*t*-Bu	54
$-(CH_2)_5-$		*c*-Hex	39

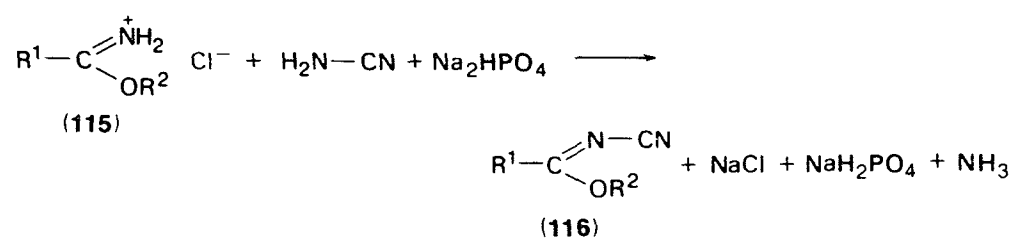


(113) (114) (314)

R = alkyl (not *t*-butyl), cycloalkyl, phenyl, benzyl

2. *Cyano compounds having the C=N—CN group*

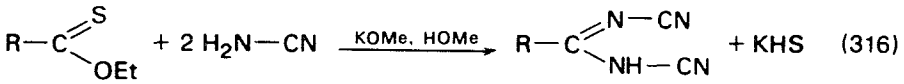
a. Alkyl N-cyanoimidates. Ethyl *N*-cyanoacetimidate (**116**; R^1 = MeCO, R^2 = Et) can be prepared (58% yield) by careful neutralization of the acid solution of ethyl *N*-acetimidate hydrochloride (**115**); R^1 = MeCO, R^2 = Et) and commercial 5% aqueous cyanimide to pH 6.5 with sodium phosphate; similarly, ethyl *N*-cyanobenzimidate (**116**; R^1 = PhCO, R^2 = Et) has been obtained in 65% yield (equation 315)[477].



(115) (116)

R^1 = MeCO, PhCO; R^2 = Et (315)

This method is based on the fact that there is a pH optimum for reactions involving nucleophilic attack on C=N carbon atoms and subsequent decomposition of the tetrahedral intermediate Y—C(—)—N<. Ethyl thiocarbonate with cyanamide in the presence of potassium methoxide affrods *N,N'*-dicyanocarboxamidines (equation 316)[483].

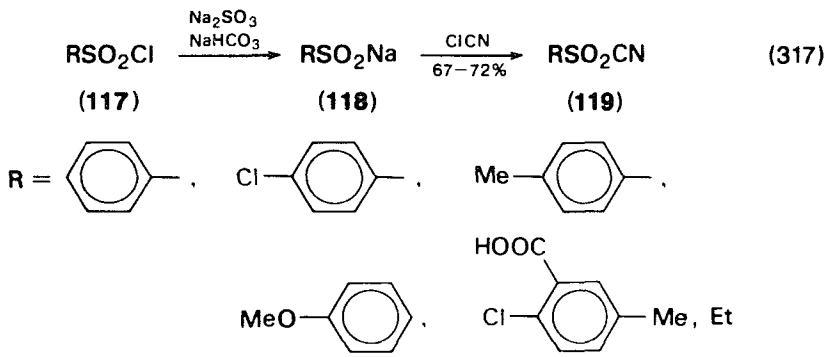


(316)

R = H, 68% yield
R = Me, 89% yield
R = Ph, 95% yield

3. *Cyano compounds having S=C—CN, O=S—CN, S—C=N—CN and O=C—S—CN groups*

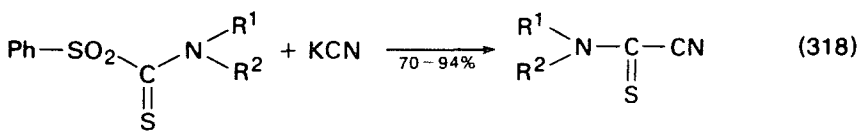
a. Sulphonyl cyanides. Aliphatic and aromatic sulphonyl cyanides (**119**) can be prepared by saturating the solution of a variety of sodium sulphinates (**118**) (prepared *in situ* by reduction of sulphonyl chlorides **117**) with cyanogen chloride at room temperature; the yields of the products are reported as 22–97%[478] or 67–72%[479] (equation 317).



(317)

(**117**) (**118**) (**119**)

b. Cyanothioformamides from C-sulphonylthioformamides. Treatment of *N,N*-dialkyl(aryl)-substituted *C*-sulphonylthioformamides (**120**) with potassium cyanide in 80% aqueous acetone for one minute produces the corresponding *N,N*-disubstituted cyanothioformamides (**121**) (equation 318)[480].



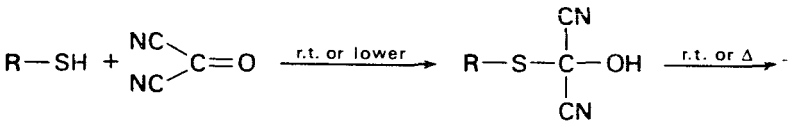
(318)

(**120**) (**121**)

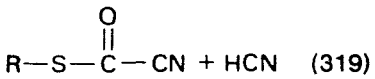
$R^1 = R^2 = Me$
$R^1—R^2 = —(CH_2)_4—$
$R^1 = Me,\ R^2 = Ph$

c. Cyanothioformates from carbonyl cyanide and thiols. Cyanothioformates (**125**) had not previously been reported in the chemical literature, but Leplawy and Redlinski[481a] found a simple method for preparation of this class of compound; the procedure involves the reaction of (the highly reactive) carbonyl cyanide (**123**)[482] with thiols

(122) via the dicyanohydrin intermediate **124** (actually isolated in the case of benzenethiol, **124**, R = Ph); elimination of hydrogen cyanide from **124** by gentle warming leads to the cyanothioformates **125** (61–84% yield) (equation 319). The preparation of thiocyanides via thiols has been reported as shown in equation (320)[481b].

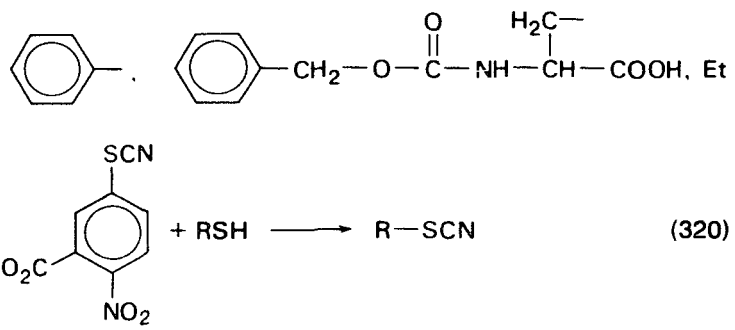


(122) (123) (124)



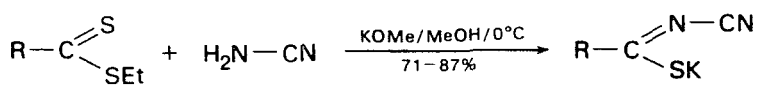
(125) (319)

R = *n*-Bu, *i*-Bu, *t*-Bu, *n*-C_5H_{11}, *n*-C_8H_{17}.



(320)

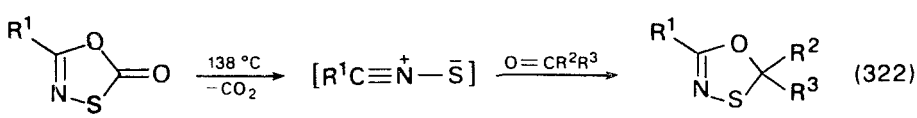
d. Potassium N-*cyanothiocarboximidates*. Ethyl dithiocarboxylates (**126**) react with cyanamide (**127**) and potassium methoxide in methanol at 0°C to give potassium *N*-cyanothiocarboximidates (**128**; R = Me, Ph). The analogous reaction of *O*,*S*-diethyl dithiocarbonate (**126**, R = OEt) affords potassium *N*-cyano-*O*-ethylthiocarbimidates (**128**, R = OEt) (equation 321)[483a]. 1,3,4-Oxathiazoles, on thermolysis, undergo



(126) (127) (128) (321)

R = Me, Ph, OEt

retro-1,3-dipolar cycloaddition to afford carbonyl compounds and nitrile sulphides. The latter may be trapped by cycloaddition with alkynes and nitriles (equation 322)[483b].



(322)

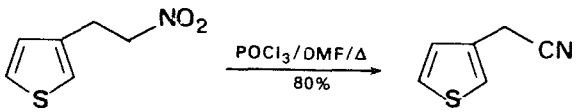
R^1 = Me, Ph

Q. Conversion of Nitroalkanes into Nitriles

1. *The conversion* $RCH_2NO_2 \rightarrow RC{\equiv}N$

The few methods[484,486] described in the literature generally either require severe conditions, or do not constitute a general method.

a. Vilsmeier–Haack reaction. When 3-(2-nitroethyl)thiophene is subjected to Vilsmeier–Haack formylation reaction[485], 3-acetonitrilothiophene is formed (equation 323), while 2-phenylnitroethane gives 90% yield of benzyl cyanide.

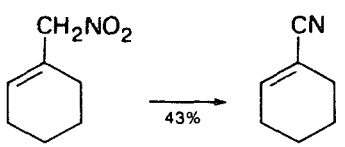


(323)

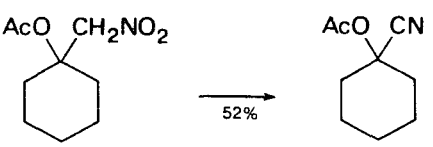
b. Phosphorus trichloride–pyridine and phosporus triiodide–triethylamine reagents. A mild conversion of nitroalkanes into nitriles can, for example, be accomplished in one step by reaction of the primary nitro compound with phosphorus trichloride and pyridine (40–75% yield) (equations 324–326)[487]. This method may also be used to convert allylic nitro compounds into α,β-unsaturated nitriles, and to prepare an aldehyde or a ketone from cyanohydrin acetates.

In an even milder procedure, phosphorus triiodide and triethylamine[53] were used for high-yield conversion of terminal nitroalkanes into nitriles (equation 327).

$$PhCH_2NO_2 \xrightarrow[60\%]{PCl_3,\ Py} PhCN \qquad (324)$$



(325)



(326)

$$RCH_2NO_2 + 2\ PI_3 \xrightarrow[82\%]{CH_2Cl_2/NEt_3} RC{\equiv}N \qquad (327)$$

$$R = C_9H_{19}$$

c. Trialkylamine–sulphur dioxide reagent. The trialkylamine–sulphur dioxide complex recently introduced for the dehydration of oximes to nitriles[28] has been successfully applied by Olah and coworkers[488] for direct conversion of primary aliphatic and arylaliphatic nitro compounds into nitriles. The authors[488] have also found that hexamethylphosphoric triamide brings about the foregoing conversion under similar reaction conditions (equation 328). The mechanism suggested[488] involves a nitrile oxide intermediate which, with an excess of the reagent, is deoxygenated to give the nitrile.

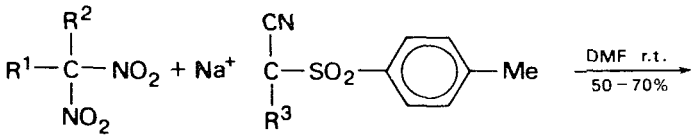
d. Reaction of dinitroalkanes with a 2-cyanosulphone salt. A new approach to the synthesis of nitriles from nitroalkanes has been described by Ono and coworkers[489a]. Thus, 2,2-dinitroalkanes (**129**) react with the sodium salt of 2-cyanosulphones (**130**) to

$$R^1CH_2NO_2 \xrightarrow[54-85\%]{(R^2)_3\overset{+}{N}SO_2^-/CH_2Cl_2 \text{ or } P(NMe_2)_3/Cl(CH_2)_2Cl} R^1CN \qquad (328)$$

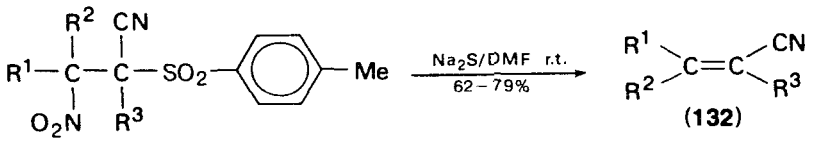
R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, PhCH=CH, 2-furyl, n-C_5H_{11}, n-C_6H_{13}, c-C_6H_{11}

R^2 = Me, Et

give the products (**131**), which are readily converted into a wide variety of α,β-unsaturated nitriles (**132**) by reductive elimination (equation 329)[489a].



(**129**) (**130**)



(**131**) (**132**) (329)

R^1 = Me

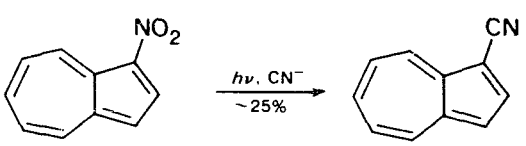
R^2,R^3 = alkyl

R^1-R^2 = $-(CH_2)_4-$, $-(CH_2)_5-$

e. Reaction of nitroalkenes with isocyanide. The reaction of a nitro olefin with isocyanide to give a cyanocarbamate is shown in equation (330)[489b].

$$R^1-CH=CH-NO_2 \xrightarrow{R^2NC} R^1-\underset{\displaystyle CN}{\underset{|}{CH}}-CONHR^2 \qquad (330)$$

f. Additional methods. Additional methods for the conversion of nitro compounds into nitriles include photoassisted displacement of the nitro group by the cyano group (equation 331)[490], reduction of an unusual nitro compound with sodium dithionate[491] and pyrolysis of nitroboranes[492].



(331)

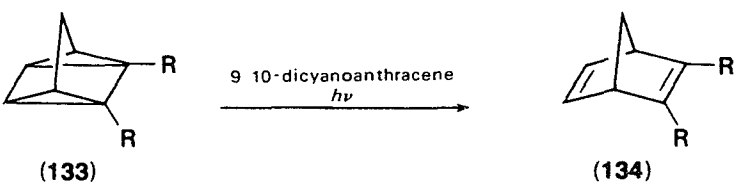
R. Photoinduced Synthesis and Reactions of Cyano Compounds

1. Photochemical reactions of nitriles

Photochemical reactions involving cyano substrates are diverse reactions from both the mechanistic and the synthetic point of view. The inter- and intra-molecular photo-

cyclization of alkenes with α,β-unsaturated chromophores[493,494], phototranspositions[495] and rearrangements[496], photochemical generation of 2-allyl-substituted nitriles and their carbene-type intramolecular 1:1 cycloadditions[497], reaction between radical-anion–radical-cation pairs produced on irradiation[498] (e.g. 1,2,4,5-tetracyanobenzene, TCNB)[499], photosubstitution of TCNB by toluene[500] or by ethers[499], photoinduced reaction of 7,7,8,8-tetracyanoquinodimethane (TCNQ)–tetrahydrofuran[501] or tetracyanoethylene(TCNE)–2-methyltetrahydrofuran[502], photochemical reactions via electron transfer followed by proton transfer[503] and photooxygenation via electron transfer[504–506] are but a few of the recent studies wherein photocyano reactions have been discussed.

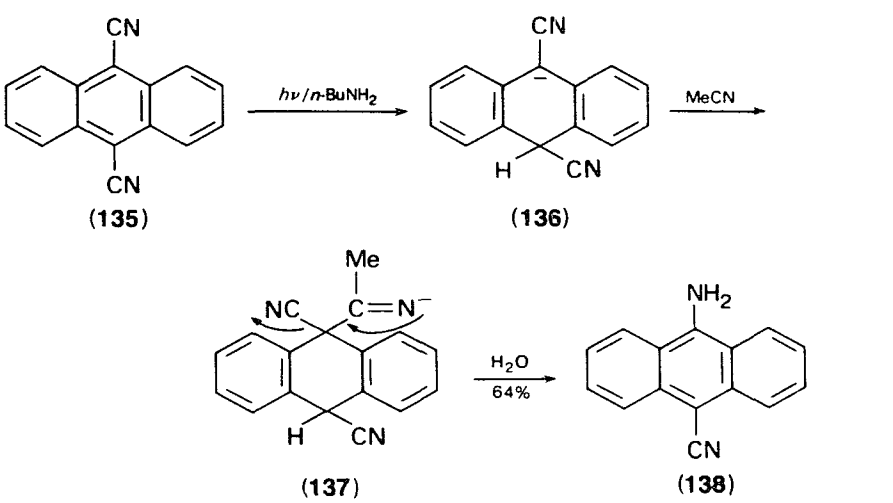
a. Fluorescence quenching of aromatic fluorophores. Irradiation of quadricyclene (**133**) in the presence of aromatic sensitizers (e.g. 9,10-dicyanoanthracene, 9-cyanoanthracene or 1-cyanonaphthalene) leads to a valence (not geometrical) isomerization product **134** (equation 332)[507a]. Photocyanation of arenes occurs readily with potassium cyanide solubilized in acetonitrile by means of 18-crown-6 ether[507b].



(133) (134) (332)

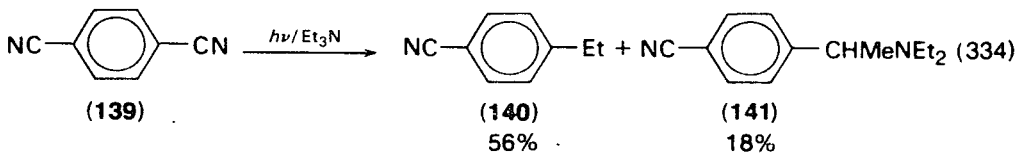
R = H, CO_2Me

b. Photochemical reaction of dicyanoanthracene with acetonitrile. Irradiation of 9,10-dicyanoanthracene (**135**), a powerful electron acceptor, in acetonitrile in the presence of butylamine, yields 9-amino-10-cyanoanthracene (**138**) via **136**, and **137**; the photochemical reaction involves electron transfer, followed by proton transfer (equation 333)[501]. Similarly, 1,4-dicyanobenzene (**139**), in the presence of



(135) (136) (137) (138) (333)

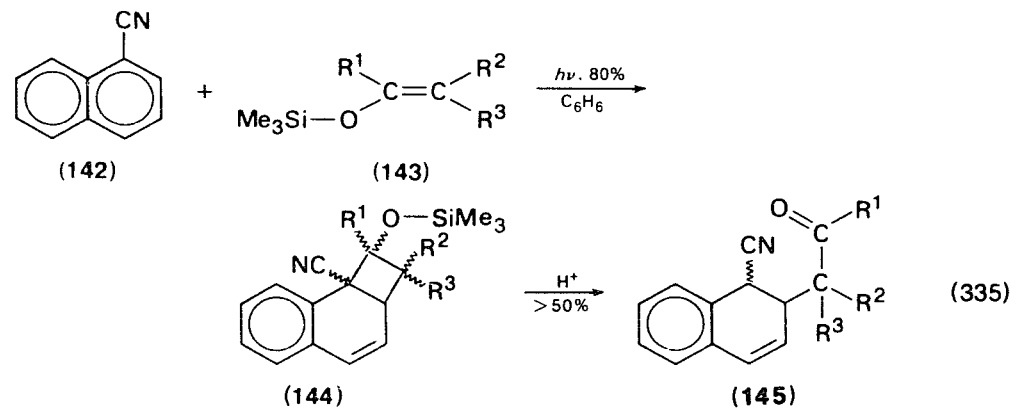
triethylamine, gives 4-cyano-1-ethylbenzene (**140**) and 4-cyano-1-[1-ethylamino)ethyl]benzene (**141**) (equation 334)[508]. However, irradiation of a solution of anthracene and a secondary amine in acetonitrile yields both the 1:1



(139) (140) 56% (141) 18%

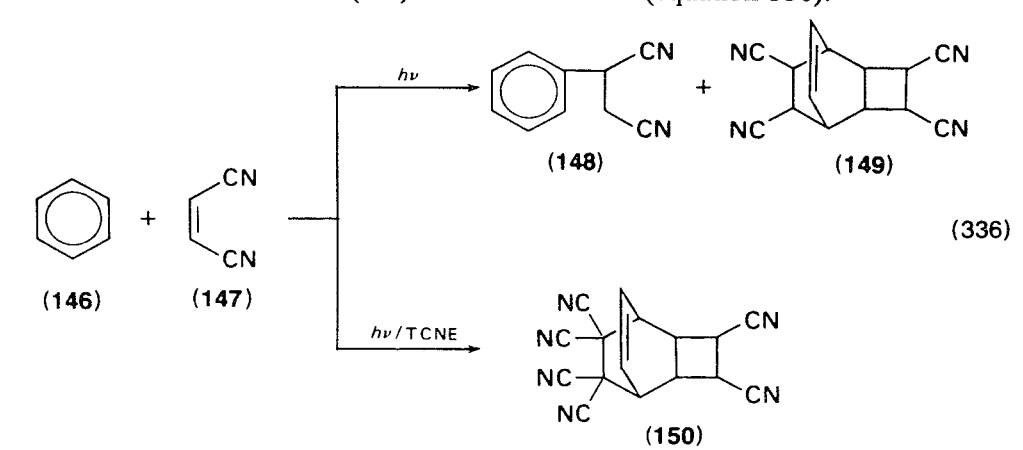
adducts and the reduction products of anthracene[509]. Irradiation of 2- or 4-chlorobenzonitrile (but not 3-chlorobenzonitrile) in the presence of anisole, or 1,3- or 1,4-dimethoxybenzene leads to the formation of biaryls via a coupling pathway, or, in certain cases, via an electron-transfer process[510].

c. A Michael-type alkylation of the naphthalene ring; regiospecific photocycloaddition. A direct Michael-type alkylation of an aromatic ring is rare in ground-state chemistry. However, a Michael-type alkylation at C-2 of the naphthalene ring has been effected by the regiospecific photocycloaddition of the trimethylsilyl enol ether **143** to 1-cyanonaphthalene (**142**) to give a mixture of isomeric dihydrocyclobutanenaphthalenes (**144**), which on hydrolysis give 2-alkyl-substituted 1-cyanonaphthalenes (**145**) (equation 335)[511].



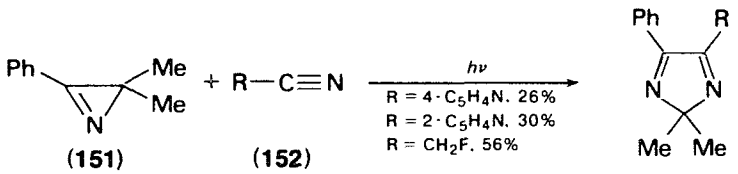
(142) (143) (144) (145) (335)

d. Photolysis of fumaronitrile in benzene. Irradiation of fumaronitrile (**147**) in benzene (**146**) gives a mixture of phenylsuccinonitrile (**148**), biphenyl and (in very small yield) a 2:1 adduct of the tricyclic tetranitrile (**149**). In the presence of TCNE, formation of a 1:1:1 adduct (**150**) can be detected[512] (equation 336).

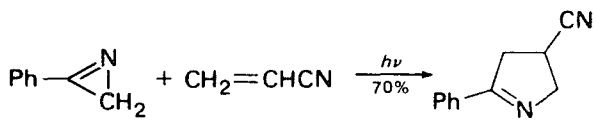


(336)

e. Photoinduced cycloaddition of 2H-azirine with nitriles. When irradiated *in situ*, electron-deficient nitriles of type **152** undergo regiospecific [2 + 3]cycloaddition to 2,2-dimethyl-3-phenyl-2*H*-azirine (**151**), to yield the 2*H*-imidazole derivatives (**153**) (equation 337)[513]. Photoinduced cycloaddition of acrylonitrile to a 2*H*-azirine derivative leads to a dihydropyrrole derivative via a ring-enlargement (equation 338)[514].

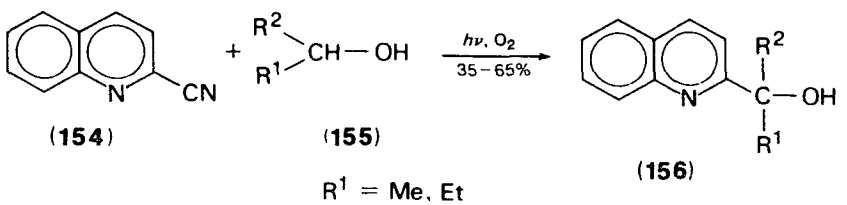


(151) (152) (153) (337)



(338)

f. Photoinduced substitution reaction of nitrogen heterocycles. 2-Cyanoquinoline (**154**) undergoes a photoinduced substitution to give 2-(1-hydroxyalkyl)quinolines (**156**) in the presence of an excess of an aliphatic alcohol (**155**) while oxygen is bubbled through the mixture (equation 339)[515]. A new method for the preparation of cyano(phenyl)carbene [Ph(NC)C:] is the photolysis of 1,2-dicyano-1,2-diphenyloxirane[516]. Conversion of *p*-hydroxybenzonitrile into *p*-hydroxybenzaldehyde can be effected by photolytic alkaline hydrolysis[517].



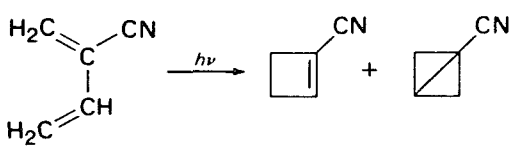
(154) (155) (156) (339)

R^1 = Me, Et

R^2 = H, Me

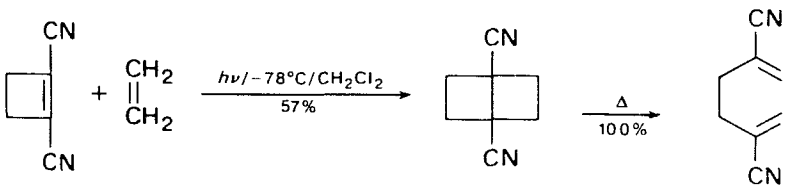
2. Photoisomerization and photorearrangement of cyano compounds

a. Photoisomerization of 2-cyanobutadiene (**157**). This occurs on irradiation in dilute ethereal solution to give 1-cyanocyclobutene (**158**) and 1-cyanobicyclobutane (**159**). The isomerization is unaffected by the presence of triplet sensitizers (equation 340)[518].



(157) (158) (159) (340)

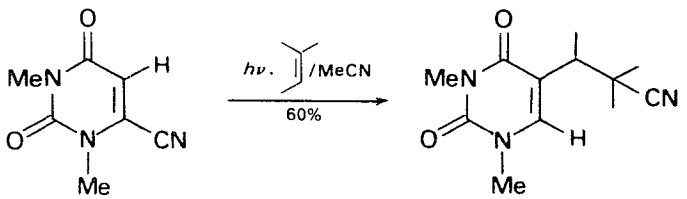
b. Photocycloaddition of 1,2-dicyanocyclobutene (**160**) *to ethylene.* This leads to a bicyclic intermediate (**161**) which rearranges thermally to **162** (equation 341)[519].



(341)

(160) (161) (162)

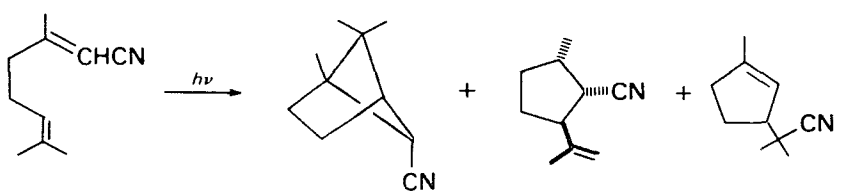
c. Photoaddition of 6-cyanouracil to an alkene, involving migration of the cyano group. Irradiation of 6-cyano-1,3-dimethyluracil (**163**) in acetonitrile at 20°C in the presence of 2-methyl-2-butene produces a rearranged adduct **164** (60%) (equation 342)[494].



(342)

(163) (164)

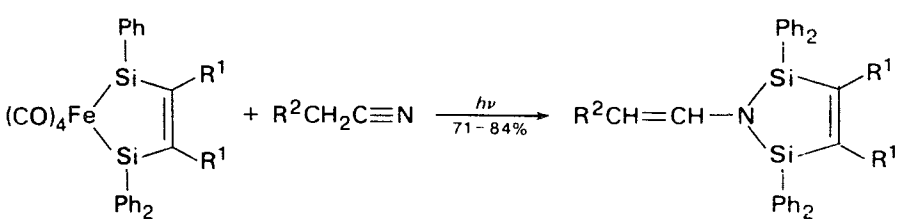
d. Photochemical rearrangement of geranonitrile at elevated temperature. Photolysis of *cis*- and *trans*-geranonitrile (**165**) in benzene, with propiophenone as the sensitizer, at 30–80% gives rearranged products, e.g. the bicyclic nitrile **166** (major product) and the nitriles **167** and **168** (minor components) (equation 343)[496].



(343)

(165) (166) (167) (168)

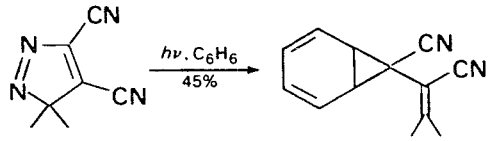
e. Photochemical reaction of organosilyl iron carbonyls(**169**) *with nitriles.* Nitriles, e.g. acetonitrile or a substituted acetonitrile, unexpectedly produced, via iron extrusion, bis(diphenylsilyl)ated enamines (**170**), a new class of compound (equation 344)[520]. Some of the novel, photoinduced isomerizations and rearrangements of cyano substrates are depicted in equations (345)–(358)[521–533].



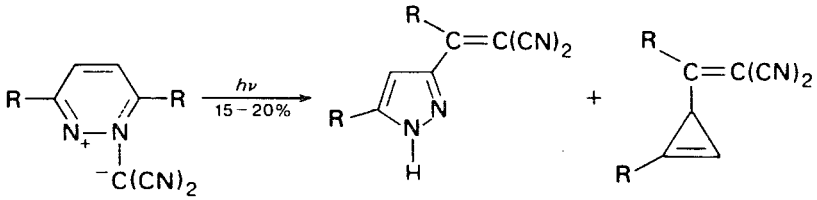
(344)

(169) (170)

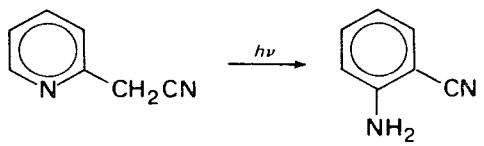
R^1 = Et, R^2 = H



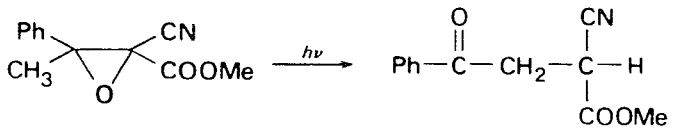
(Ref. 521) (345)



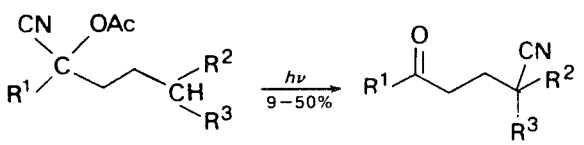
(Ref. 522) (346)



(Ref. 523) (347)

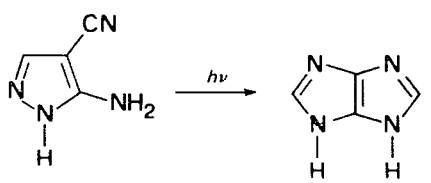


(Ref. 524) (348)

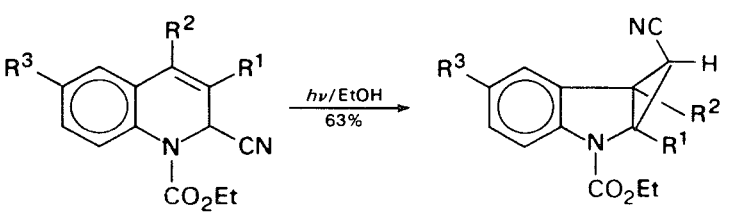


(Ref. 525) (349)

R^1, R^2, R^3 – alkyl, aryl

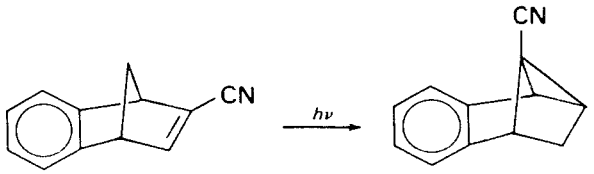


(Ref. 526) (350)

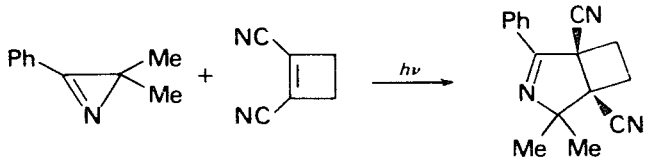


(Ref. 527) (351)

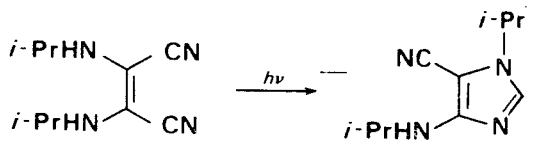
$R^1 = H$, $R^2 = R^3 = Me$



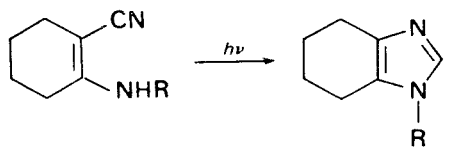
(Refs. 528, 529) (352)



(Ref. 513) (353)

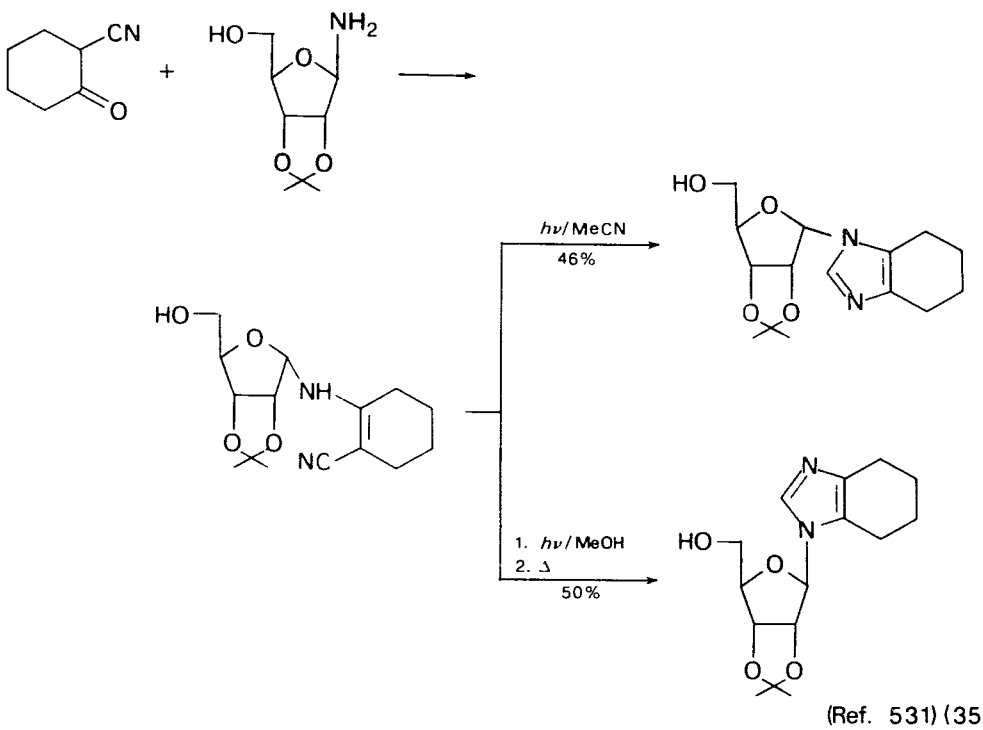


(Refs. 526, 530) (354)

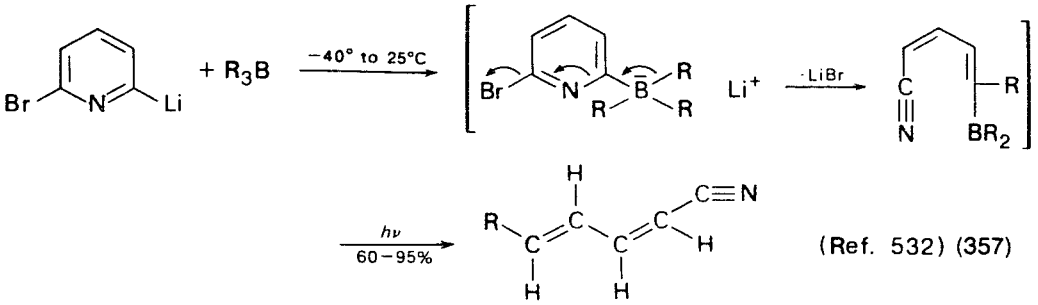


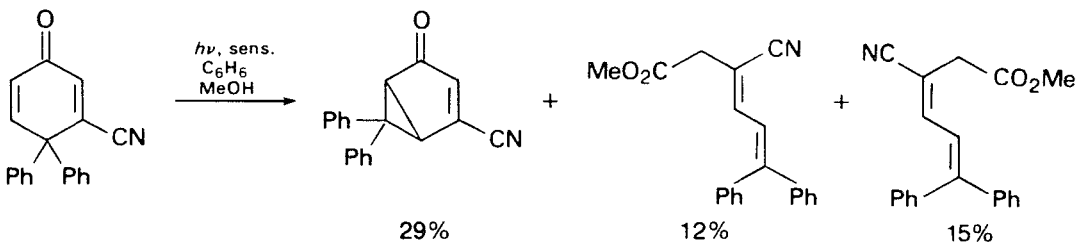
(Refs. 526, 530) (355)

R = H, Me



(Ref. 531) (356)



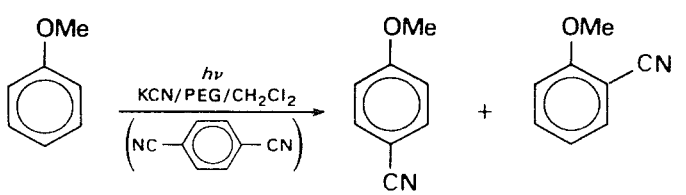


(Ref. 533) (358)

3. Addendum

a. Photocyanation of anisole in the presence of polyethylene glycol. Photochemical nucleophilic substitutions of aromatic ring-systems in protic solvents have been well documented[534]. When crown ether is present the photocyanation proceeds better in aprotic solvents than in protic solvents[535], while addition of an electron acceptor, such as terephthalonitrile, improves both the yield of the photocyanation products and the specifity of substitution[536].

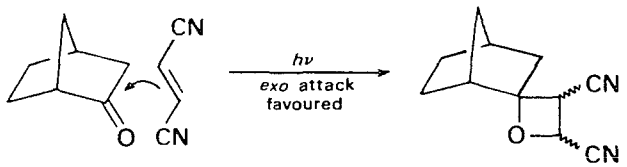
In a new procedure[537] polyethylene glycol (PEG) replaces crown ether as a cosolvent in the photochemical substitution of anisole with potassium cyanide in methylene chloride, to give a mixture of *p*- and *o*-cyanoanisoles (equation 359). The ratio of *p*-CH:*o*-CN isomers is much larger in Pyrex cells than in a quartz cell; the yield of the product increases with longer irradiation.



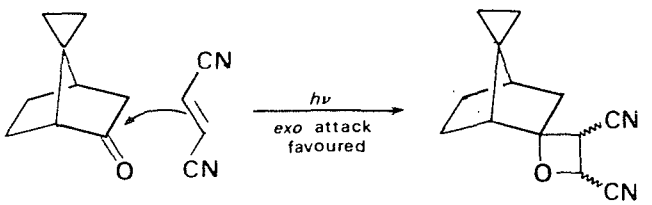
(359)

b. The influence of steric hindrance on oxetane formation. The photoinduced oxetane formation from 2-norbornanone and derivatives with electron-poor ethylenes, e.g. *trans*-dicyanoethylene has recently been examined. The quantum yield increases with increasing steric hindrance toward *exo* approach of the olefin (equations 360–362)[538].

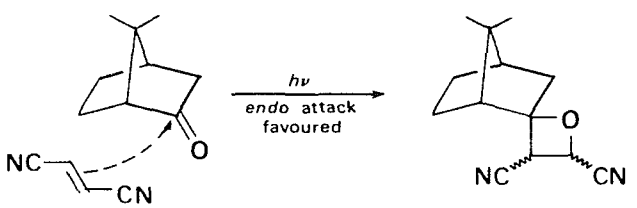
c. Photochemical benzylation of 1,4-dicyanonaphthalene. Aromatic nitriles (and esters) have been shown to sensitise, through electron transfer, the photochemical



(360)

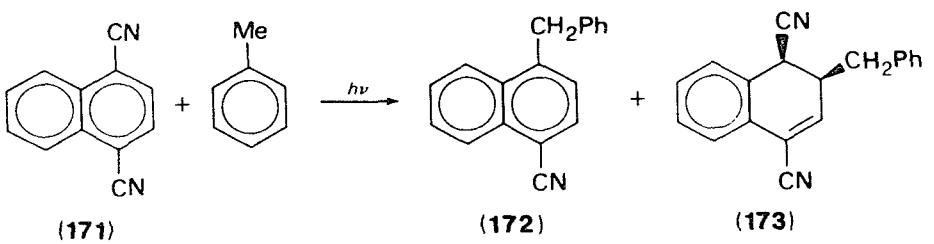


(361)

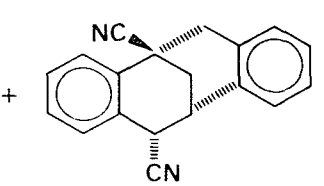


(362)

reactions of phenyl-substituted alkenes[539], β-phenylethyl ethers[540], diphenyloxirans[541] and diphenylcyclopropanes[542]. However, no such reaction has been reported with simple arenes, although the fact that these are known to form exciplexes with aromatic nitriles[543] suggests that the electron-transfer step could take place. However, irradiation of the preformed ground state complex between tetracyanobenzene and toluene has been found to lead to a reaction with elimination of hydrogen cyanide, e.g. explaining the benzylation of tetracyanobenzene[544]. It has been found[545] that a photochemical reaction also occurs in a system which does not form a ground-state complex, offering a further example of photoreaction via radical ions. Thus the irradiation of 1,4-dicyanonaphthalene (**171**) in the presence of toluene in acetonitrile gives adducts bearing the benzyl group in positions 1 and 2 of the naphthalene nucleus; at complete conversion, three products, e.g. 1-cyano-4-benzylnaphthalene (**172**), **173** and a novel further photoreaction product (**174**) are isolated in yields of 12, 7 and 23% respectively (equation 363).



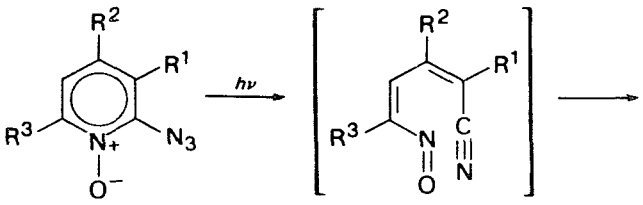
(171) (172) (173)



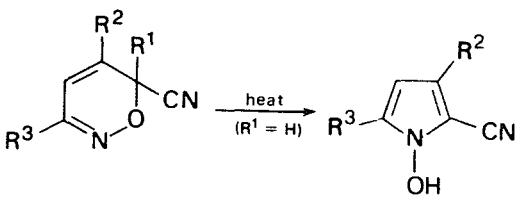
(174)

(363)

d. Photolysis of 2-azidopyridine-1-oxides; a convenient synthesis of 1,2-oxazines. Photolysis of 2-azidopyridine 1-oxides (**175**) in benzene leads to nitrogen elimination and ring-opening (e.g. formation of **176**) followed by recyclization to give 6-cyano-1,2-oxadines (**177**) which then usually rearrange thermally to 2-cyano-1-hydroxypyrroles (**178**) (equation 364)[546]; the photolysis thus provides a ready, high-yield route to 1,2-oxazines (70–96% yield).



(**175**) (**176**)



(364)

(**177**) (**178**)

70–96%

$R^1 = R^2 = R^3 = H$

$R^1 = Me, R^2 = R^3 = H$

$R^1 = R^3 = H, R^2 = Me$

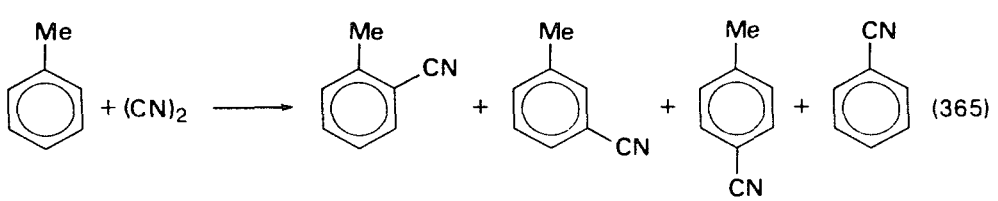
$R^1 = R^2 = H, R^3 = Me$

III. SELECTED SYNTHETIC METHODS AND REACTIONS INVOLVING CYANO SUBSTRATES

A. Selected Sytheses of Cyano Compounds

1. Direct cyanation of arenes

Methods for the direct replacement of hydrogen of aromatic compounds by the cyano group are: (*i*) electrolysis of methoxyarenes and cyanide[547], (*ii*) photolysis of



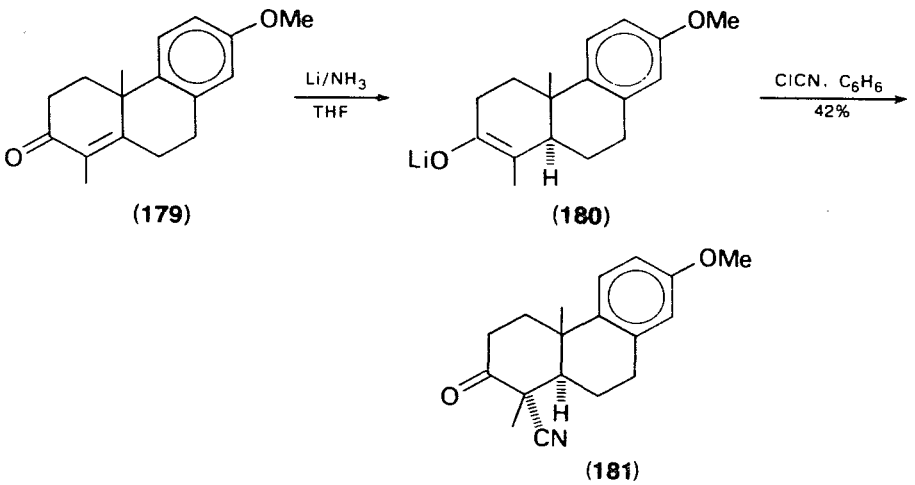
(365)

26% 21% 13% 11%

certain arenes in cyanide solution or in the presence of cyanogen iodide[534], (*iii*) diazotation of cyanamide in the presence of aromatic compounds[548] and (*iv*) pyrolysis of benzene and cyanogen in the presence of supported metal catalysts[549]. A recent method involves the application of plasma chemistry[550]. Cyanogen and the arene are distilled through a discharge zone when, for example, toluene is converted into a mixture of substituted products (equation 365)[550].

2. C-Cyanation reactions

a. C-Cyanation of metal enolates. *C*-Cyanolations of metal enolates are reactions related to the acylation of ketones[551]. Reactions of regiospecifically generated lithium enolates with cyanogen chloride have been used to produce the corresponding α-cyanoketones in moderate yields. Thus, the tricyclic lithium enolate **180** which is prepared from the enone **179** gives the α-cyanoketone **181** on treatment with cyanogen chloride (equation 366)[552]. *O*-Cyanation of **180** apparently occurs when THF is used as the solvent[552].



(179) (180) (181)

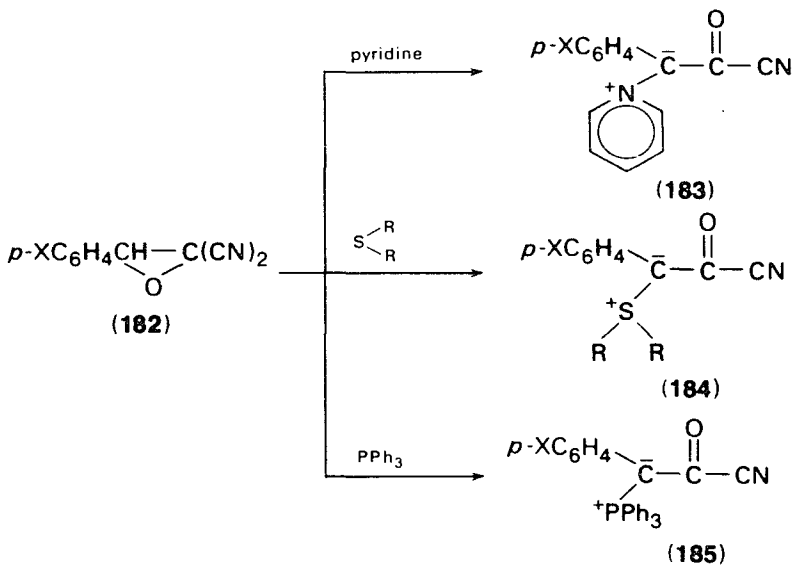
(366)

3. New ylides from gem-dicyanoepoxides; a novel ring-opening

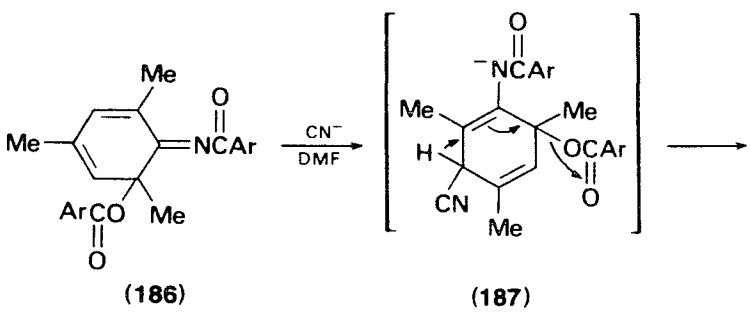
The reaction of the trisubstituted *gem*-dicyanoepoxides with nucleophilic compounds (pyridine, dialkyl sulphide or triphenylphospine) proceeds with a novel epoxide ring-opening, to give new pyridinium (**183**), sulphonium (**184**) or phosphonium (**185**) ylides (40–90% yield), stabilized by the reactive cyanocarbonyl group (equation 367)[553]. Carbonyl cyanide is not formed in this reation.

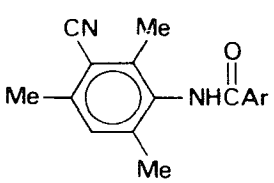
4. Aromatization with potassium cyanide in N,N-dimethylformamide (DMF)

A facile conversion of esters of 2,4-cyclohexadien-1-ols to benzene derivatives is achieved with potassium cyanide in DMF. Thus, treatment of the *p*-nitrobenzoic ester of 1,3,5-trimethyl-6-(*p*-nitrobenzoylimino)-2,4-cyclohexadien-1-ol (**186**) with the reagent (KCN–DMF) at room temperature, gives 3-cyano-2,4,6-trimethyl-*N*-(*p*-nitrobenzoyl)aniline (**188**) in 61% yield. Attack on **186** by a nucleophile (e.g. a cyanide ion), and expulsion of the ester group to give **188**, apparently involves the intermediate **187** (equation 368)[554]. Analogous conversions of **189**



(367)





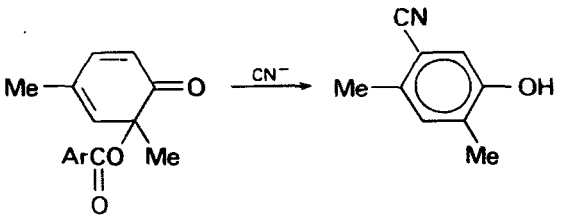
(368)

Ar = p-$O_2NC_6H_4$ (188)

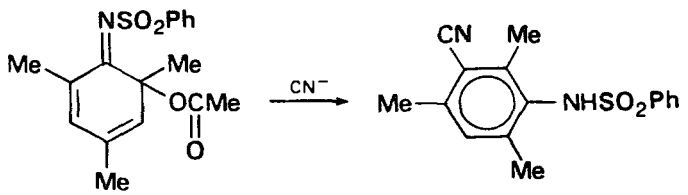
or **191** with cyanide ion, to give, respectively, **190**[555] or **192**[556] have been reported (equation 369).

5. *Aromatization of quinone monoacetal adducts*

Much of the known chemistry of quinones results from the Michael type of addition (e.g. 1,4-addition) of nucleophiles to the enone moiety contained in the quinone ring[557]. The conjugate addition of active methylene compounds to quinone monoacetals is generally regiospecific, to give mono- or bi-cyclo adducts; the latter are readily aromatized[558–560]. For example, ethyl cyanopropionate added to quinone acetal (**193**) in the presence of 0.1 equivalent of sodium ethoxide in ethanol yields the adduct **194**;

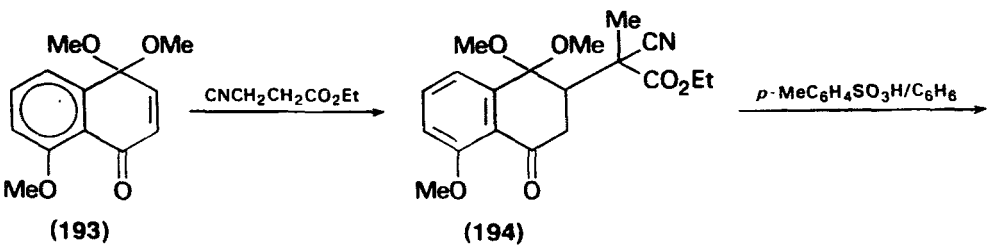


(189) (190)

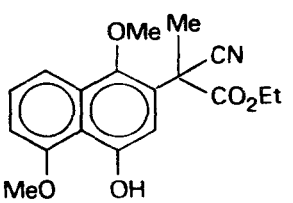


(191) (192) (369)

on aromatization with *p*-toluenesulphonic acid, this gives the hydroquinone monoether **195** in 84% yield (equation 370)[558]. The method is a useful synthetic procedure for analogous Michael addition to quinone monoacetals. The conjugate 1,4-addition of cyanide to 2,5-cyclohexadienone has been demonstrated[561].



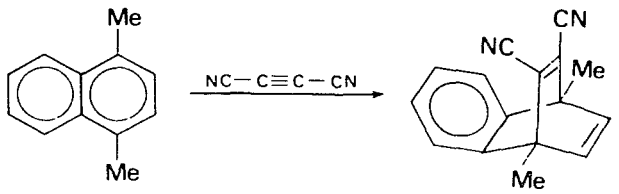
(193) (194)



(195) (370)

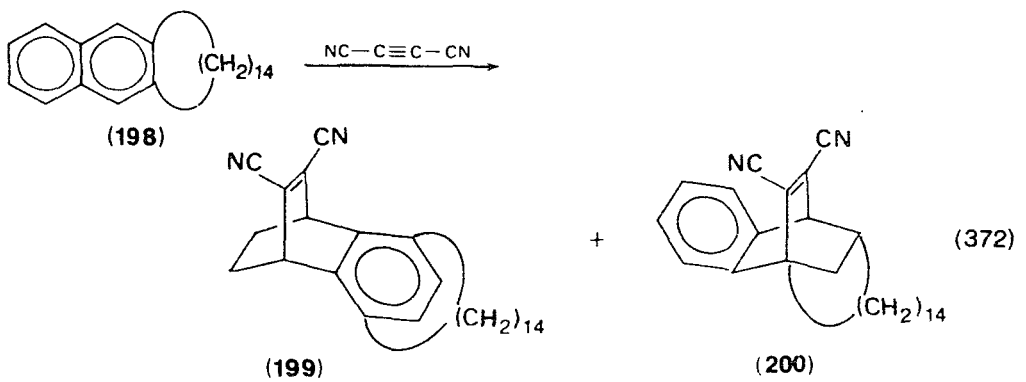
6. *Diels–Alder adducts with dicyanoacetylene*

Aromatic systems are relatively unreactive when normal dienophiles are used, but the highly reactive dicyanoacetylene is known to add to such aromatic systems as benzene[562] and naphthalene[563], to give [4 + 2]adducts. The addition of dicyanoacetylene to [2,2]paracyclophane occurs *ortho* to the polymethylene bridge[562]. The electron-rich 1,4-dimethylnaphthalene **196** gives the bridged adduct **197** as the major product (54%), along with a small proportion (4%) of the adduct derived from addition to the unsubstituted ring (equation 371)[564]. However, on similar treatment with the dienophile, [*n*]-(1,4)-naphthalenophanes (*n* = 8, 9, 10 and 14) give,

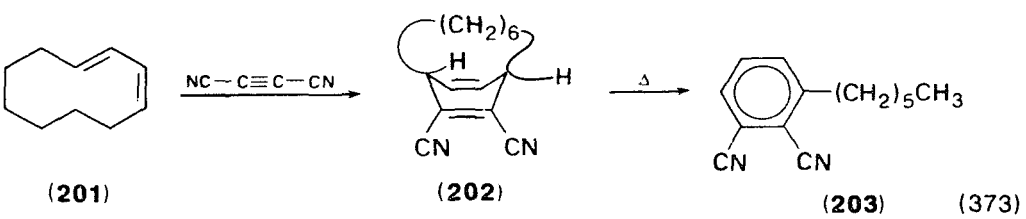


(196) (197) (371)

in all cases, the Diels–Alder adduct at the unsubstituted aromatic ring as the major product. For example, with the [14](1,4)naphthaleneophane (**198**), the major product (54%) is the Diels–Alder adduct (**199**) (to the unsubstituted ring), and a minor product (7%) proves to be the paddlane (**200**) (a bridge adduct, similar to **197**) (equation 372). The reaction[565] of **201** (*cis, trans*-1,3-cyclodecadiene) gives the adduct (**202**); on heating (165°C), the latter rearranges to give the 1,2-dicyanobenzene derivative (**203**) (equation 373).



(198) (199) (200) (372)



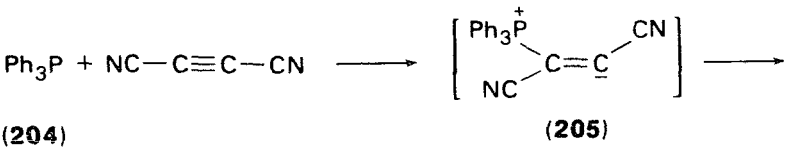
(201) (202) (203) (373)

7. *Reaction of triphenylphospine* **204** *with dicyanoacetylene*

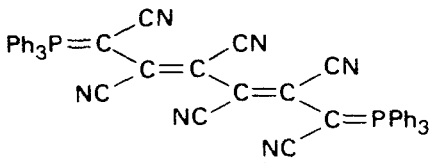
This reaction gives polymerized acetylene in addition to the stable alkylidene-1,6-diphosphorane (**206**) (an ylide)[566]; the reaction, as recently shown[567], involves the betaine intermediate **205** (equation 374).

8. *1,2-Dicyanocyclobutene*

Bellus and coworkers[568] have reported an improved method for the preparation of 1,2-dicyanocyclobutene (**209**), a highly versatile starting material for organic synthesis; the procedure involves chlorination of a mixture *cis, trans*-1,2-dicyanocyclobutane (**207**), followed by dehydrochlorination of the intermediate (**208**) (equation 375)[68].

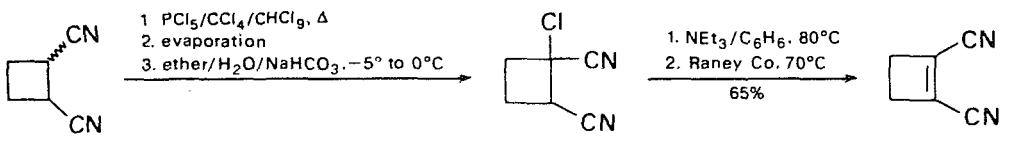


(204) (205)



(206)

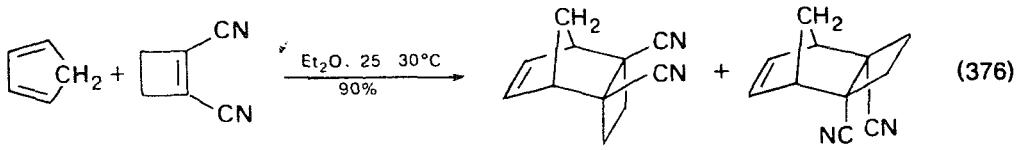
+ polymerized acetylene (374)



(207) (208) (209)

(375)

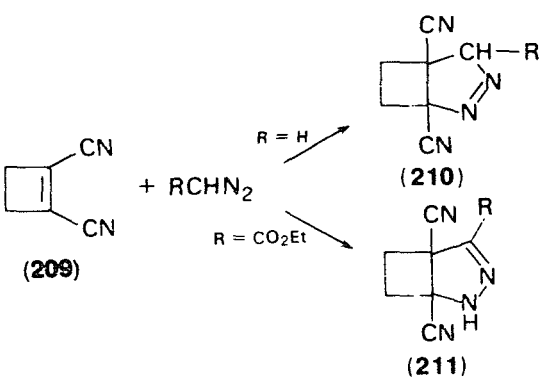
a. Diels–Alder adducts. The strain present in the cyclobutene ring-system allows the Diels–Alder reaction to occur with **209** (a reactive dienophile) under mild conditions (equation 376)[569].



(209) *endo* *exo*

(376)

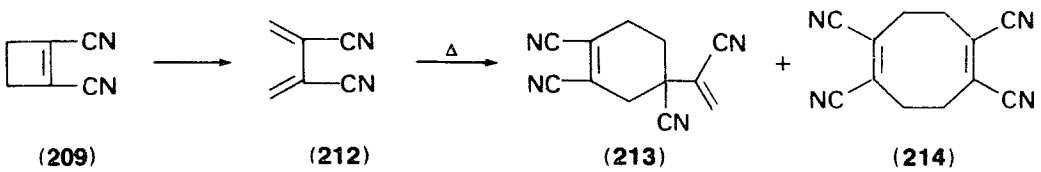
b. Other important reactions. Because of the ring-strain factor, **209** shows unusual chemical reactivity; much of its chemistry has been studied by Bellus and coworkers[570] and Cobb and coworkers[571–574]. The reaction of diazomethane with **209** occurs readily at room temperature, to give the [3 + 2]cycloadduct **210** (R = H). A similar reaction



(209) (210) (211)

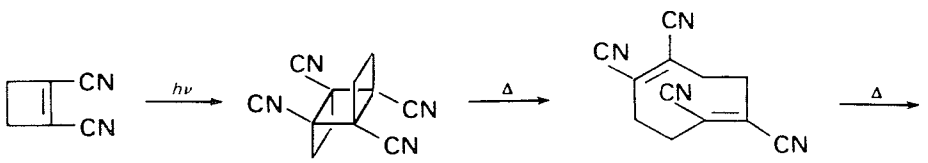
(377)

with ethyl diazoacetate gives the cycloadduct **211** (R = CO_2Et), arising by a [1,3]prototropic rearrangement of the adduct **210** (R = CO_2Et) initially formed (equation 377)[573]. However, the reaction of diazomethane with **212** (the valence tautomer of **209**) produces a dipyrazoline derivative[574]. **209** and **212** exhibit a rich and varied chemistry. For example, thermal dimerization of **212** produces mixtures of **213** and **214** (equation 378)[573]. **209** is a strong absorbent of light at ~234 nm and forms a photodimer (**215**) which can be thermally converted, via a skeletal rearrangment, into **216** → **214** → **217** (equation 379)[573].

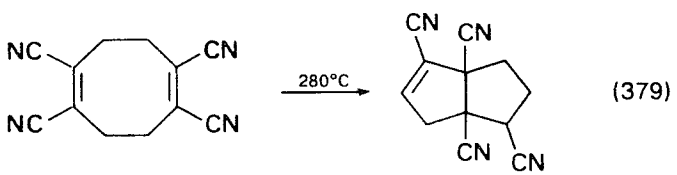


(209) (212) (213) (214)

(378)



(209) (215) (216)

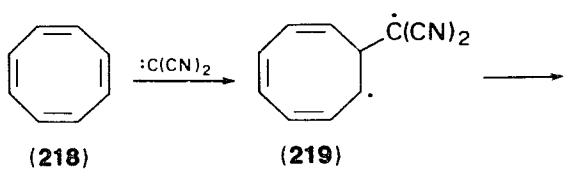


(214) (217)

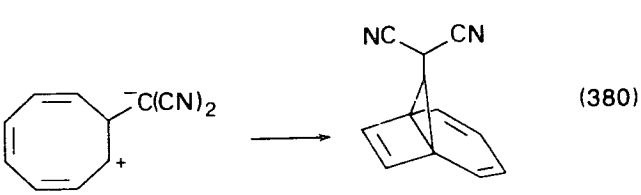
(379)

9. 1,4-Addition of dicyanocarbene to cyclooctatetraene

Triplet dicyanocarbene [$:C(CN)_2$][575,576] does not generally add to dienes to give 1,4-addition; however, it adds in this fashion to cyclooctatetraene (**218**) to give the 1,4-adduct (**221**)[577], in contrast to the fact that, with other triplet carbenes[576,578], **218**



(218) (219)



(220) (221)

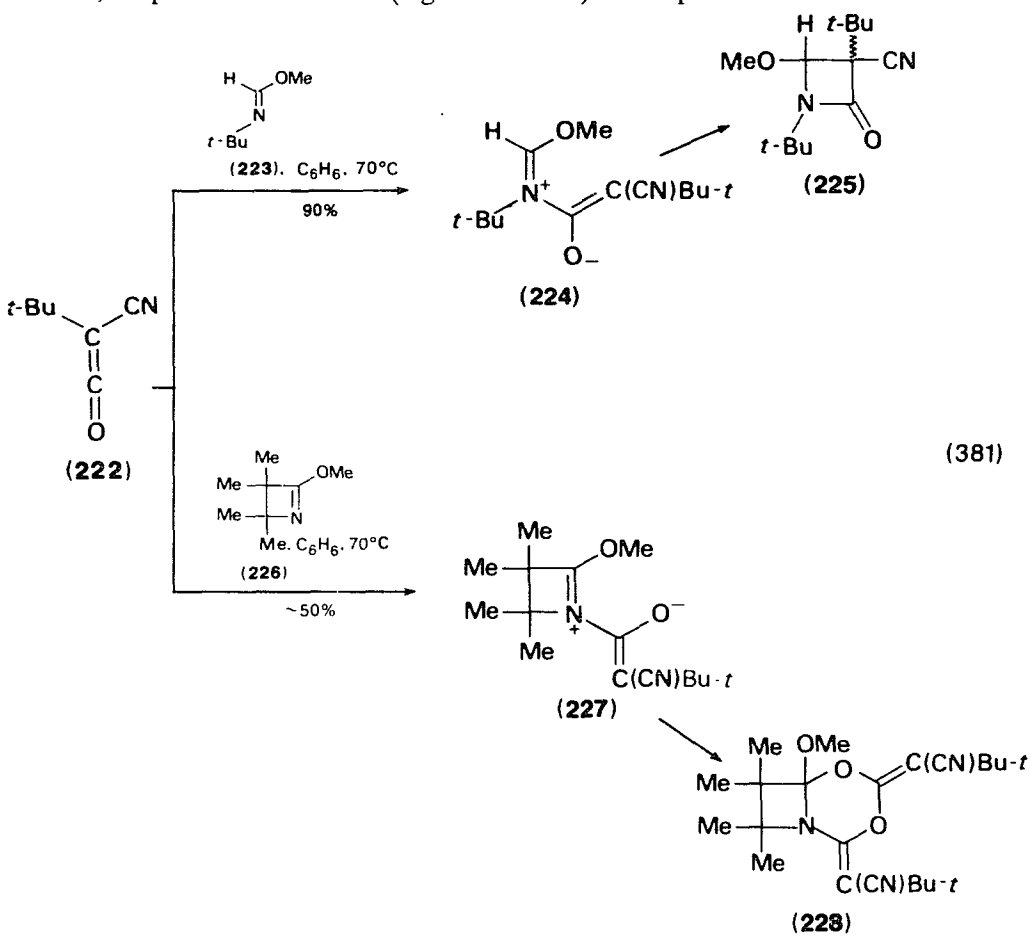
(380)

gives 1,2-addition exclusively. The only cogent explanation for this singular behaviour comes from work by Hendrick[579], who suggests that electron transfer may occur in the diradical intermediate originally formed (**219**) to give a zwitterion (**220**) containing both a homotropylium ion and a well-stabilized carbanion (equation 380).

10. Cyanoketenes: t-butylcyanoketene

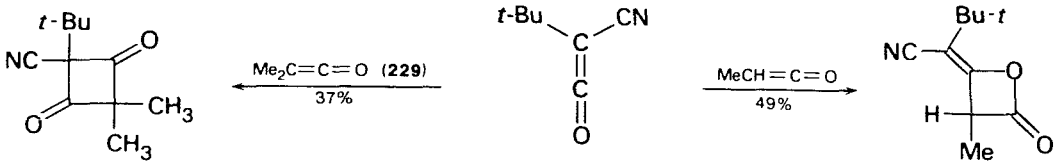
A convenient source of the sterically hindered *t*-butylcyanoketene (**222**) is the thermolysis of 2,5-diazido-3,6-di-*t*-butyl-1,4-benzoquinone[580–582a]. The reagent has been used exclusively in studies of addition and cycloaddition with, for example, alkenes, methyl- and dimethyl-ketones, imino ethers and certain heterocycles. The topic has recently been reviewed by Moore and Gheorghiu[582b].

In the addition of *t*-butylcyanoketene (**222**) to imino ethers, steric effects may control the formation of the product[583]. Thus, treatment of methyl *N*-*t*-butylformimidate (**223**) with (**222**) results (via the intermediate **224**) in a 90% yield of the β-lactam (**225**). However, treatment of 2-methoxy-3,3,4,4-tetramethylazetine (**226**) with **222** shows no evidence of production of a β-lactam, but results in the formation of the 2:1 cycloadduct **228**, via the intermediate **227** (equation 381)[583]. Steric and conformational factors of the 1,4-dipolar intermediates (e.g. **224** vs. **227**) can explain the reaction course.



(381)

t-Butylcyanoketene (**222**) and dimethylketene (**229**) cycloadd to give only the 1,3-cyclobutanedione (**230**); however, cycloaddition of **222** with methylketene produces the 2-oxetanone **231** (equation 382)[584]; cycloadditions are likely to involve the respective zwitterionic intermediates.



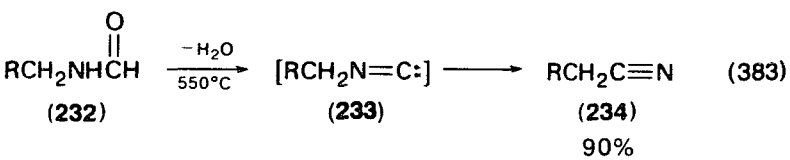
(**230**) (**222**) (**231**)

(382)

The preparations of chloro-[585], bromo- or iodo-cyanoketenes[586], and their stereospecific cycloadditions to a variety of formimidates, have been reported[587]. In addition, **222** reacts stereospecifically with *cis*- and *trans*-cyclooctene (to give cyclobutanones)[581] and combines with thiazine[588] and 2-(dimethylamino)thiazole[589] to yield either 1:1[590] or 2:1[589] cycloadducts. Reactions of the *t*-butylisonitrile reagent have been reported[590].

11. One-carbon chain-extension from primary amines to nitriles via formamides

A new procedure for the conversion of primary amines via formamides (**232**) into nitriles (**234**) (with one-carbon chain-extension) requires a new bismuth phosphomolybdate catalyst and a temperature of 400–550°C. The dehydration reaction involves a rearrangement of the intermediate **233** (equation 383)[591].



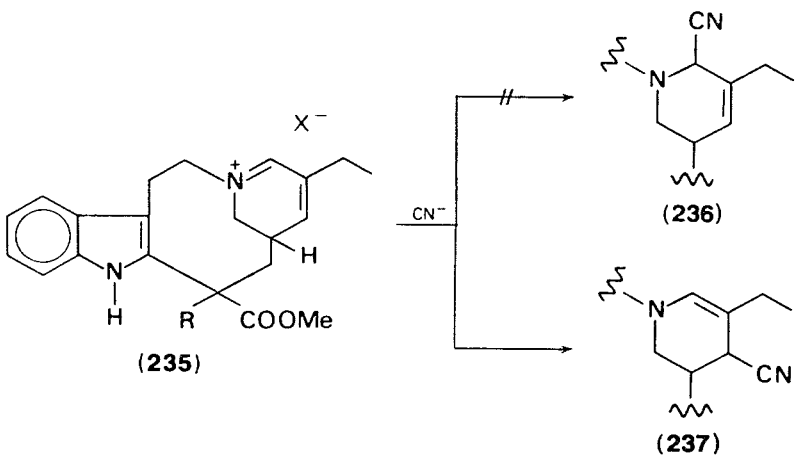
(**232**) (**233**) (**234**) (383)

12. Attack of cyanide ion on the conjugated immonium system

Treatment of the conjugated immonium salt (**235**) with cyanide ion did not lead to a 1,2-addition product (i.e. **236**) but rather to a 1,4-addition product (i.e. **237**) (equation 384)[592]. The formation of **237** most probably results from a S_N1 substitution. The intermediate **235** is needed for the synthesis of certain antitumour alkaloids.

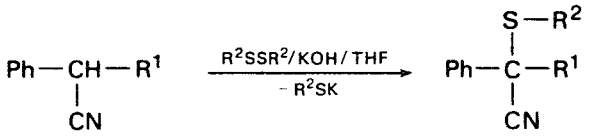
13. The sulphenylation of nitriles

There are many reports on the α-sulphenylation of nitriles with lithium amide at −78°C and diphenyl disulphide, dimethyl disulphide[593,594], benzenesulphenyl chloride[595] or phenyl benzenethiosulphonate[596]. Foucaud and coworkers[597] have described an easier method for the α-sulphenylation of nitriles in a two-phase system (solid–liquid) without a catalyst; the procedure is based on the utilization of anhydrous potassium hydroxide and carbon tetrachloride for chlorination of nitriles in the α-position[598]. When the carbanions, generated by using anhydrous potassium or



(384)

sodium hydroxide in THF are allowed to react with a disulphide at room temperature, near quantitative yields of the appropriate α-cyanosulphide are generally obtained[597] (equation 385).

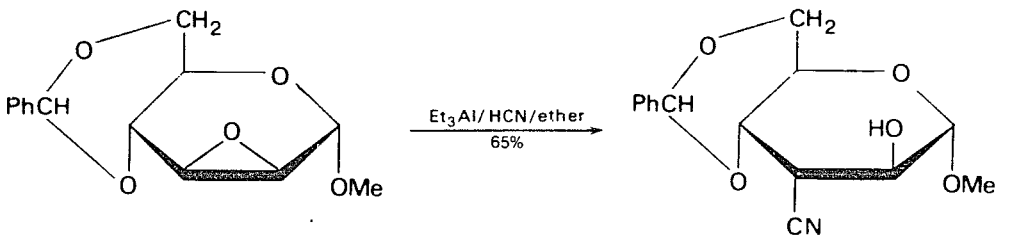


(385)

R^1 = H, Me
R^2 = Me, Ph

14. *Methods for synthesis of cyano sugars*

a. Cyano glycosides and other cyano sugars. 3-Cyano-3-deoxyglycosides (**239**) may be prepared[599] by treating the corresponding sugar 2,3-epoxides (**238**) with hydrogen cyanide and triethylaluminium in ether (the Nagata reagent); this provides a useful route to branched-chain sugar derivatives having a cyano group (equation 386).



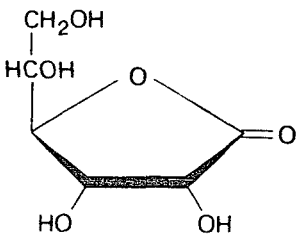
(238) (239)

(386)

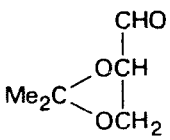
Other methods involve the conversion of 2-deoxy-2-*C*-(nitromethyl) and 3-deoxy-3-*C*-(nitromethyl) sugar derivatives into their respective *C*-cyano analogues via α,α-dibromination of the methylene group followed by treatment with triphenylphosphine[600,601], or the action of potassium cyanide complexed with 18-crown-6 on sugar tosylates[602]. The reaction of tetra-*O*-acetyl-α-D-gluco- and -galacto-pyranosyl bromide with

metallic cyanides has recently been studied[603,604]. The synthesis of isocyanide sugars has been reported[603].

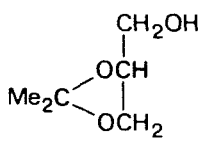
b. Synthesis of chiral compounds via carbohydrates. Recently, great advances have been made in the total synthesis of optically active natural products from readily available chiral precursors, among them carbohydrate derivatives, particularly D-glucose[605,606]. It has now been found[607] that L-ascorbic acid (vitamin C) (**240**) is a useful chiral precursor, permitting rapid preparation of the difficultly accessible 1,2-*O*-isopropylidene (*S*)-glyceraldehyde (**241**) and the derived 1,2-*O*-isopropylidene (*R*)-glycerol (**242**) and the nitrile **243**. These compounds have been shown to be useful intermediates in the synthesis of chiral, biologically active materials such as 3-amino-3-deoxy-L-glyceronic acid [(*R*)-γ-amino-β-hydroxybutyric acid] (**244**), 1-*O*-aryl-3-(arylamino)-3-deoxy-L-glycerol [(*S*)-aryloxypropanolamine] (**245**) and the antibiotic pyridindolol (**246**)[607].



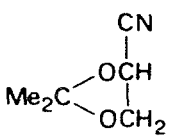
(240)



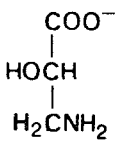
(241)



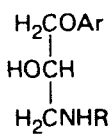
(242)



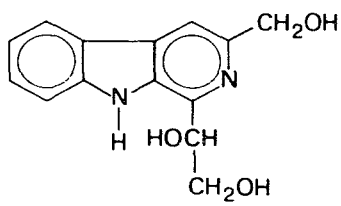
(243)



(244)



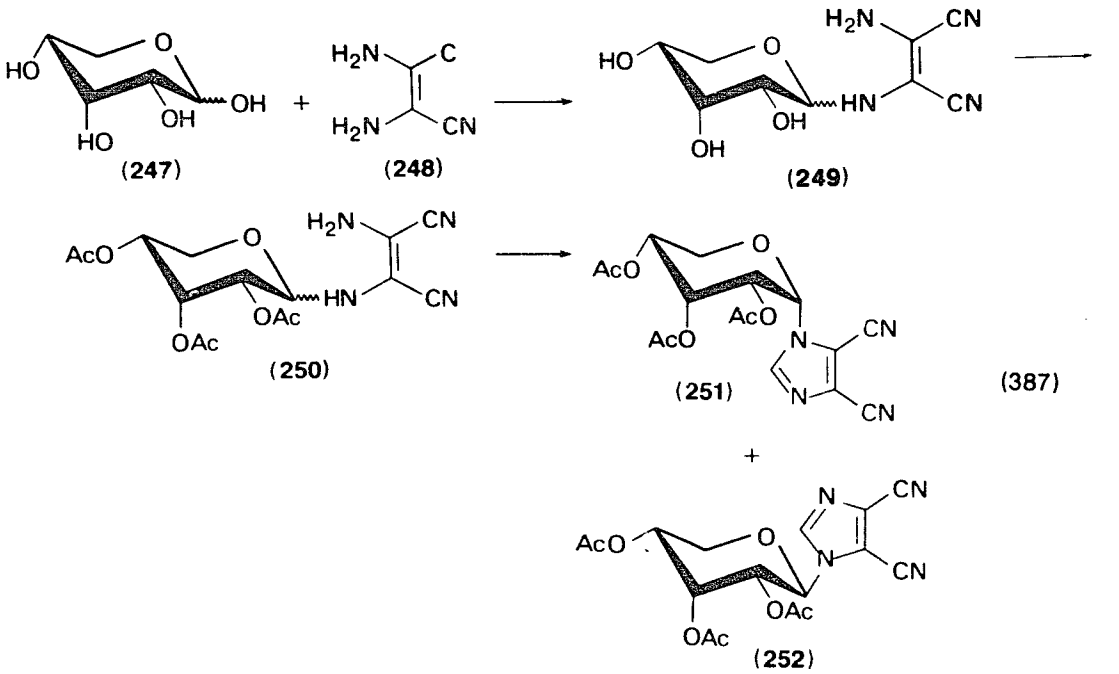
(245)

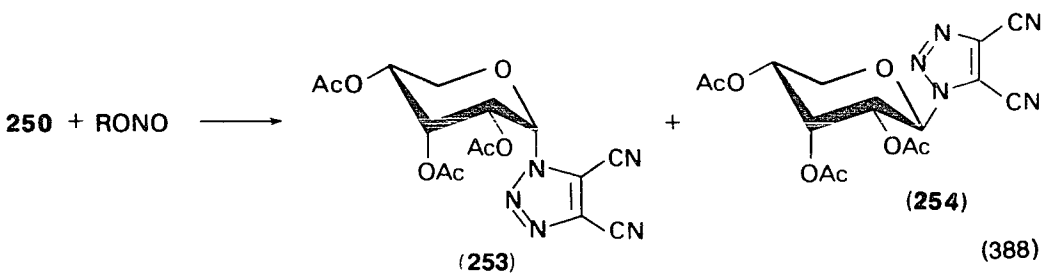


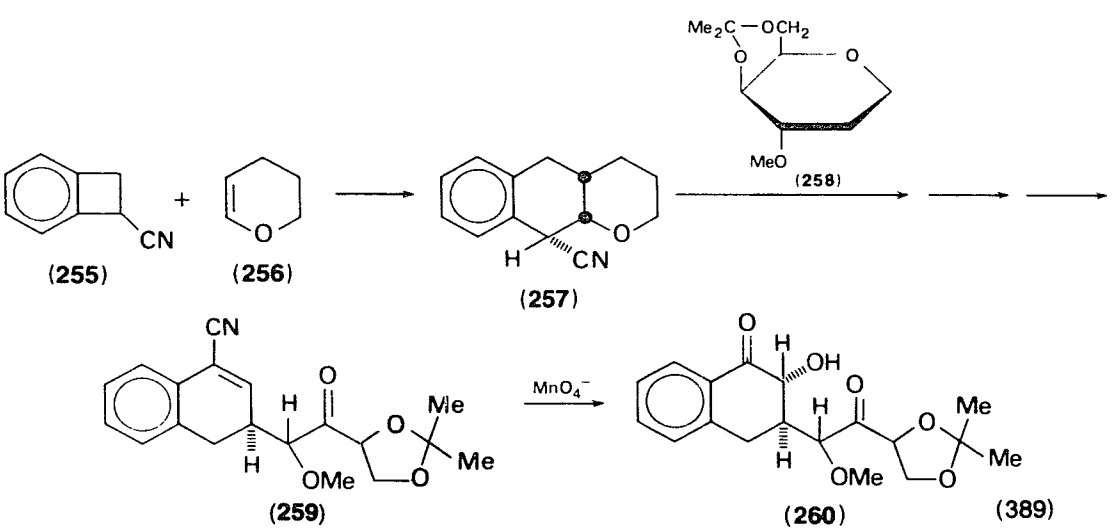
(246)

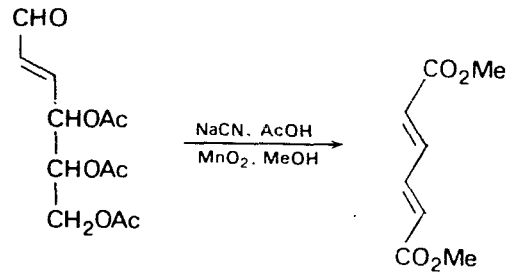
c. Synthesis of cyano nucleosides. D-Ribosyl derivatives of diaminomaleonitrile (DAMN, see Ref. 345) (**248**) constitute strategic intermediates for the synthesis of novel, nucleoside antitumour agents. The preparation of ribopyranosyl-DAMN (**249**) and the triacetate intermediate **250**, and its conversion into the D-ribopyranosyl-imidazoles (**251** and **252**) has been described (equation 387)[608]. The triazole nucleosides (**253** and **254**) are readily synthesized from D-ribopyranosyl-DAMN in the reaction of **250** with isopentyl nitrite in methanol (equation 388)[608].

d. Stereocontrolled synthesis via Diels—Alder reaction of an unsaturated sugar. The model aureolic acid aglycon (**260**) has been prepared starting with a Diels–Alder reaction between cyanobenzocyclobutene (**255**) and dihydropyran (**256**) to afford a predominantly tricyclic epimer (**257**); this is condensed with the glycal derivative (**258**) followed by ring-opening of the isomeric adducts to give a nitrile **259** (also a stereoselective and regioselective reaction). The final permanganate oxidation of **259** is also stereospecific (equation 389)[609]. A unique oxidative elimination ($NaCN + MnO_2$) of a 2,3-dideoxyhex-2-enose triacetate has been reported (equation 390)[610].


HO
OH
HO
OH
(247)
H_2N
C
H_2N
CN
(248)
HO
OH
OH
HN
H_2N
CN
CN
(249)
AcO
OAc
OAc
HN
H_2N
CN
CN
(250)
AcO
AcO
AcO
N
N
CN
CN
(251)
AcO
OAc
OAc
N
N
CN
CN
(252)
(387)


250 + RONO
AcO
OAc
AcO
N
N
N
CN
CN
(253)
AcO
OAc
OAc
N
N
N
CN
CN
(254)
(388)


CN
(255)
O
(256)
H
CN
O
O
(257)
Me_2C
O
OCH_2
O
O
MeO
(258)
CN
H
O
Me
O
H
OMe
Me
O
(259)
MnO_4^-
O
H
OH
H
O
H
OMe
Me
O
Me
(260)
(389)

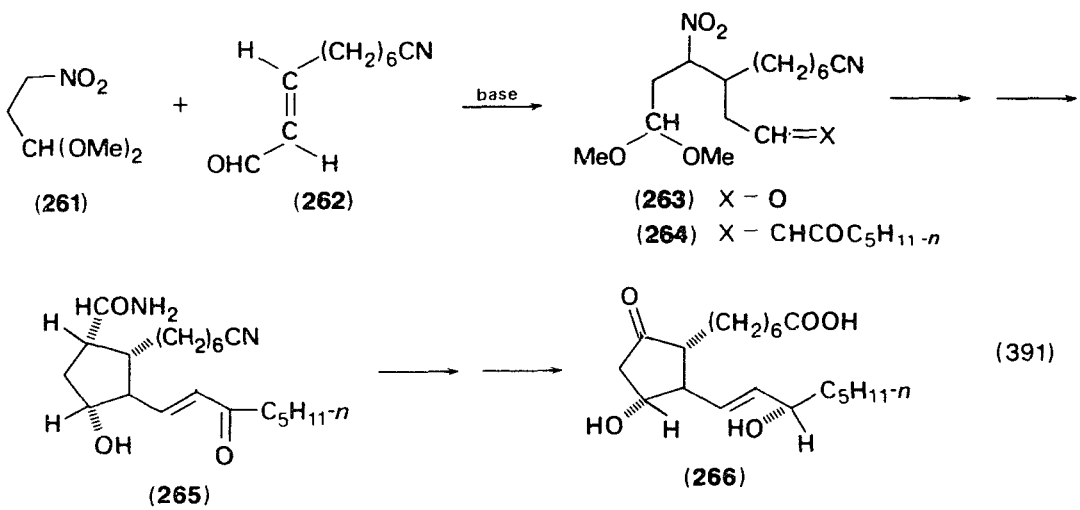


(390)

B. Selected Reactions and Transformations of Cyano Compounds

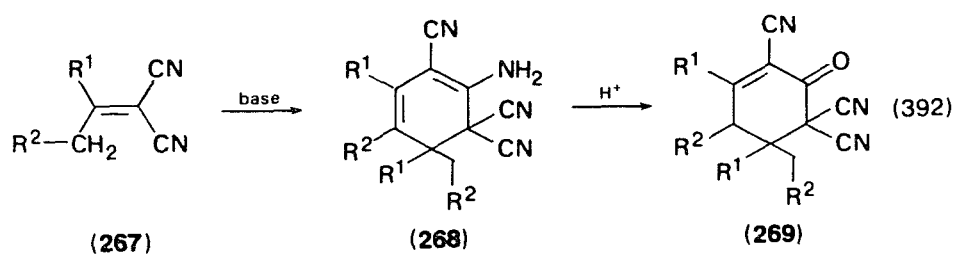
1. Synthesis of carbocyclic compounds via nitriles

a. Synthesis of prostaglandins. Corey and coworkers[611] have reported the use of cyano intermediates for the synthesis of natural products. Thus, the reaction of 3-nitropropanol dimethyl acetal (**261**) with 9-cyano-2-nonenal (**262**) leads to the Michael adduct **263** (X = O) which is converted into the conjugated enone **264** (X = $CHCOC_5H_{11}$-*n*). The latter is cyclized, to give four stereoisomers (separated by chromatography). The isomer **265** was transformed into pure *dl*-prostaglandin E_1 (**266**) (equation 391).

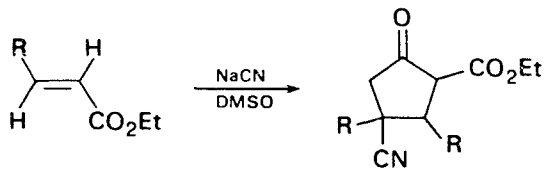


(391)

b. Other cyclization reactions. The dimerization of alkylidenemalononitriles **267** to 2,6,6-tricyano-2-cyclohexanones **269** via hydrolysis of **268** (equation 392)[612], dimerization of unsaturated esters **270** to the cyclopentanone derivatives **271** (equation 393)[613] and cyclization of a saturated nitrile (equation 394)[614] have been described.

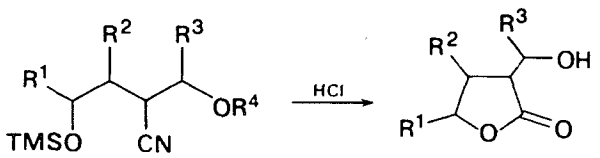


(392)



(270) (271) (393)

31–72%

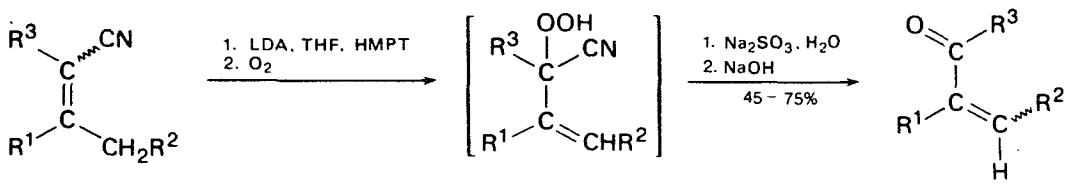


TMS = Me_3Si (394)

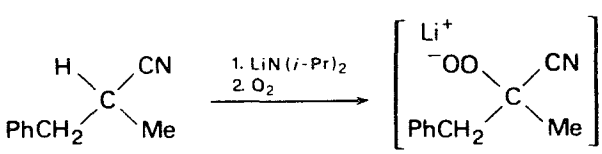
48–85%

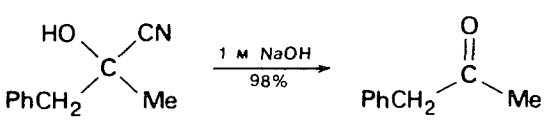
2. Decyanation of nitriles

a. Oxidative decyanation leading to ketones. A new route to α,β-unsaturated ketones starting with α,β-unsaturated nitriles involves oxygenation of a carbanion followed by reductive hydrolysis (equation 395)[615]. This oxidative decyanation is not suitable for the synthesis of α,β-unsaturated aldehydes, or for synthesis of α,β-unsaturated ketones that do not possess at least one β-hydrogen atom. Similar oxidative decyanation of secondary nitriles to alkyl aryl ketones or diaryl ketones, either via the lithium α-cyanohydroperoxide intermediate (equation 369)[616], or by *N*-silylation of a carbanion followed by treatment with iodine and silver oxide (equation 397)[617],

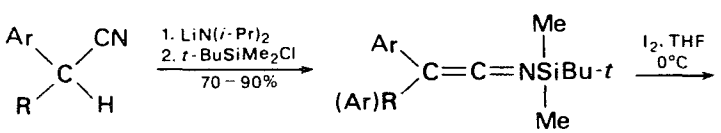


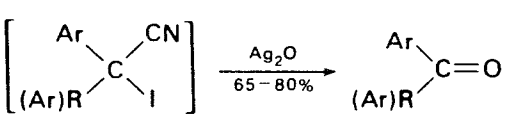
(395)





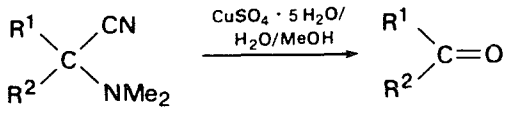
(396)





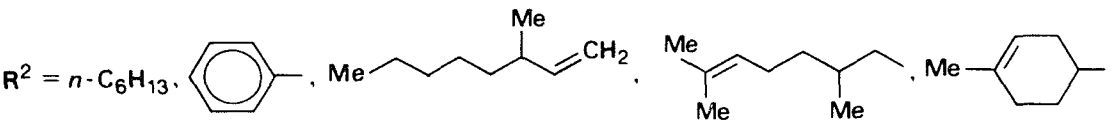
(397)

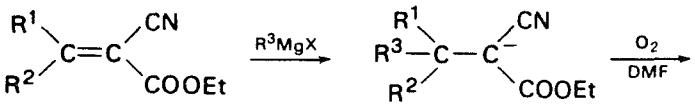
have been described by Watt. Other conversions of nitriles into carbonyl compounds include the use of copper sulphate in aqueous methanol (equation 398)[618] and a Grignard reagent followed by oxygen (equation 399)[619a]; also the use of trimethylaluminium in the presence of nickel(II) acetylacetonate (equation 400)[619b], lithium in 1,2-dimethoxyethane (DME) (equation 401)[620] or a triethyloxonium fluoroborate reagent (equation 402)[621a], or *N*-alkylation followed by reduction of *N*-alkylimines by organosilicon hydride and mild hydrolysis (equation 403)[621b].

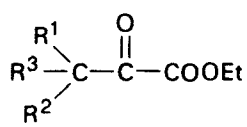


(398)

R^1 = H, Me

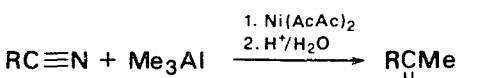






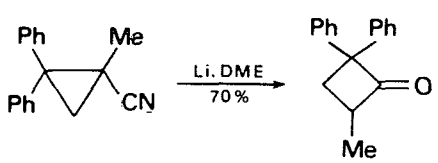
(399)

good yields

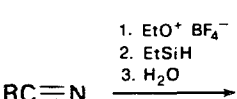


(400)

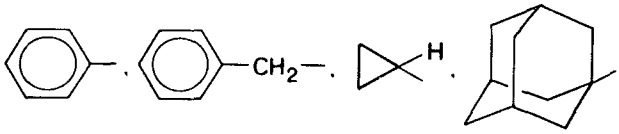
R = *n*-$C_{12}H_{25}$, Ph, $PhCH_2$, Ph_2CH, 4-$ClC_6H_4CH_2$



(401)

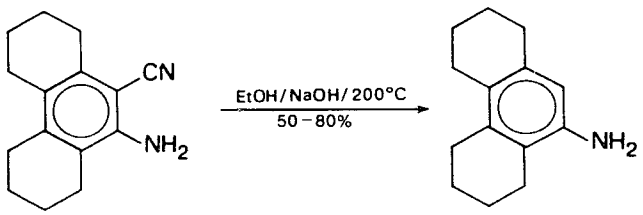


(402)

R = *i*-Pr, *n*-Bu, *t*-Bu, 

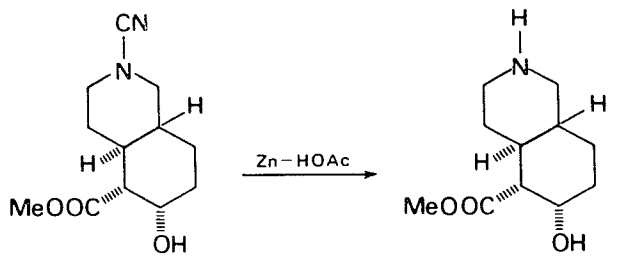
$$R^1C{\equiv}N + R^2X \longrightarrow R^1C{\equiv}\overset{+}{N}R^2X^- \xrightarrow{Et_3SiH} R^1CH{=}NR^2 \longrightarrow RCH{=}O \quad (403)$$

b. Decyanation via elimination. The nitrile group of certain *o*-aminonitriles is eliminated when the compound is heated with ethanolic sodium hydroxide in an autoclave for some hours at 200°C (equation 404)[622]. The reaction probably occurs via the *o*-aminocarboxylic acid.

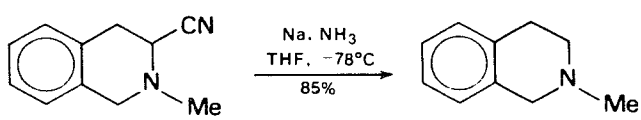


(404)

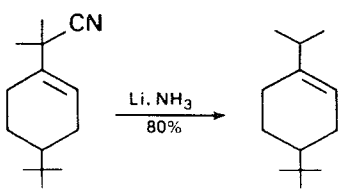
c. Reductive decyanation. Reductive decyanation can be effected with zinc in acetic acid[623,624], e.g. decyanation of a cyanamide derivative (equation 405)[624], and, also with solutions of alkali metals in HMPT in the presence of *t*-butyl alcohol[625a] with sodium naphthalenide in HMPT[625b], with sodium (equation 406)[626] or lithium (equation 407)[627] in liquid ammonia or by treatment with iron(III) acetylacetonate and sodium sand in dry benzene at room temperature (under argon), e.g. conversion of primary, secondary and tertiary cyanides into hydrocarbons (RCN → RH) (58–100% yield)[628]. Recently, dispersed potassium over neutral alumina (K/Al_2O_3) in hexane has been used for converting nitriles into corresponding alkanes (70–90% yield) (equation 408)[629].



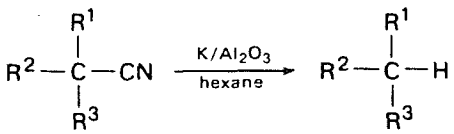
(405)



(406)



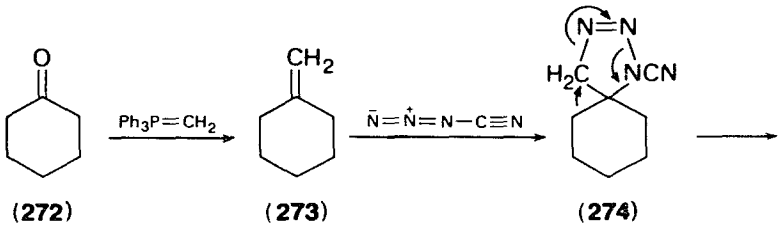
(407)



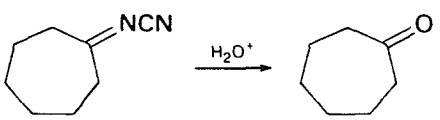
(408)

3. 1,3-Dipolar addition of cyanogen azide to alkenes; a ring-expansion reaction

In the classical view[630,631], 1,3-dipolar addition of organic azides to electron-rich alkenes, although concerted, takes place by a weak, dipolar transition state, to give the most stable carbocation on the alkenic part. The regiospecificity of 1,3-dipolar additions has been predicted by perturbational, molecular orbital (PMO) theory[632]. Hermes and March[633] have reported that cyanogen azide (N_3CN) and alkenes give additional products that are, in some cases, rearranged ketone precursors. McMurry and Coppolino[634] have investigated the synthetic utility of the ring-enlargement following the addition of cyanogen azide to alkylidenecycloalkanes. For example, when methylenecyclohexane (**273**) is treated with cyanogen azide, and the product (**275**) (formed via an intermediate **274**) hydrolysed, cycloheptanone (**276**) results (equation 409)[634]. The reaction is applicable both to saturated and α,β-unsaturated ketones, including the ring-enlargement of a typical 5α-3-keto steroid (equation 410). The reaction is a useful alternative to other methods of one-carbon ring-expansion. In cyanogen azide additions, the authors[634] have also observed vinyl migration, in preference to alkyl migration, in the conjugated alkene **277** (R = H). In contrast, **278** (R = Me) reacts with preferential alkyl migration (equation 411; cf. Reference 635).

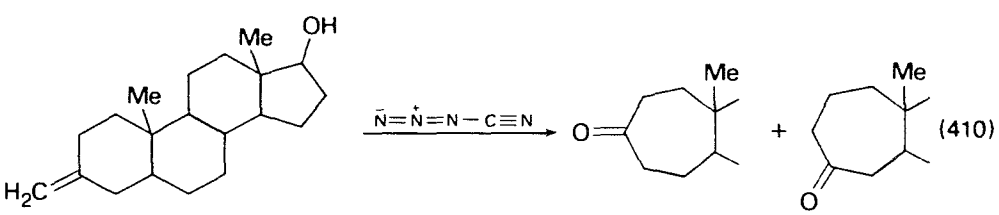


(**272**) (**273**) (**274**)



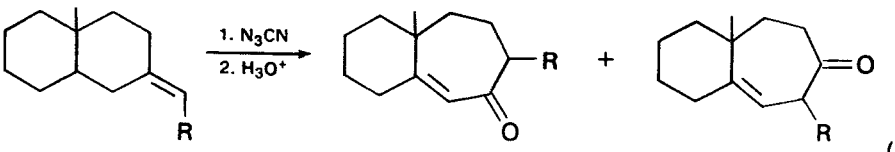
(409)

(**275**) (**276**) Overall yield 80%



(410)

56 : 44



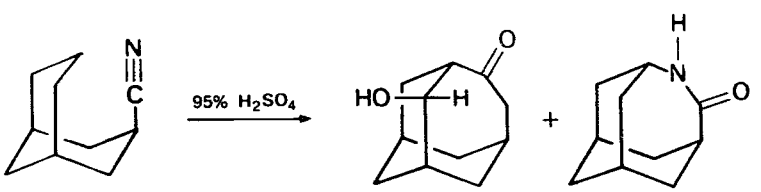
(411)

(**277**) R = H
(**278**) R = Me

Ratio of products	
~Vinyl	~Alkyl
70	30
13	87

4. *Transannular cyclization of bicyclic nitriles*

In principle, a nitrile may act as both an electrophile and a nucleophile[636], and this behaviour is evident from the following transannular reaction of a bicyclic nitrile. The original study[637] reported the cyclization of the cyano group in bicyclo[3.3.1]-6-nonene-3-*endo*-nitrile (**279**) to give **280** and **281**. The analysis of the reaction by Hassner and coworkers[638] revealed that the major product, 3-*exo*-hydroxy-homoadamantanone (**280**), is formed by initial protonation of the nitrile, followed by transannular double-bond participation; the formation of **281**, however, may arise from initial protonation of the double bond followed by an intramolecular Ritter reaction (equation 412). The nitrile group in **279** has also been shown to participate in cyclization under oxidizing and reducing conditions.

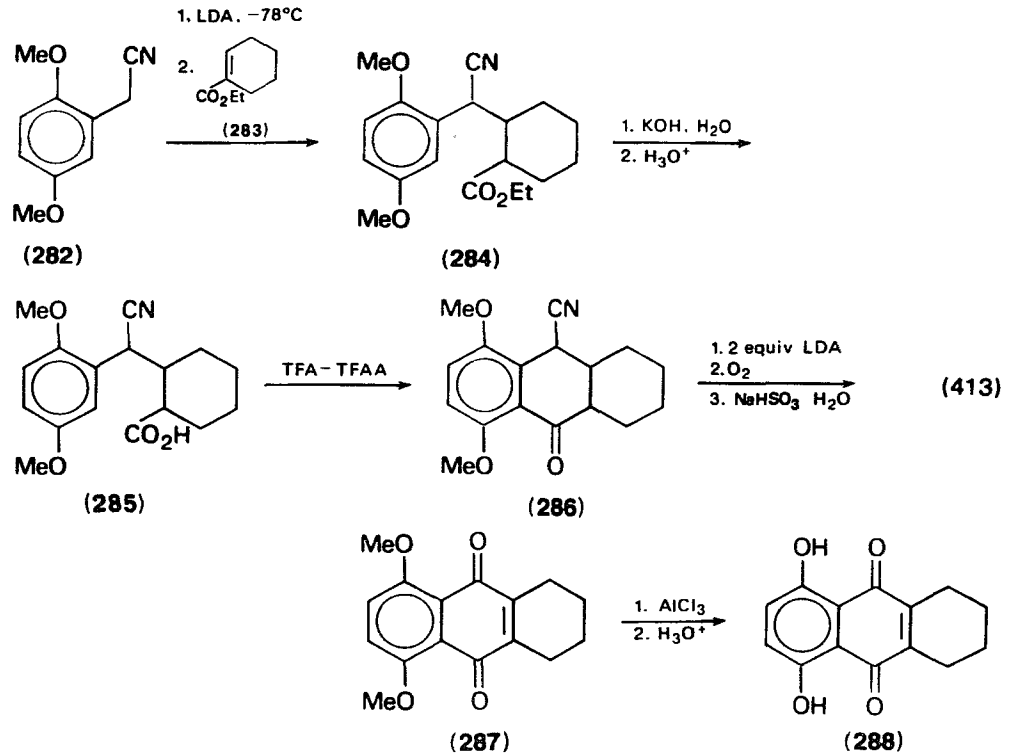


(412)

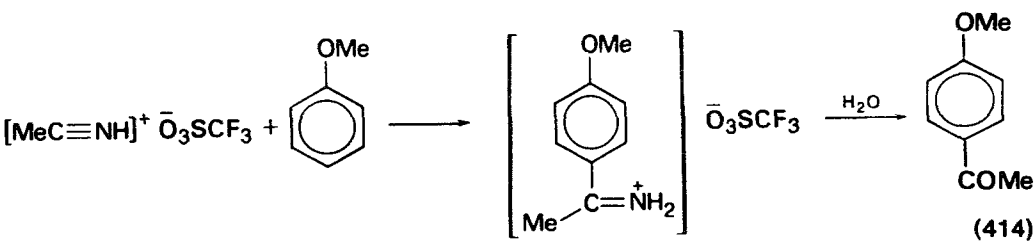
(**279**) major (**280**) minor (**281**)

5. *The conjugate addition of arylacetonitriles to cyclohexene esters*

The Michael reaction of arylacetonitrile enolates with an α,β-unsaturated ester constitutes an important step in the synthesis of antitumour anthracycline antibiotics[639,640]. Parker and Kallmerten found[640] that when the lithium enolate of the phenylacetonitrile (**282** + lithium diisopropylamide, LDA)[641] is treated with the α,β-unsaturated ester **283**, the Michael adduct **284** is obtained; the latter is converted into tetrahydroquinizarin (**288**) via intermediates **285** to **287** (equation 413). It is interesting that only the application of Watt's oxidative decyanation sequence[616,617] (1 equivalent of LDA oxygen gas, followed by sodium bisulphite and sodium hydroxide washes) enabled the authors to convert the keto nitrile **286** into the quinone **287**. Treatment of **286** with alkaline hydroperoxide, conditions that effect the oxidative decyanation of 9-cyano-10-anthrols to anthraquinones[642,643a] resulted only in recovery of starting material.



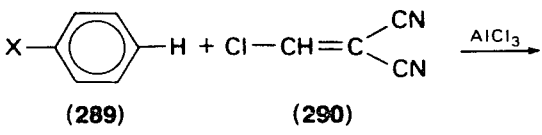
a. Acylation of phenols and phenol esters with nitriles and trifluoromethanesulphonic acid. In the classical Houben–Hoesch procedure, the acylation of phenols and phenol ethers can be achieved by reaction with an aromatic or aliphatic nitrile and dry HCl, usually in the presence of a Lewis acid, such as $ZnCl_2$ or $AlCl_3$. In a new procedure[643b], aliphatic nitriles RCN (R = Me, n-Pr, CH_2Cl and CCl_3) in the presence of trifluoromethanesulphonic acid (triflic acid) have been found to react with mono-, di- and tri-substituted phenols and phenol ethers at room temperature to give ketones, after hydrolysis of the intermediate ketiminium salt. Thus anisole gives 4-methoxyacetophenone in 58% yield (equation 414)[643b].



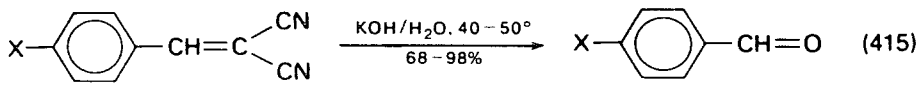
(414)

6. *Aromatic aldehydes from hydrocarbons*

A novel synthesis of aromatic aldehydes **292** is based on (*i*) conversion of arenes **289** into the dicyanovinyl compounds **291** on treatment with (chloromethylene)malononitrile (**290**) and (*ii*) hydrolysis of **291** to give **292** (equation 415)[644]. The ready cleavage



(289) (290)



(291) (292)

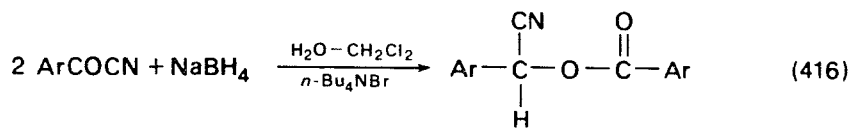
49–65%

X = H, Cl, Me, MeO (415)

of the dicyanovinyl group in aqueous alkali under mild conditions, to give **292**, is an example of a reversal of the Knoevenagel reaction.

7. *A new synthesis of cyanohydrin esters*

Cyanohydrin esters are obtained by acylation of cyanohydrins, which are often generated *in situ* or by the reaction of carbonyl compounds with specialized cyanation reagents[308]. The reduction of acyl cyanides with sodium borohydride has not been studied; however, it is known that borohydride does not react with the cyano group of ordinary nitriles[646] unless the reagent is chemically modified[647]. In a new procedure[648], an acyl cyanide (**293**) in dichlomethane is treated with a solution of sodium borohydride in water in the presence of a phase-transfer catalyst, e.g. tetrabutylammonium bromide, and the cyanohydrin ester **294** is obtained in quantitative yield (equation 416)[648].

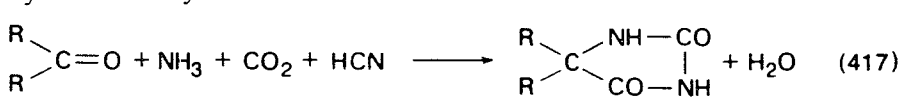


(293) (294)

Ar = Ph, *m*-MeC_6H_4, *p*-MeC_6H_4 (416)

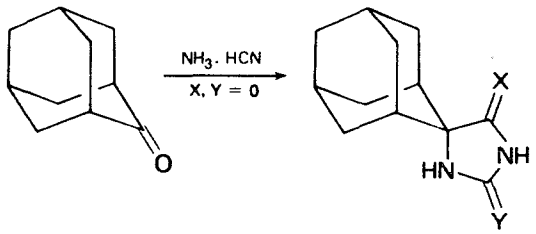
8. *Synthesis of hydantoins and thiohydantoins via the Bücherer–Bergs reaction*

Aldehydes and ketones undergo the Strecker reaction, to give α-aminonitriles which may be hydrolysed to α-amino acids[649]. The latter are often more conveniently obtained by hydrolysis of hydantoins (**296**), synthesized from ketones (**295**) by reaction with hydrogen cyanide, ammonia and carbon dioxide (e.g. ammonium carbonate). This is the Bücherer–Bergs reaction (equation 417)[650]. Employment of carbon disulphide instead of carbon dioxide provides 2,4-dithiohydantoin[651], and use of carbon disulphide yields 4-thiohydantoin[652].



(295) (296) (417)

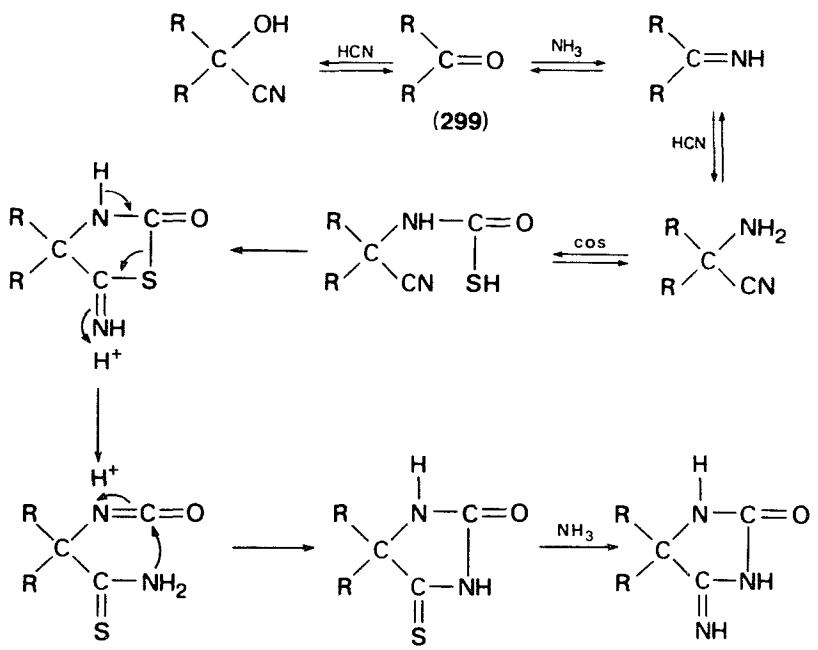
For sterically hindered ketones, even the Bücherer–Bergs reaction sometimes fails unless drastic conditions are used. Thus, Nagasawa and coworkers[653] obtained the



(418)

(297) (298)

hydantoin **298** (X, Y = O) from adamantanone (**297**), by the original (CO_2) procedure, only by carrying out the reaction at 120°C for 3h in a pressure vessel (equation 418). Edward and coworkers[654] optimized the yields of *spiro*-4-thiohydantoins (**300**) [R,R = $(CH_2)_5$] from cyclohexanone and of **298** (X = S, Y = O) from adamantanone, by systematic variation of the concentration of the reactants, the temperature, the time period and the composition of the solvent, as guided by the simplex evolutionary operation. A possible mechanism for the formation of a 4-thiohydantoin (**300**) from a ketone (**299**) is shown in Scheme 1[654].

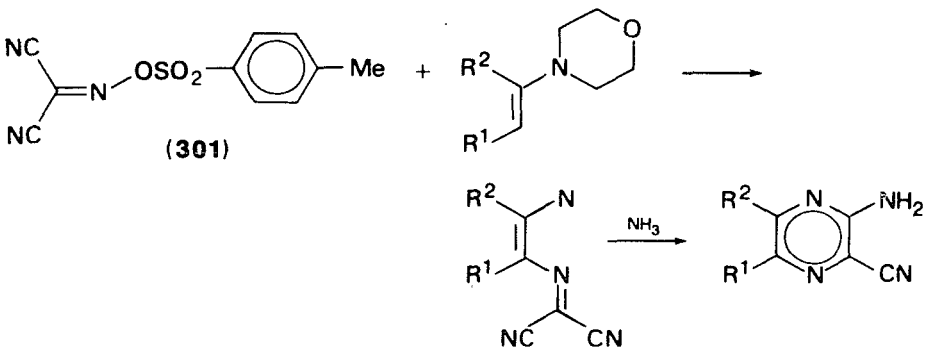


(**300**)

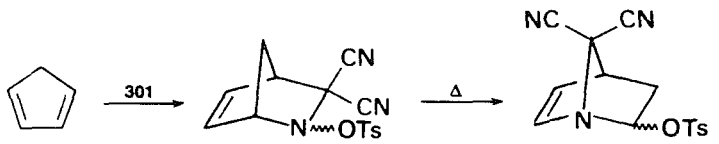
SCHEME 1

9. *(O-p-Tosylisonitroso)malononitrile* (**301**), *a high reactive, electrophilic azomethine*

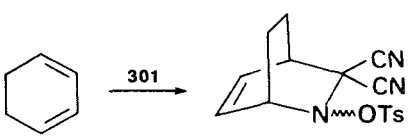
Compound **301** is a reagent useful for the synthesis of heterocycles, particularly aminopyrazines (equation 419)[655,656]. The reagent also functions as a Diels–Alder dienophile (equations 420 and 421)[657].



(419)



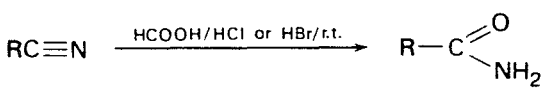
(420)



(421)

10. Conversion of nitriles into amides, N-alkylamides and thioamides

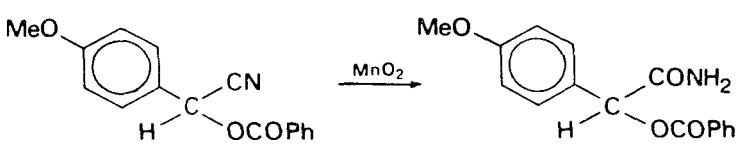
a. Conversion of nitriles into amides. The conversion of nitriles into amides may be achieved with formic acid plus hydrogen chloride (equation 422)[658], active manganese dioxide (equation 423)[659], basic hydrogen peroxide under phase-transfer catalysis (equation 424)[660], or sodium peroxide in dimethyl sulphoxide at room temperature (equation 425)[661].



(422)

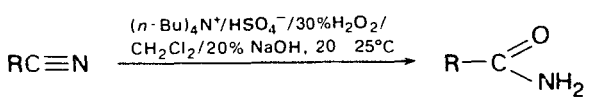
85 - 99%

R = *n*-C_5H_{11}, *c*-C_6H_{11}, $-CH_2Ph$, $-CH_2CH_2OPh$

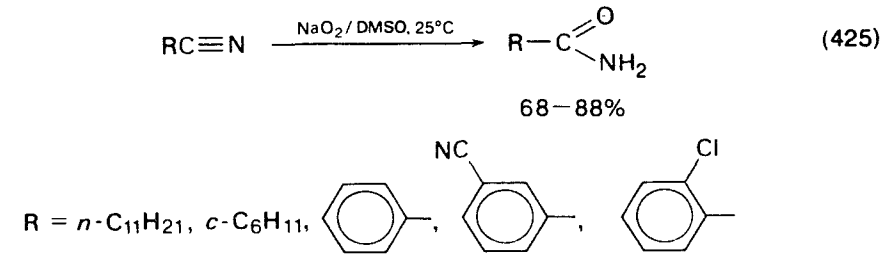


(423)

66%

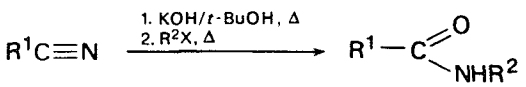


(424)

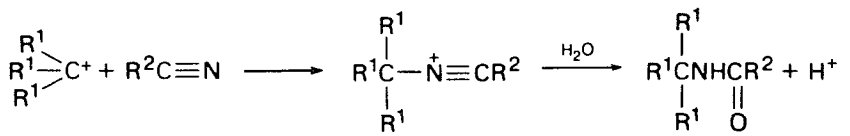


(425)

b. Conversion of nitriles into N-*alkylamides*. This involves their reaction with potassium hydroxide–*t*-butyl alcohol, followed by an alkyl iodide (equation 426)[662], or with a carbenium ion intermediate stabilized by a chromium tricarbonyl complex, e.g. $Cr(CO)_3$ (equation 427)[663].

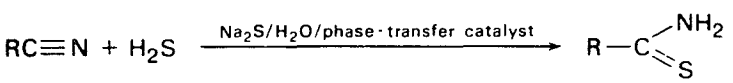


(426)

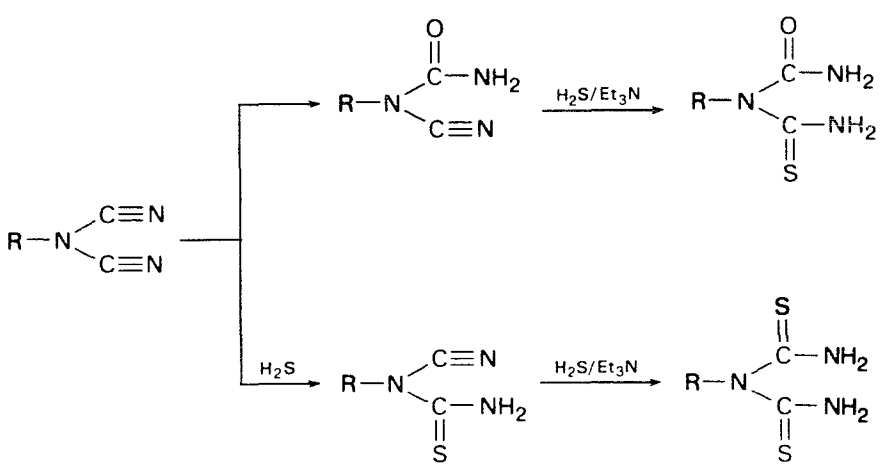


(427)

c. Conversion of nitriles into thioamides. This involves reaction with hydrogen sulphide in the presence of phase-transfer catalysts (equation 428)[664]. The synthesis of 1-alkyl-1-cyano-2-thioureas, 3-alkyl-2-thiobiurets and 3-alkyl-2,4-dithiobiurets can be achieved by the reaction of 1-alkyl-1-cyanoureas with hydrogen sulphide and triethylamine (equation 429)[665].



(428)



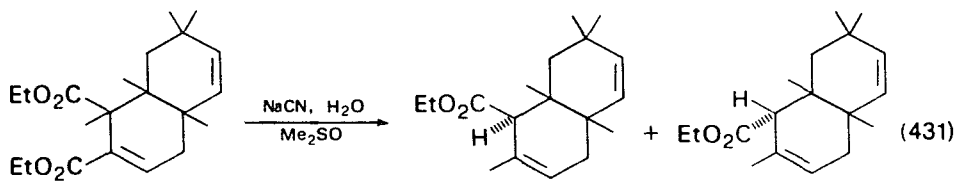
(429)

11. Hydrolysis and decarboxylation

a. t-Butoxide-catalysed oxidative hydrolysis of nitriles. Potassium *t*-butoxide in oxolane (THF) in presence of 18-crown-6 oxidatively cleaves long-chain nitriles to give a carboxylic acid with loss of the cyano carbon atom (equation 430)[666]. The yields are the highest for such long-chain, aliphatic nitriles as cyanohexadecane (89% conversion).

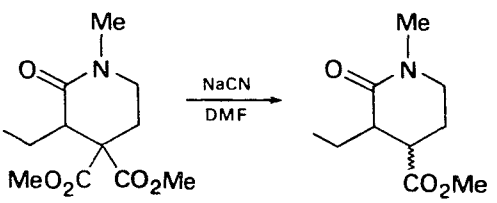
$$RCH_2CN + t\text{-BuOK} \xrightarrow{O_2} RC(O)CN \xrightarrow{H_2O} \underset{21-93\%}{RCOOH} \qquad (430)$$

b. Decarboxylation of cyclic geminal diesters: stereochemistry. Although the decarboxylation of geminal diesters and related systems has been known and used for a number of years, there are few reported examples on its stereochemistry. Van Tamelen and coworkers[667] have reported that the decarboxylation of **302** results in **303** and **304** in the ratio of 8:1, in an overall 70% conversion (equation 431)[668]. Dolby and

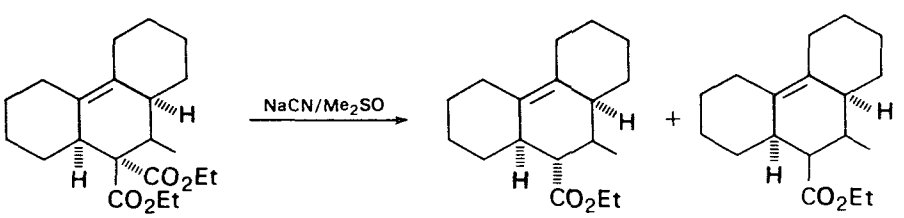


(302) (303) (304) (431)

Biere[669] have reported that the demethoxycarbonylation of **305** with NaCN–DMF leads to **306**, as an undefined mixture of diastereomers, in 70% yield (equation 432)[669]. Christol and coworkers[670,671] have reported stereochemical studies of tricyclic systems; for example, the decarboxylation of **307** gives 98% **308** and only 2% **309** (equation 433).



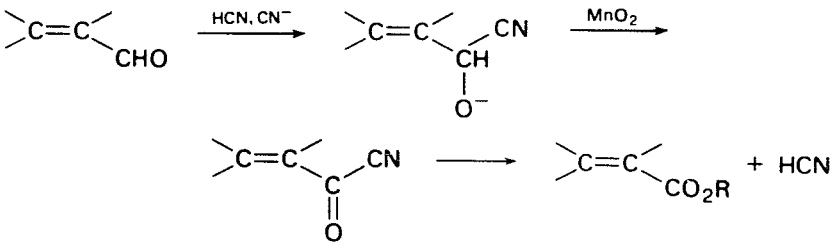
(305) (306) (432)



(307) (308) (309) (433)

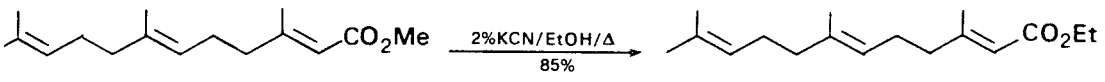
98% 2%

c. Mild transesterification. Corey's oxidative esterification of α,β-unsaturated aldehydes uses hydrogen cyanide and proceeds with no *cis–trans* isomerization of the double bond (equation 434)[672]. It has been found[673] that potassium cyanide is a mild



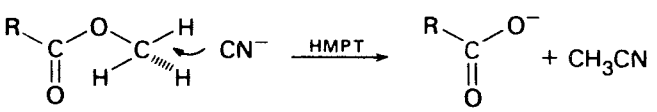
(434)

and effective catalyst in transesterification of α,β-unsaturated esters, without isomerization of the conjugated double bond. For example, methyl *trans,trans*-farnesoate (**310**) is readily converted into the ethyl ester **311**, with only very slight *cis–trans* isomerization (isomer ratio = 2-*trans*: 2-*cis* = 9:1) (equation 435)[673]. The method is particularty useful in the case of substrates sensitive to strong acids and bases[674].

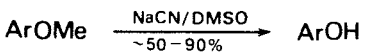


(**310**) (**311**) (435)

d. Selective cleavage of methyl esters and ethers. Sodium cyanide in HMPT selectively cleaves methyl esters in the presence of ethyl esters. The reaction probably proceeds via a $B_{A1}2$ mechanism, that is, displacement of carboxylate by attack of the cyanide ion on the alcohol carbon atom (equation 436)[675]. Sodium cyanide in DMSO is an effective reagent for the cleavage of aromatic ethers (equation 437)[676].



(436)



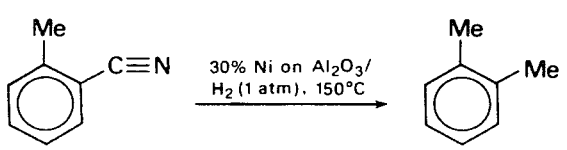
(437)

Ar = subst. Ph, subst. naphthyl, pyrimidyl, etc.

12. *Direct transformation of a cyano into a methyl group*

The direct transformation of a cyano group into a methyl group by catalytic hydrogenation has seldom been reported, although gas-phase reduction of a few nitriles to hydrocarbons has been examined for analytical purposes[677].

It has now been found[678] that aromatic and tertiary nitriles are converted into the corresponding methyl hydrocarbons when heated at 120–150°C with hydrogen at normal pressure in the presence of 30% nickel-on-alumina. For example, *o*-toluonitrile (**312**) has been reduced to *o*-xylene (**313**) (equation 438), and, similarly



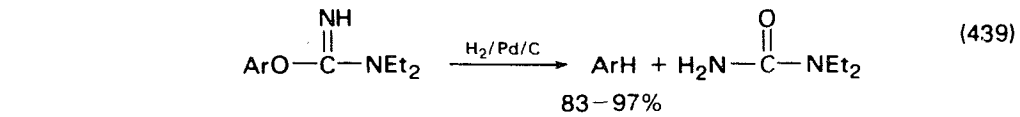
(**312**) (**313**) (438)

92%

1-adamantanecarbonitrile gives 1-methyladamantane (99%), and cyclopentanecarbonitrile gives cyclopentane (83%) and methylcyclopentane (11%).

13. Dehydroxylation of phenols

Phenols can be converted into hydrocarbons by the sequence formulated; the procedure involves reductive cleavage of the intermediate *O*-aryl-*N*,*N*-diethylpseudourea (equation 439)[679] or of a diaryl carbonimidate (equation 440)[680].



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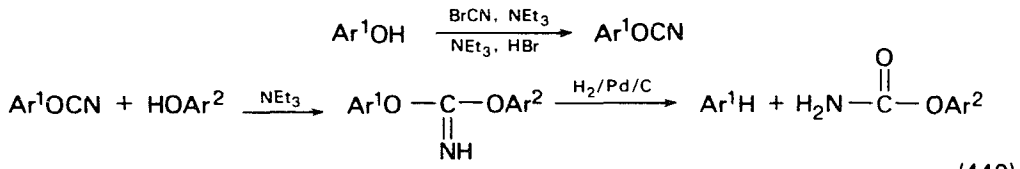
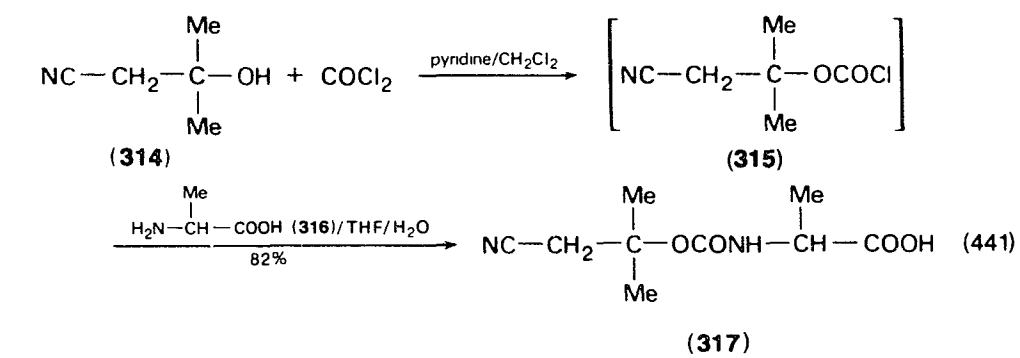


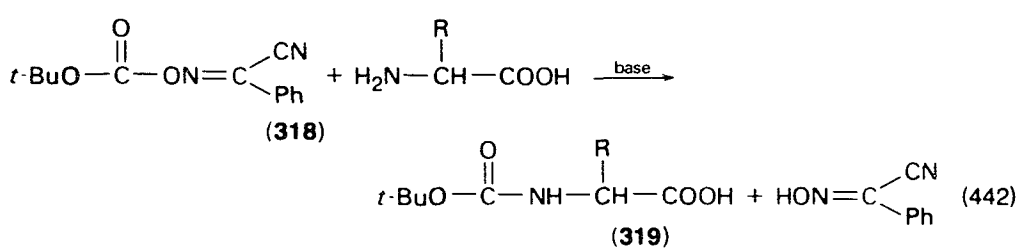
(440)

14. New amino-protecting groups

N-(Cyano-*t*-butoxy)carbonyl (CyOC)-protected amino acids (**317**) may be prepared in a one-step synthesis involving condensation of (cyano-*t*-butoxy)carbonyl chloride (**315** prepared from **314**) with amino acids (e.g. **316**) in THF–water at pH 8.5; compounds **317** can be coupled with amino acids and peptides (equation 441)[681]. A new, amino-protecting reagent, i.e. 2-(*t*-butoxycarbonyl) oxyimino-2-phenylacetonitrile (BOC-ON) (**318**) is at present the reagent of choice for *t*-butoxycarbonylation of amino groups, affording contaminant-free *t*-BOC-amino acids (**319**) in high yield (equation 442)[682].



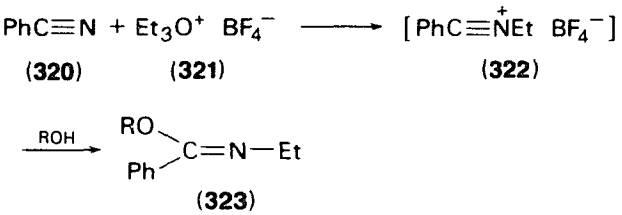
(441)



(442)

15. Conversion of nitriles into nitrilium ions and imidates

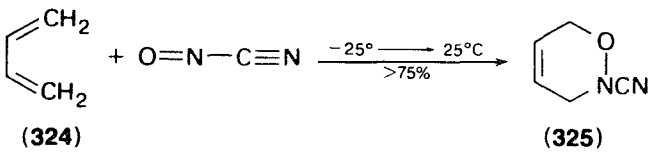
1,3-Dipolar ions, e.g. nitrilium ions ($R-C\equiv N^+-R\ X^-$), nitrile oxides, ($-C\equiv N^+-O^-$), nitrile imines ($-C\equiv N^+-N^-$) and nitrile ylides ($-C\equiv N^+-C^-$) are important synthons for stereospecific organic synthesis[683]. Nitrilium ions (e.g. **322**) can be readily prepared by alkylation, or protonation, of nitriles; they can be isolated as such (usually as BF_4^- salts [684] or may react further with nucleophiles *in situ*. An example is the alkylation of benzonitrile (**320**) with the Meerwein reagent **321** to give **322**[684], which, by reaction with alcohol, provides a useful route to imidates (**323**)[685] (equation 443). The Ritter reaction[686] of an alcohol or diol with a nitrile in the presence of an acid probably follows a similar course.



(443)

16. The electrophilic dienophile, nitrosyl cyanide

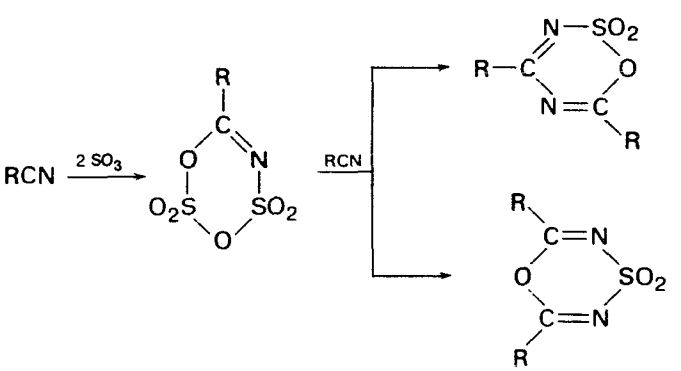
Nitrosyl chloride and silver cyanide react at −78°C to give nitrosyl cyanide (O=N—C≡N) a powerful electrophilic dienophile which undergoes Diels–Alder reactions. For example, *N*-cyanooxazine (**325**) has been prepared from butadiene (**324**) (equation 444)[687a]



(444)

17. Additional synthetic methods

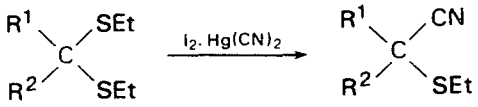
Nitriles react readily with sulphur trioxide (SO_3) to give cycloadducts (e.g. 1,3-dioxa-2,3,6-diathiazine-2,2,6,6-tetraoxide) (via donor–acceptor n and π complexes); on further reaction with nitriles these yield heterocycles (equation 445). A study has shown[687b] that nitrile–SO_3 adducts interact with a wide range of organic reagents (e.g.



(445)

aromatics, amides, pyridines), to give new open-ring products, different from those expected from the reaction of the parent nitriles. The chemistry of nitrile–sulphur trioxide adducts is still a challenge for a synthetic chemist.

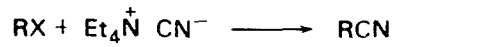
A few additional synthetic methods involving either cyano substrates or cyano reagents are depicted in equations (446)–(464)[688–704].



(Ref. 688) (446)

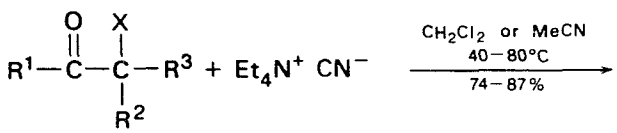
R^1 R^2 = H, alkyl, aryl

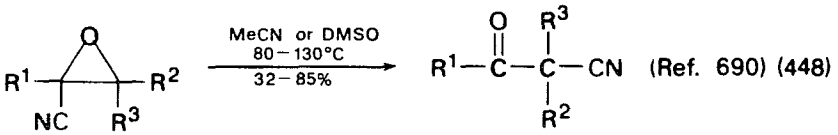
Yields generally 40–70%



(Ref. 689) (447)

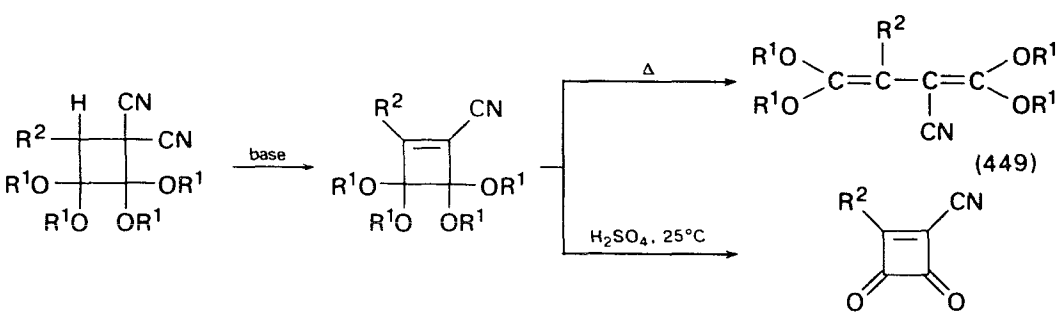
RX	Solvent	Yield (%)
n-BuBr	CH_2Cl_2	74
s-BuBr	MeCN	80
t-BuBr	MeCN	54



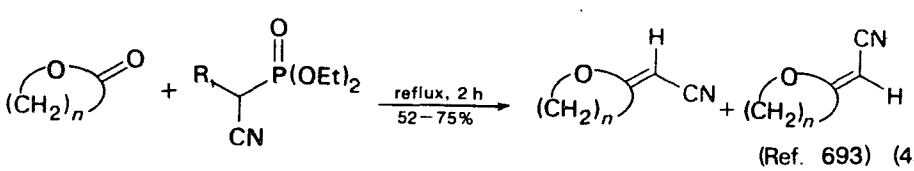


(Ref. 690) (448)

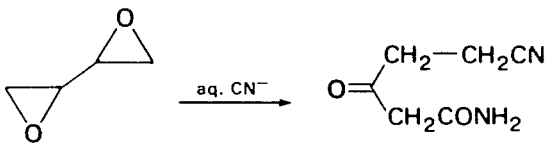
R^1 = Me, *i*-Pr, Ph
R^2 = H, Me, Ph
R^3 = Me, Ph
X = Cl, Br



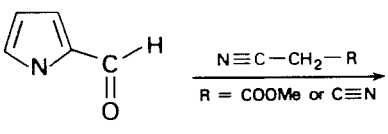
(449)



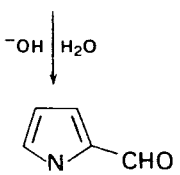
(Ref. 693) (450)

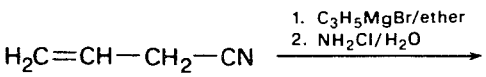


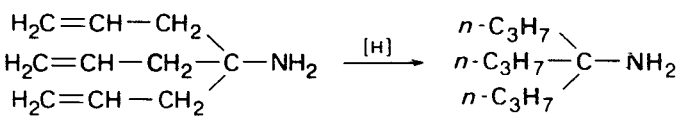
(Ref. 694) (451)



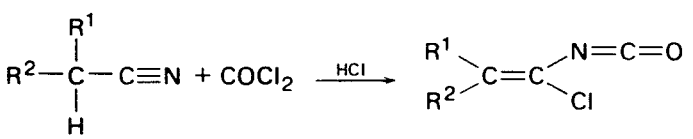
(Ref. 695) (452)



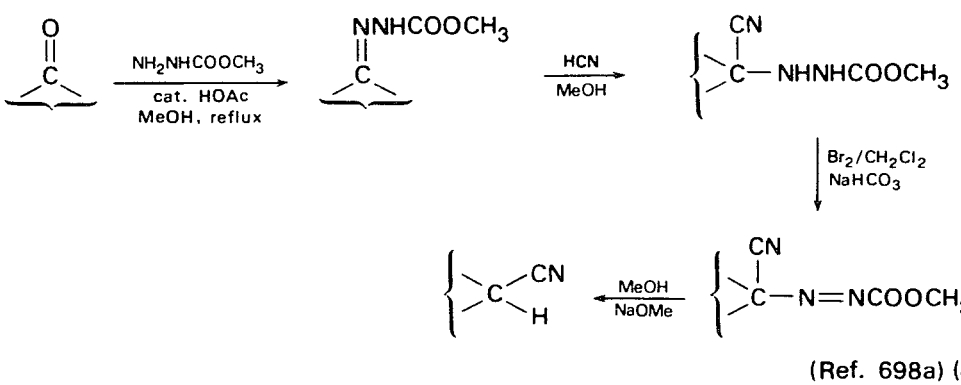




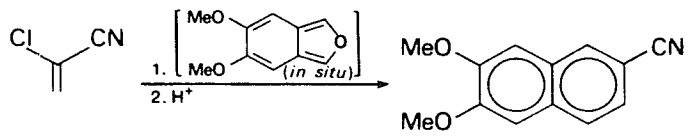
(Ref. 696) (453)



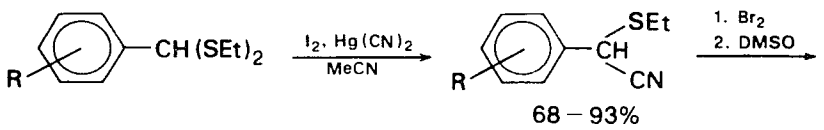
(Ref. 697) (454)



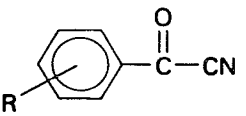
(Ref. 698a) (455)



(Ref. 698b) (456)

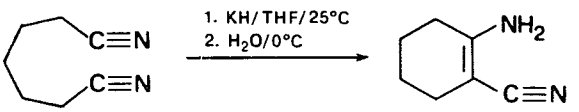


68 – 93%



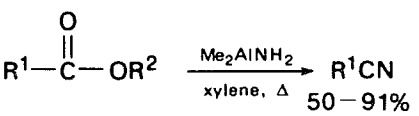
(Ref. 699) (457)

70 – 90%



(Ref. 700) (458)

83%

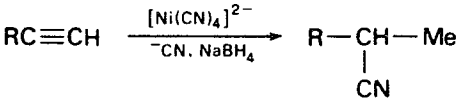


50 – 91%

(Ref. 701) (459)

R^1 = alkyl, aryl, cinnamyl

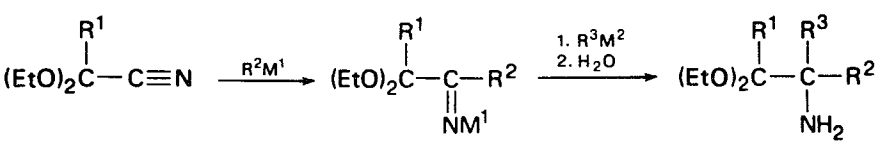
R^2 = Me, Et



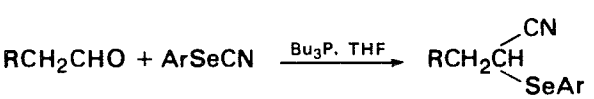
85 – 98%

(Ref. 702) (460)

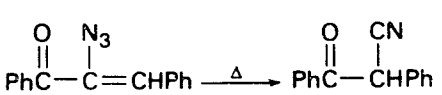
R = Ph, $PhCH_2CH_2$, c-C_6H_{10}(OH)



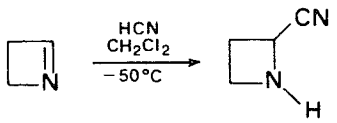
(Ref. 704a) (461)



(Ref. 704b) (462)



(Ref. 704c) (463)

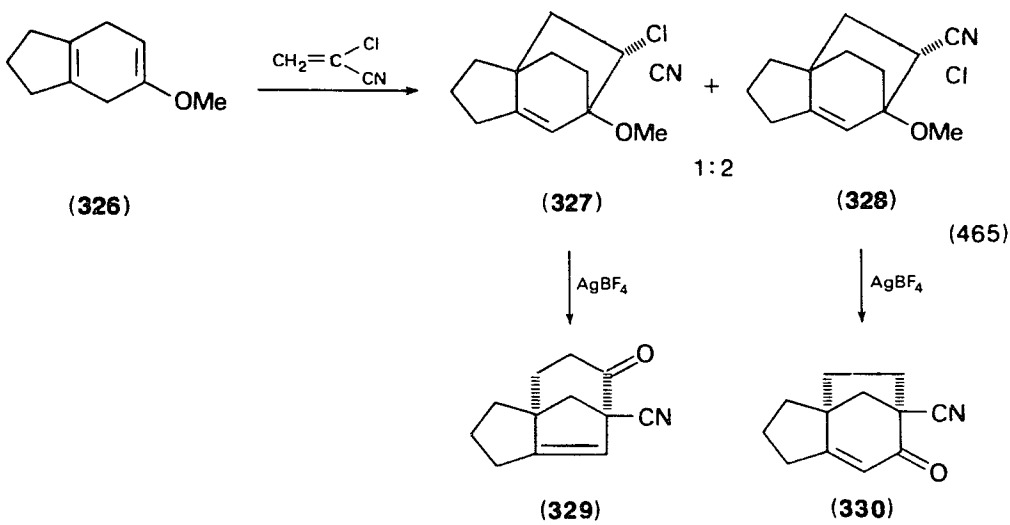


(Ref. 704d) (464)

C. Rearrangement of Cyano Compounds

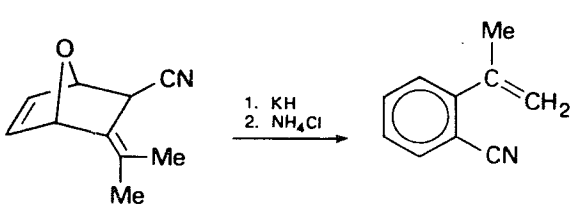
1. *Rearrangement of the Diels–Alder adducts*

The adducts **327** and **328** from the Diels–Alder reaction of 2-chloroacrylonitrile with 4,7-dihydro-5-methoxyindane (**326**) are rearranged uniquely by silver ion to novel bicyclo[3.2.1.]octane derivatives **329** and **330** (equation 465)[705].



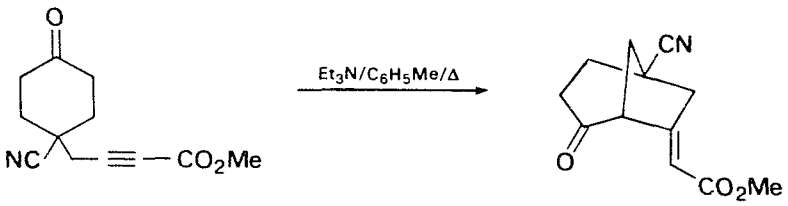
2. *β-Elimination of a heteroatom bridge*

Treatment of the Diels–Alder adduct **331** with potassium hydride in THF for 1 hr at 20°C gives **332**, formed by a molecular rearrangement involving β-elimination of the heteroatom bridge (equation 466)[706]. However, the bridged keto enoate **334** is



(466)

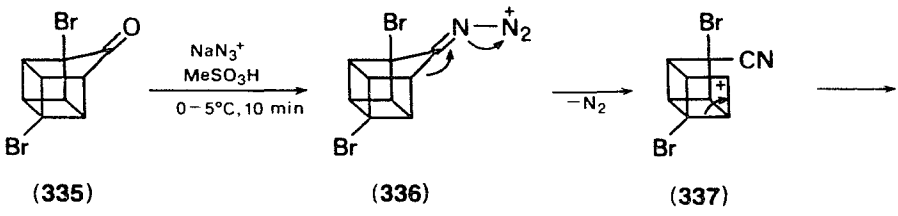
obtained from the cyclohexanone **333** (an acetylenic Michael acceptor) following treatment with triethylamine in refluxing toluene (equation 467)[707]. The acid- and base-catalysed isomerizations of *cis*-diarylacrylonitriles have been studied[708].



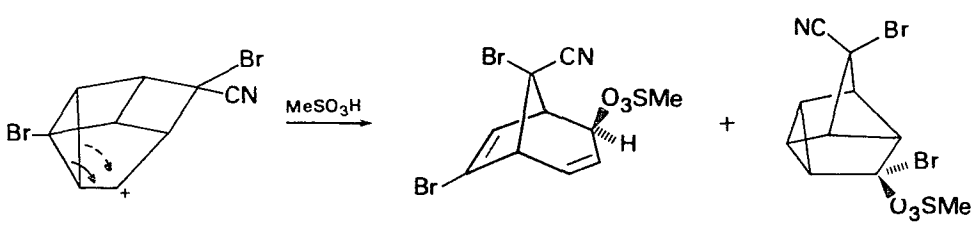
(333) (334) 70% (467)

3. *Novel rearrangement of strained polycyclic ketones*

The Schmidt reaction of homocubanone (**335**) gives as the major product (5:1, 75%) the bicyclic diene **339** and as the minor product, the tetracyclic compound **340**; a plausible mechanism involves multiple cyclobutyl–cyclopropylcarbinyl–homoallylic types of carbonium-ion rearrangements with **336** → **338** (equation 468)[709] as possible intermediates.



(335) (336) (337) (468)

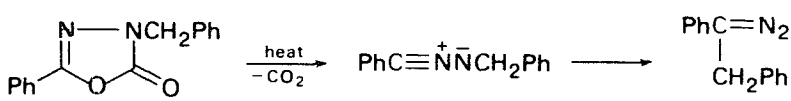


(338) (339) (340)

4. *1,3-Sigmatropic rearrangement of a nitrile* N*-benzylimide to a* C*-benzyl-substituted diazoalkane*

The synthetic usefulness of the 1,3-dipolar cycloaddition reactions of nitrile *N*-imides has been described[630,710]. The thermolysis of 1,3,4-oxadiazolin-5-ones in the gas phase, or in inert solvents, also gives nitrile *N*-imides which, in the absence of trapping agents, undergo intramolecular reorganization[711,712].

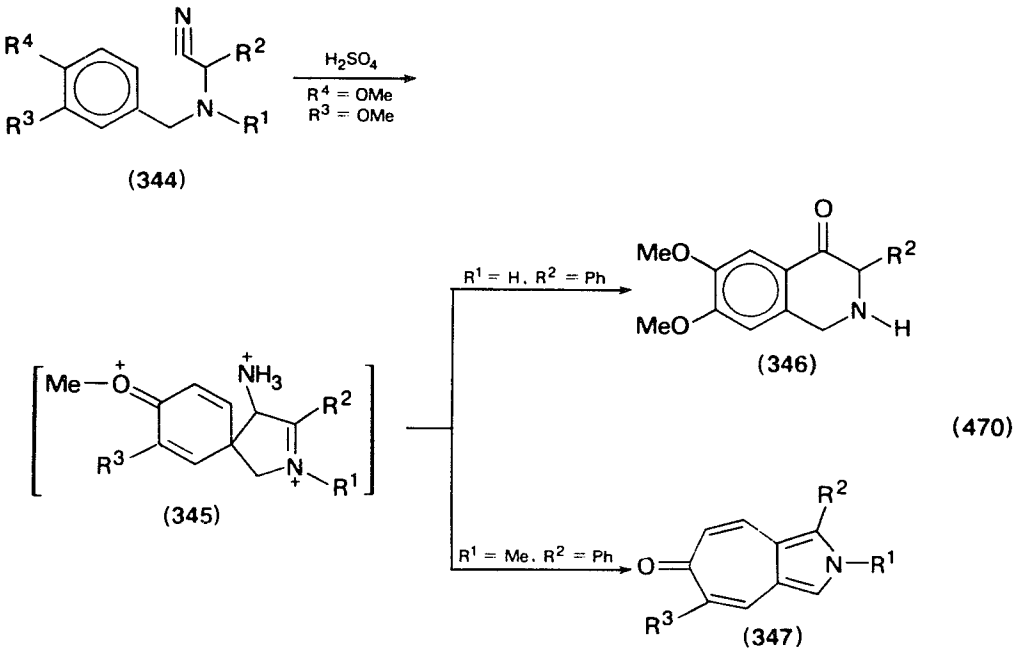
Recently, Padwa and coworkers[713] have discovered that the flash vacuum-pyrolysis of 3-benzyl-5-phenyl-1,3,4-oxadiazolin-2-one (**341**) generates a nitrile *N*-imide (**342**) which rearranges to a diazoalkane (**343**) via a 1,3-sigmatropic benzyl shift (*C*-benzyl substitution) (equation 469).



(341) (342) (343) (469)

5. *Rearrangement of benzylaminonitriles in sulphuric acid to isoquinolines*

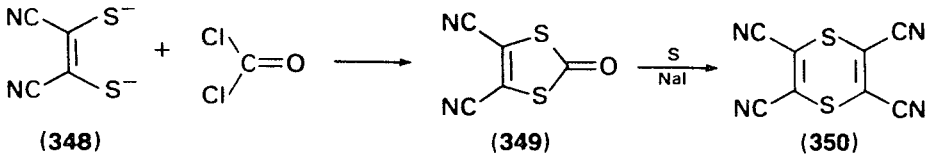
Benzylaminonitriles (**344**; R^1 = H, R^2 = Ph) cyclize in concentrated sulphuric acid, via the *spiro* intermediate **345** (R^1 = H), to give good yields of the isoquinoline **346** (R_2 = Ph)[714]. It has now been found[715] that the *N*-alkyl analogues of **344** (R_1 = Me, R^2 = Ph) rearrange to give instead the cyclohepta[*c*]-pyrrol-6(2*H*)-ones (**347**; R^1 = Me, R^2 = Ph) (equation 470). The difference in behaviour can be explained[715] as follows: under very strongly acidic conditions, protonation of **344** (R^1 = H) would occur on both nitrogen atoms, with cleavage of the five-membered ring in **345** to give the product **346**. However, when R^1 is alkyl, this pathway is blocked, and the formation of **347** (R^1 = Me) is due to a rearrangement within the spiro intermediate **345** (R^1 = Me), with *O*-demethylation, followed by a 1,2-shift with elimination of ammonia.



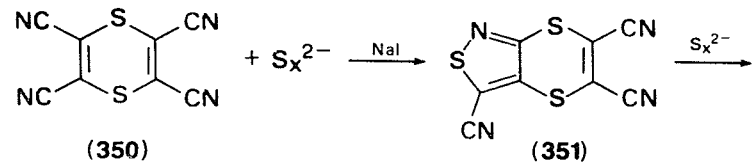
(470)

6. *Sulphur insertion–rearrangement reaction. Synthesis of heteroarenes via rearrangements*

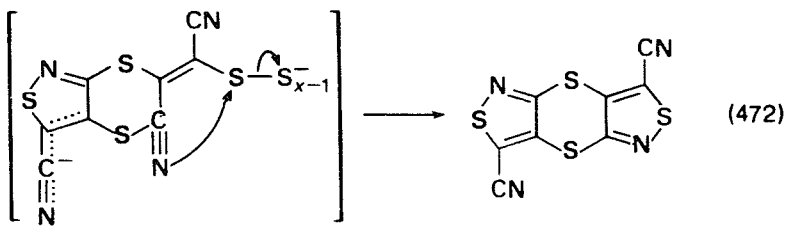
Thiocyanocarbons[716] constitute an interesting class of compounds, in that they can be prepared entirely from inorganic sources, namely, sodium cyanide, carbon disulphide and sulphur. Their versatility as intermediates for the synthesis of novel heterocycles, e.g. tetracyano-1,4-dithiane (**350**), has been demonstrated[716,717]. Compound **350** is conveniently prepared from the disodium salt of 1,2-dicyanoethane-1,2-dithiol (**348**)[718] via **349** (equation 471)[719]. The reaction of (**350**) with sulphur in the presence of a basic catalyst, (NaI or tertiary amines) affords **353** (100% yield) via an intermediate isothiazole **351**[720]. The sulphur insertion–rearrangement mechanism predicts that the negatively charged sulphur nucleophile adds to **351**, followed by ring-opening, to give **352**; this can then cyclize to **353** (equation 472)[720]. These rearrangements leading to the formation of heterocyclic compounds constitute an important synthetic methodology.



(348) (349) (350) (471)



(350) (351)



(352) (353) (472)

IV. SELECTED CYANO REAGENTS FOR ORGANIC SYNTHESIS (AN OVERVIEW)

This section is concerned with a group of cyano reagents having specialized synthetic applications. The group includes reagents for cyanation (the Wittig reagent, the Nagata reagent, the trimethylsilyl cyanide reagent and a cyanide-on-solid-support reagent) the reagent serving as the reaction intermediate (cyanoboration) and the reagent that catalyses organic reactions (palladium dichloride–nitrile complexes). Also discussed are an oxidizing agent (2,3-dicyano-5,6-dichloro-1,4-benzoquinone, DDQ) and a reducing agent (sodium cyanoborohydride, $NaBH_3CN$).

A. The Wittig Reaction

The Wittig reaction ranks second only to the aldol reaction as a general synthetic method for the two-carbon extension of aldehydes and ketones, to produce α,β-unsaturated carbonyl compounds or their derivatives; the topic has been studied[142] and reviewed[721–723].

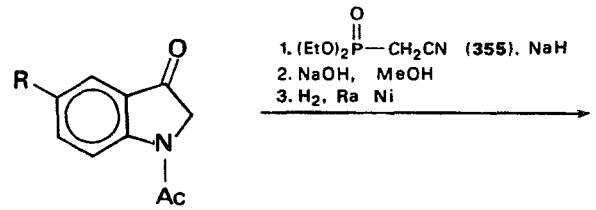
1. The Wittig reaction for cyanation

The Wittig reaction[412–414] and the Wittig–Horner reaction[150–153,415,724] are important procedures for the conversion of carbonyl compounds into α,β-unsaturated nitriles; the subject has been reviewed[725].

2. Synthesis of tryptamines via the Wittig–Horner reaction

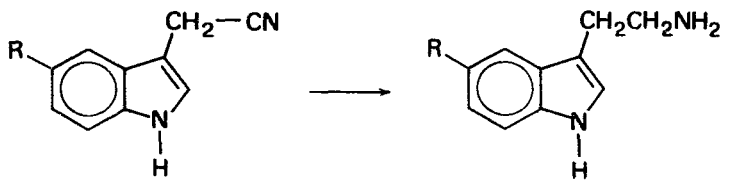
The Wittig–Horner reaction of 1-acetyl-3-indolinones (**354**) is an efficient method for the preparation of tryptamine precursors[726]. Thus, the carbonyl alkenation of the ketone **354** is conducted with a slight excess of the sodio derivative of diethyl

cyanomethanephosphonate (**355**). Hydrolysis and deacetylation (NaOH + MeOH) give the 3-(cyanomethyl)indole intermediate **356** which, on hydrogenation (H_2 + Raney nickel, 25°C), gives the tryptamine **357** in 57–65% overall yield (equation 473).



(**354**)

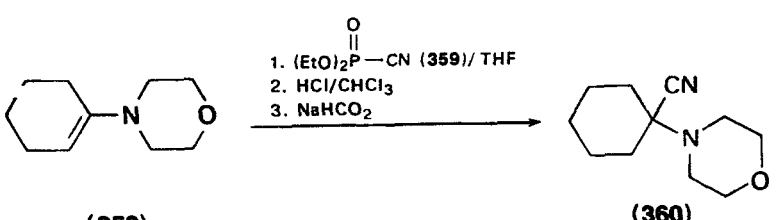
R = H, Me, Cl, OMe



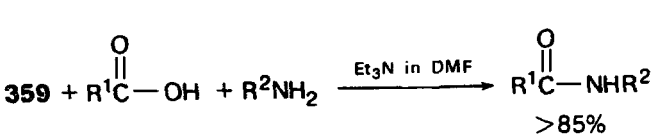
(**356**) (**357**) (473)

3. *The new Wittig–Horner reagents*

A series of new cyanophosphonates has been developed and successfully applied in the Wittig–Horner reactions; among them, diethyl cyanoethanephosphonate [$(EtO)_2P(O)CH_2CH_2CN$] has been applied to steroids[727]. The new reagent diethyl phosphorocyanidate (**359**) has been found to be useful for the preparation of α-aminonitriles from enamines. Thus, the morpholine enamine of cyclohexanone (**358**) was allowed to react with **359** in THF to give 1-cyano-1-(morpholin-4-yl)cyclohexane (**360**) in 67% yield (equation 474)[728]. The reagent **359** is also useful in the preparation of amides (equation 475), and in peptide synthesis, because no racemization results[729]. *C*-Alkylation of cyanomethanephosphoric tetramethyldiamide [$(MeN)_2P(O)CH_2CN$] using phase-transfer catalysis[730] and alkylation of $(EtO)_2P(O)CH_2CN$ by ion pair extraction[731] have been described. Reverse-Wittig reactions have been reported[732].



(**358**) (**360**) (474)



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B. The Nagata Reagent

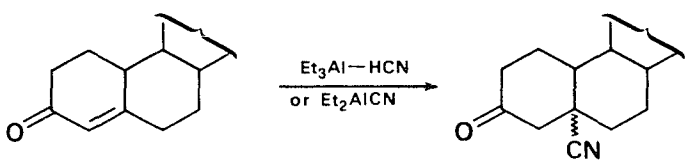
1. Hydrocyanation via the Nagata reagent

New hydrocyanation methods (methods A and B) have been developed by Nagata and coworkers[302–305,465,733,734], and the topic has been reviewed[668]. Method A uses a combination of hydrogen cyanide[735a] and trialkylaluminium (R_3Al–HCN) and method B employs diethylaluminium cyanide (Et_2AlCN). The main difference between the two is that method A is irreversible, and is thus controlled kinetically[735b], whereas method B is reversible and can therefore be controlled both kinetically and thermodynamically, that is, the product is kinetically controlled in the early stages[668].

The most useful application of the new methods is in conjugate hydrocyanation of α,β-unsaturated ketones, conjugated dienones, and conjugated enamines[734], and in the preparation of α-cyanohydrins from carbonyl compounds having low reactivity[736].

2. Stereochemistry of the Nagata hydrocyanation

The stereochemical preference of the conjugate hydrocyanation has been noted; indeed, in cyclic α,β-unsaturated ketones, only axial addition of cyanide is observed, and the *trans* isomer preponderates (equations 476[737] and 477[738]); also, noted in nonconjugate hydrocyanation (equation 478)[739].



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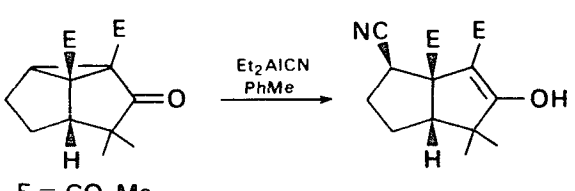
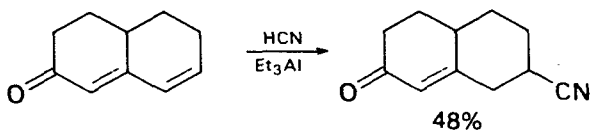


(478)

3. *Additional uses of the Nagata reagent*

The Nagata reagent has been used in hydrocyanation of 1,3-cyclopentenedione[740], 2,3-cyclohexen-1-one[741], γ-conjugated ketones (equation 479)[742] and α,β-unsaturated carboxylic acids (equation 480)[733]. The reagent has also been applied to the preparation of β-cyano aldehydes from α,β-unsaturated aldehydes (equation 481)[743], the cleavage of steroidal epoxides to give *trans*-diaxial β-hydroxynitriles (equation 482)[744], the conversion of a carbonyl compound into a cyanohydrin (equation 483)[736] and the synthesis of 3-cyano-1-methylenecyclohexane-2,2,4,4,6,6-d_6 (equation 484)[745].



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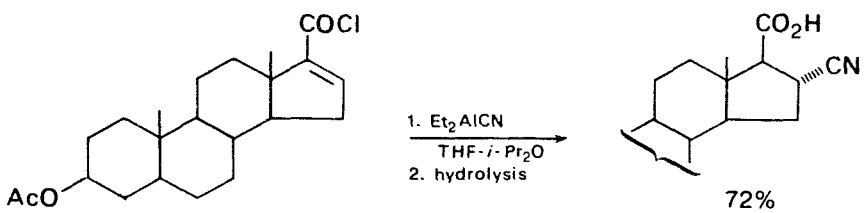

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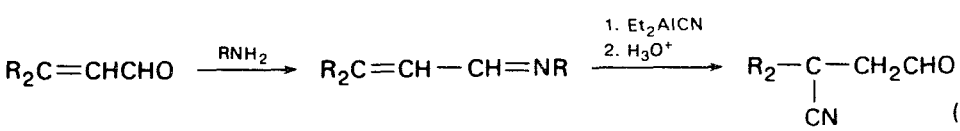

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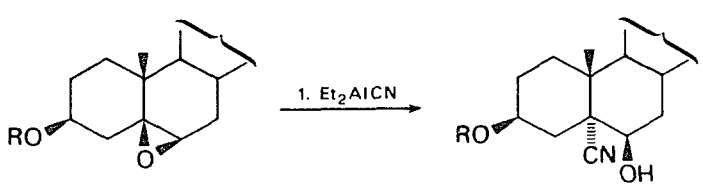

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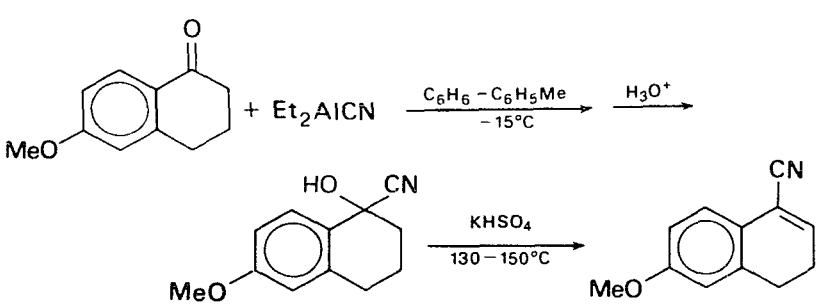

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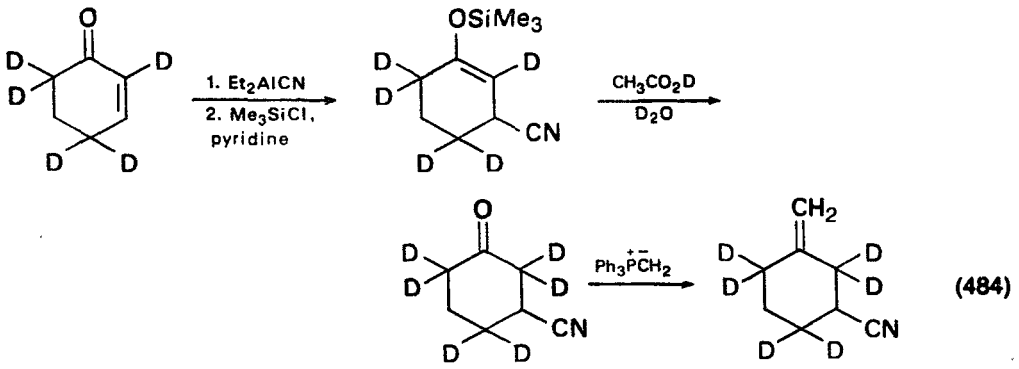


(484)

4. Catalytic hydrocyanation of acetylenes by tetracyanonickelate without the use of hydrogen cyanide

Acetylenes are readily hydrocyanated to saturated secondary nitriles by tetracyanonickelate, $[Ni(CN)_4]^{2-}$, in ethylene glycol or water in the presence of an excess of cyanide ion and $NaBH_4$ or Zn; in two-step reactions (hydrocyanation and hydrogenation), hydridotricyanonickelate functions as an active species only in the first step[746].

C. Trimethylsilyl Cyanide

The reactions of trimethylsilyl cyanide (**361**), a versatile, modern cyanosilylation reagent, have been summarized[747–749] and its synthetic applications reviewed[750].

Spectroscopic data[751,752] indicate that only a very small fraction (1.5 ± 0.5 mmol at 25°C) of the isocyanide **362** is present in the liquid phase of **361**; a rapid exchange of CN groups occurs between the two forms[753] (equation 485).

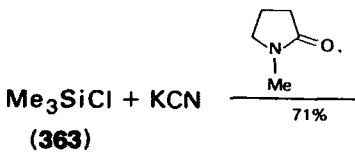
$$\underset{\textbf{(361)}}{Me_3SiCN} \rightleftharpoons \underset{\textbf{(362)}}{Me_3SiNC} \qquad (485)$$

1. Preparation of trimethylsilyl cyanide

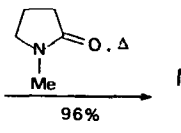
Methods for preparation of the reagent may involve chlorotrimethylsilane (**363**) and silver cyanide (equation 486)[754,755], hydrogen cyanide[756] or a hydrogen cyanide–triethylamine–ether reagent (equation 487)[757]. Additional methods involve the use of sodium[758] or potassium[759] cyanide in 1-methylpyrrolidinone in the presence of a phase-transfer catalyst, or potassium cyanide in LiCl–KCl eutectic mixture at high temperature[760]. Alternatively, the reagent can be generated *in situ* (potassium cyanide in 1-methylpyrrolidinone without a phase-transfer catalyst) (equation 488)[761]. A recent, high-yield procedure[762] uses a bis(trimethylsilyl)sulphate **364** and dry KCN in 1-methylpyrrolidinone at high temperatures; **361** distils directly (equation 489)[307].

$$\underset{\textbf{(363)}}{Me_3SiCl} + AgCN \xrightarrow[74\%]{\Delta} \underset{\textbf{(361)}}{Me_3SiCN} \qquad (486)$$

$$\underset{\textbf{(363)}}{Me_3SiCl} + HCN \xrightarrow[70\%]{N(C_2H_5)_3,\ ether} \underset{\textbf{(361)}}{Me_3SiCN} \qquad (487)$$



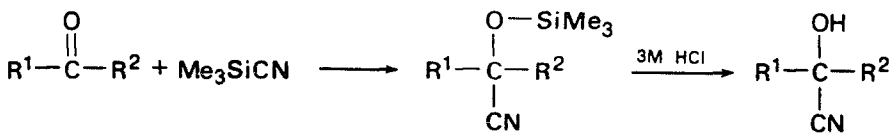
$$\underset{\textbf{(363)}}{Me_3SiCl + KCN} \longrightarrow \underset{\textbf{(361)}}{Me_3SiCN} \qquad (488)$$



$$\underset{\textbf{(364)}}{(Me_3SiO)_2SO_2} + KCN \longrightarrow \underset{\textbf{(361)}}{Me_3SiCN} \qquad (489)$$

2. *Cyanosilylation of carbonyl compounds. Silylated cyanohydrins*

The most significant reaction of trimethysilyl cyanide (**361**) is its addition to carbonyl compounds **365** to afford silylated cyanohydrins (**366**) (equation 490)[307,309,761,763–765]. The reaction is catalysed by Lewis acids, e.g. zinc iodide and by



(490)

(365) **(361)** **(366)** **(367)**

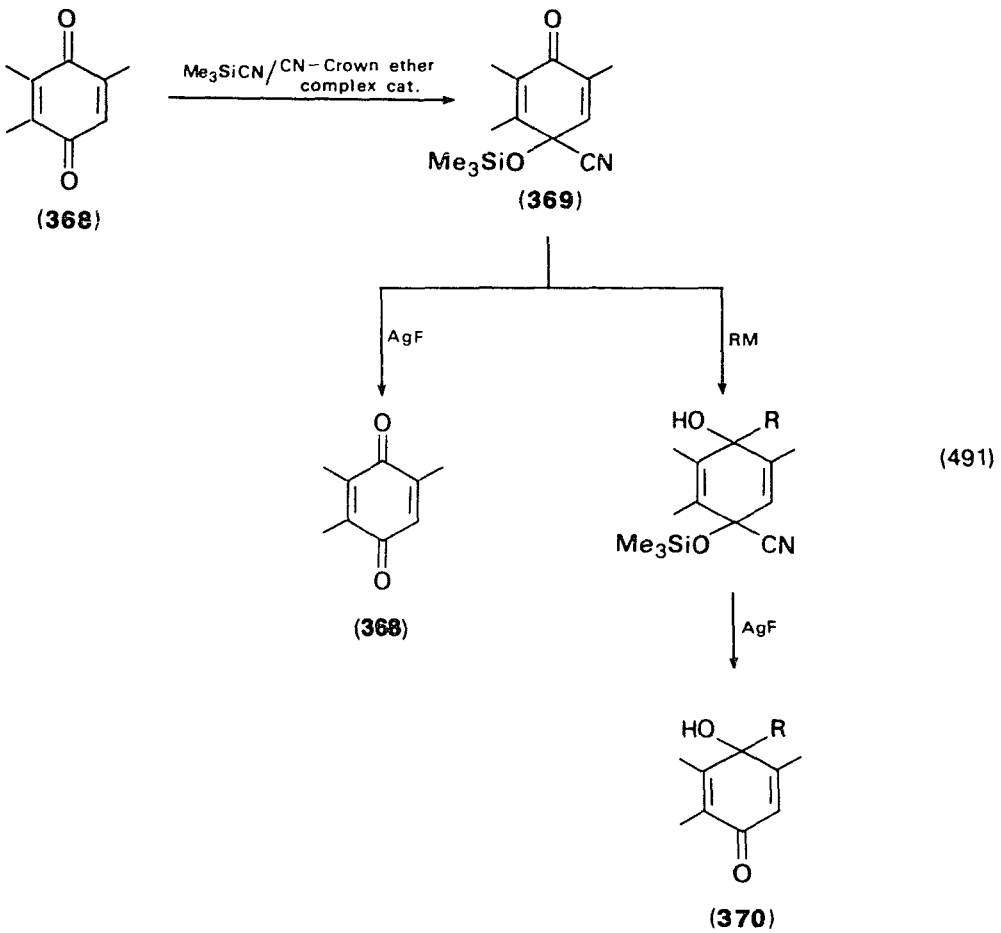
such anionic catalysts as KCN–18-crown-6 complex and tetrabutylammonium cyanide[307], which can be used to advantage with acid-labile, carbonyl substrates. The reaction gives high yields, even with such sterically hindered ketones (which are normally resistant to cyanohydrin formation) as *t*-butyl phenyl ketone, benzophenone or camphor and is one of the few truly general transformations in synthetic organic chemistry. The intermediates **366** can be isolated and used as key intermediates in a number of important synthetic transformations. Mild hydrolysis[765] of **366** gives almost quantitative yields of cyanohydrins (**367**) (equation 490).

3. *Protection of the quinone carbonyl group*

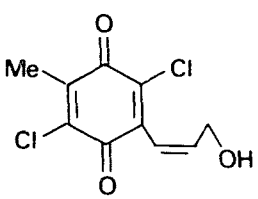
Reaction of the reagent with *p*-benzoquinones (e.g. **368**) or naphthoquinones provides a means of protecting the carbonyl group of the quinone. The monoprotected quinones **369**, for example, can be converted to *p*-quinols **370** in good yield by reaction with an organometallic reagent (e.g. Grignard or alkyllithium), followed by deprotection with silver fluoride (equation 491)[766]. The 1,4-benzoquinone **371**[767], the naturally occurring quinol, jacaranone **372**[768], naphthoquinones, e.g. deoxylapachol (**373**) and vitamin K_2 (**374**) have been synthesized by this route[769,770].

4. *Additional useful reactions of trimethylsilyl cyanide*

The trimethylsilyl cyanohydrins formed from aromatic or heterocyclic aldehydes and the reagent **361** can be used to generate masked acyl anions which can react with alkyl halides to give ketones (equation 492)[306,326]. With ketones, acyloins are formed[326,771]; α,β-unsaturated aldehydes undergo a similar reaction sequence with α-acylation, to form either unsaturated ketones or the α-trimethylsilyloxyenones[324].



(368) (369) (368) (370) (491)



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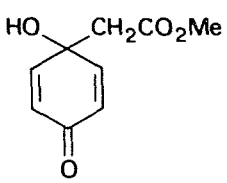

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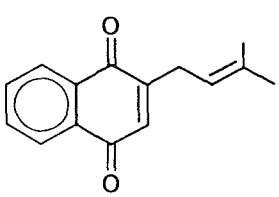

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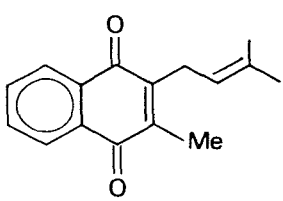

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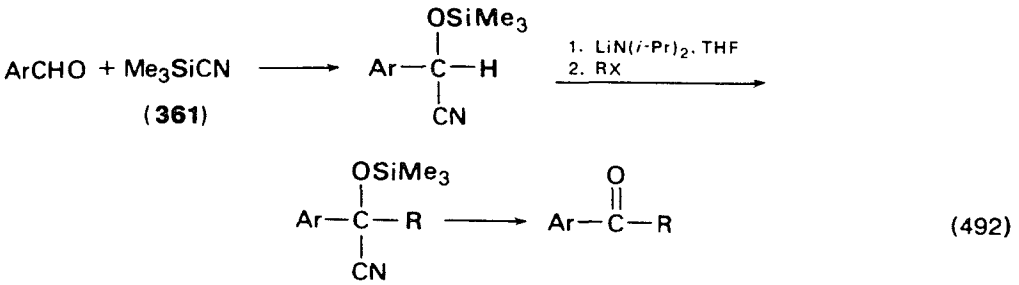
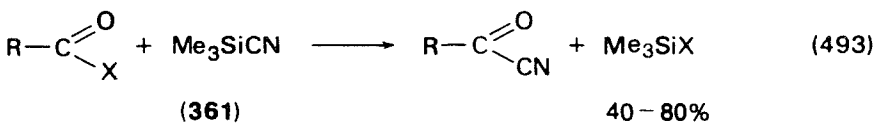


(492)

Trimethylsilyl cyanide (**361**) converts aliphatic acyl chlorides into acyl cyanides (equation 493)[772], and sulphenyl chlorides into thiocyanates (equation 494)[773]; ketenes give addition across the C=O rather than the C=C bond, producing β-substituted α-(trimethylsilyl)oxyacrylonitriles (equation 495)[774]. In the presence of aluminium chloride, the reagent opens up the oxirane ring (equation 496)[309]; it can also be used to prepare trimethylsilylhydroxy aldehydes which are used in the preparation of esters of α-fluoro acids (equation 497)[775].



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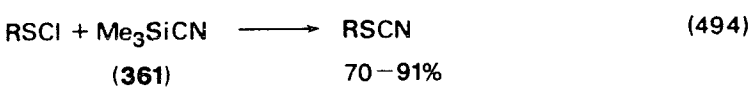
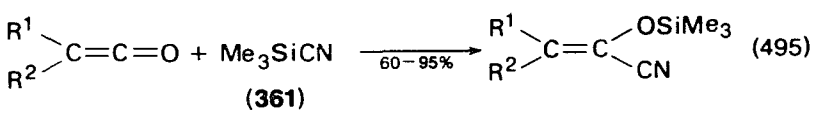


(494)

R = alkyl, aryl



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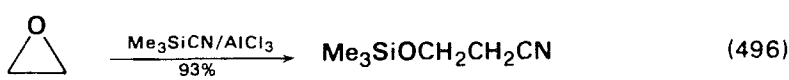

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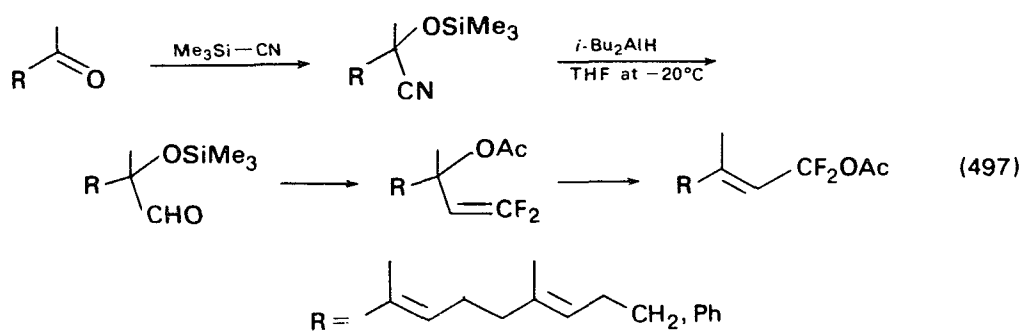
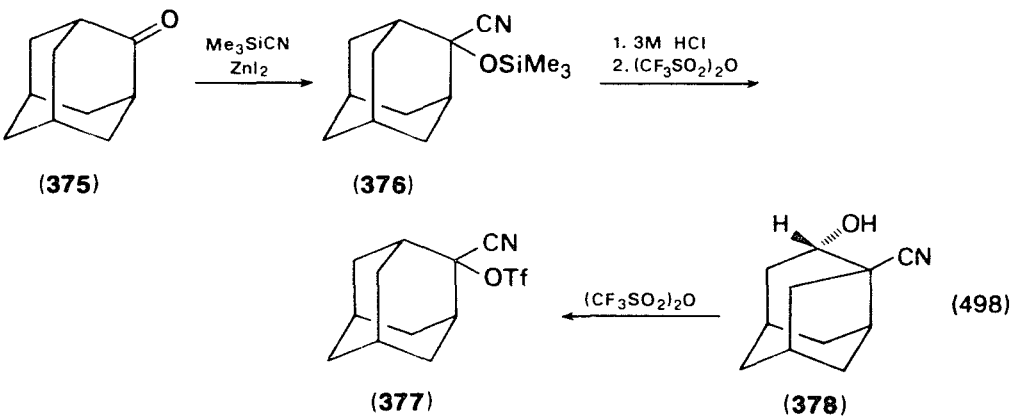


(497)

The trimethylsilyl cyanohydrins **366** have been used in the synthesis of prostaglandins[776]; they can also be readily reduced with $LiAlH_4$ to β-aminomethyl alcohols[307] which have been utilized in new syntheses of indole derivatives[777], including tryptamines[778] and steroids[779], and, via the Tiffeneau–Demjanov ring-expansion reaction, extended to a series of bridged polycyclic compounds[780–783].

5. *Stability of structurally rigid cyanohydrins*

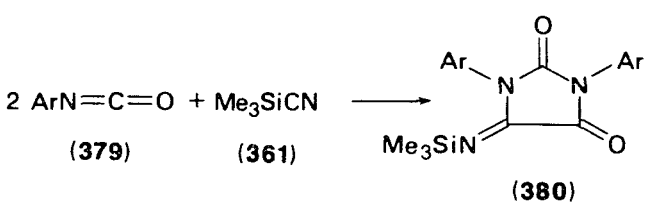
Gassman and coworkers have shown[784,785] that the α-cyano-substituted cation in the adamantanone cyanohydrin **377** [prepared as shown (**375** → **376** → **377**) in equation (498)] is more stable than the β-substituted cation in **378**. Consequently, **378** readily rearranges to a more thermodynamically stable triflate cyanohydrin (**377**), for example, on simply acylation (e.g. with trifluoromethanesulphonic anhydride).



(498)

6. *Addition of trimethylsilyl cyanide to C=N and C≡N bonds*

The reagent **361** reacts with a variety of C=N-containing compounds. For example, with aryl isocyanates (**379**), it forms 2:1 adducts, e.g. substituted imidazolidines (**380**) (equation 499)[786]; with alkyl isocyanates (e.g. *p*-tosyl isocyanate), only the 1:1 adduct can be obtained[786]. A similar reaction occurs with trifluoroisocyanate[787]. The cyanosilylation of Schiff bases (equation 500) or oximes (equation 501) with the reagent, catalysed by Lewis acids, provides a useful route to aminonitriles[205].



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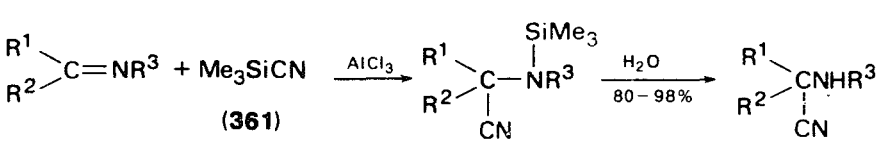

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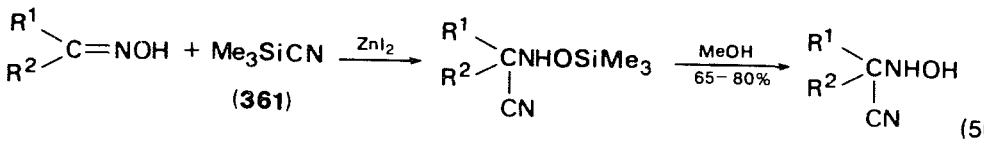
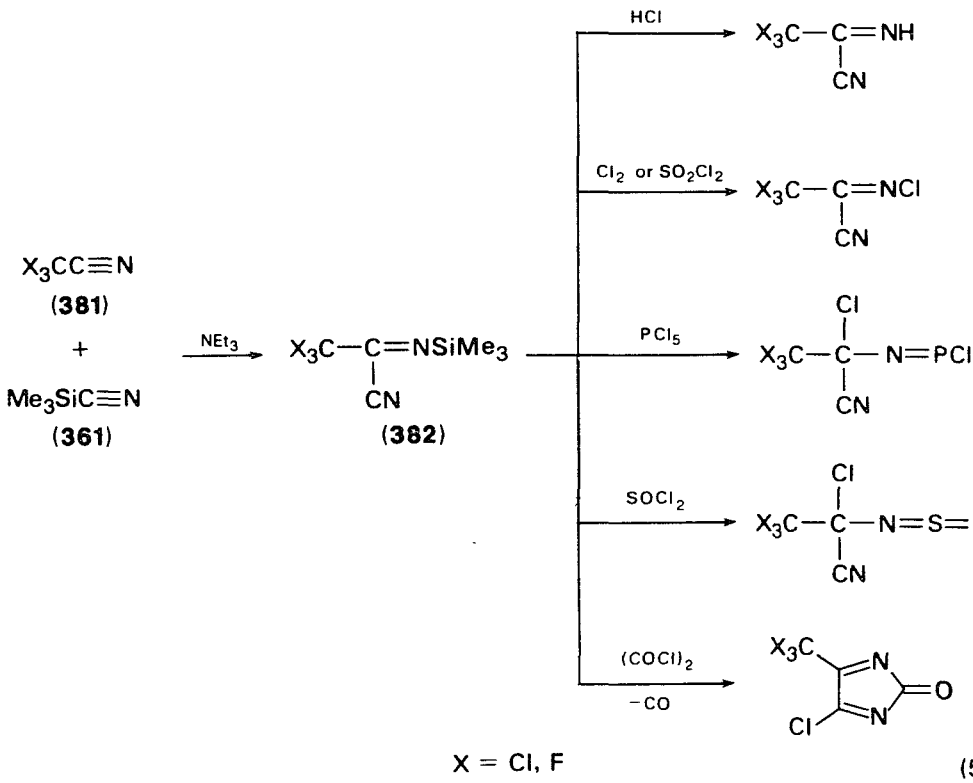


(501)

Carbodiimides (R—N=C=N—R) give 1:1 adducts; these can cycloadd to more carbodiimide (or isocyanate), to afford heterocycles[788]. **361** also undergoes addition to the C≡N bond of nitriles bearing electronegative substituents[789], e.g. with trichloro- and trifluoro-acetonitriles (**381**) in the presence of triethylamine to give 2-*N*-(trimethylsilyl)iminopropanonitriles (**382**). The latter react with a variety of reagents, providing useful, synthetic routes (equation 502)[789].

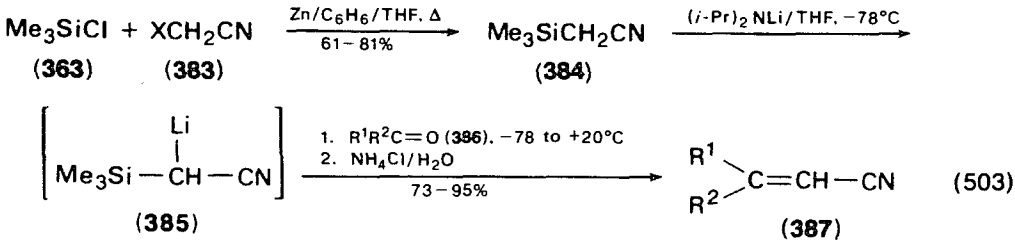


(502)

7. *Analogues of trimethylsilyl cyanide*

a. (Trimethylsilyl)acetonitrile. (Trimethylsilyl)acetonitrile, Me_3SiCH_2CN (**384**), has broad synthetic applicability since it possesses two reaction sites. The (trimethylsilyl)methyl group is reactive towards proton-specific bases, and the cyano group reacts with nucleophiles or acids. The presence of the trimethylsilyl group facilitates generation of the anion, and results in extraordinary reactivity, because of the remarkable affinity of organosilyl groups for oxygen, which is well known for intramolecular migration[790,791], and for intermolecular, oxygen-abstraction reactions[792–794].

Reaction of chlorotrimethylsilane (**363**) and a halogenoacetonitrile (**386**) gives **384** in 61% (X = Cl) and 81% (X = Br) yield. The lithiated derivative (**385**) is readily generated by LDA. Addition of carbonyl compounds **386** gives α,β-unsaturated nitriles **387** (equation 503)[795]. The results obtained with benzaldehyde, cinnamaldehyde



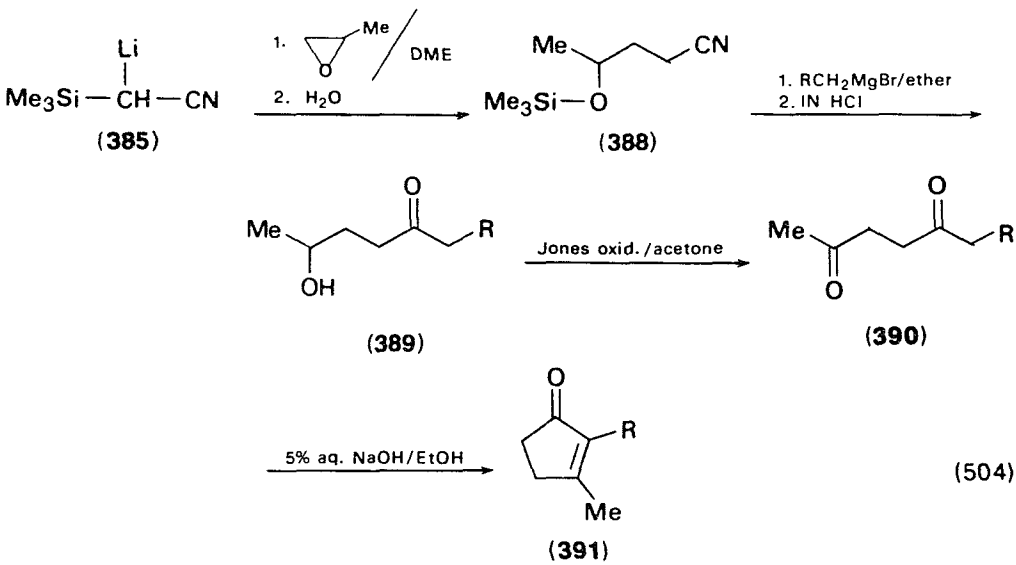
X = Cl, Br

R^1 = Ph, PhCH=CH, R^2 = H

R^1— R^2 = —$(CH_2)_5$—

and cyclohexanone show that **385** can be used instead of cyanomethylenetriphenylphosphorane or diethyl cyanomethylphosphonate (the Wittig reagents), with high reactivity and greater ease of handling. The anion **385** is also an efficient reagent for cyanomethylation (Section II.M).

Starting with the lithio salt **385**, Murata and Matsuda[796] have described a novel route to 1,4-diketones **390** and 3-oxocyclopentenes **391** [e.g. *cis*-jasmone, **392** (**391**, R = *cis*-2-pentenyl) 76% yield] via intermediates **388** and **389** (equation 504). A convenient synthesis of a series of new jasmonoid compounds (cyclopentenones) from 4-(trimethylsiloxy)butanonitrile has recently been described by the same group[797].



R = *n*-Bu, *n*-C_5H_{11}, *cis*-2-pentenyl

b. Other analogues. *t*-Butyldimethylsilyl cyanide (Me_3CSiMe_2CN) has been used for the cyanosilylation of ketones in a total synthesis of camptothecin[798]. Dicyanodimethylsilane [$Me_2Si(CN)_2$] is a useful reagent for concurrent silylation and cyanosilylation of β-diketones; the reaction affords 5-cyano-2,6-dioxa-1-sila-3-cyclohexanones in high yield[799].

D. Synthesis of Nitriles on Solid Supports

1. *Inorganic supports*

The use of inorganic supports is becoming increasingly widespread in synthetic organic chemistry[800,801]. Such media involve milder reaction conditions, simpler processing, and, often, higher selectivity. The principle involved is the generation of anions[802] on 'basic' inorganic supports (silica and alumina gels) whereon they undergo either intra- or inter-molecular alkylation reactions.

2. *Procedures for the synthesis of nitriles*

Regen and coworkers[452,803] have described the synthesis of nitriles by alkylation of cyanide anions on solid inorganic supports (e.g. basic alumina) using toluene as the cosolvent. For example, reaction of sodium cyanide on neutral alumina, with iodobenzene in toluene in the presence of tetrakis(triphenylphosphine)palladium(0) catalyst affords a quantitative yield of benzonitrile[804]. Bram and coworkers[805] have carried out the reaction in 'dry media'[806], i.e., in the absence of any organic solvent, and this may have interesting theoretical consequences.

The general procedure[805,806] involves the addition of a concentrated, aqueous solution of KCN to a particular solid support. After removal of water the adsorbed cyanide anion may be alkylated in high yield by addition of the pure organic halide. The products are obtained simply by eluting with ether. In agreement with a previous study[803] 'basic' alumina provides the highest yields. For example, 1-bromooctane with KCN on alumina gives 1-cyanooctane in 95% yield. This method of synthesis of nitriles (and esters) compares favourably with reactions carried out in dipolar, aprotic solvents[807,808], or under phase-transfer conditions[809]

3. *Polymeric supports*[810]

Commercial anion-exchange resins are the simplest and most readily available polymer-supported reagents[811,812]. The polymer-supported cyanide is prepared[813] by stirring the chloride form of Amberlyst A26 (a macroporous resin containing quaternary ammonium groups) with aqueous potassium cyanide. After washing and drying, the reaction is conducted in benzene or toluene; conversions into cyanide range from 54 to 100%, e.g. 1,12-dicyanododecane is obtained in 100% yield from the dibromo compound[813]. The method may thus be considered to be an alternative to phase-transfer catalysis.

4. *Phase-transfer reactions*

Polymer-supported, phase-transfer-catalysed reactions have been studied[814,815], and the topic has been reviewed by Regen[816]. Insoluble, polymer-supported, quaternary ammonium[814a] and phosphonium[814b] salts catalyse reactions between water-soluble anions and organic substrates under triphasic (aqueous, organic, polymer) condi-

tions[814c]. The catalyst can be separated from reaction mixtures by simple filtration, and can be reused. A recent rate study[817] of the reaction between aqueous sodium cyanide and 1-bromooctane in toluene shows the importance of mass transfer, the diffusion of reactant and the structure of the active site in polymer-supported, phase-transfer-catalysed reactions.

5. *Additional polymeric reagents for synthesis*

Insoluble polymeric reagents have been developed that oxidize[818], acylate[819], epoxidize[820], halogenate[821] and hydrogenate[822], e.g. anion-exchange resin cyanoborohydride[823] or the solid reducing agent poly(2- or 4-vinylpyridine–BH_3)[824]. Processing of the reaction mixture is simple and the spent polymer can be recycled.

E. Cyanoboration

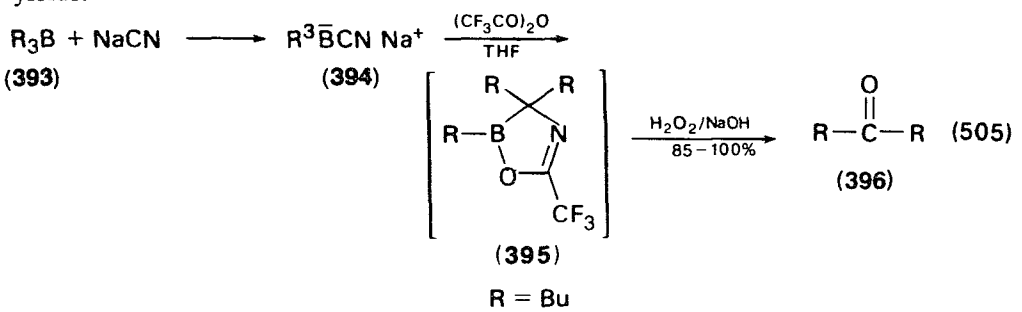
Reactions of organoboranes with cyanides and isocyanides[825], and the applications of boranes and organoborates,including cyanoborates, in organic synthesis[826,827], have been reviewed.

1. *The cyanidation reaction*

The term cyanoboration covers reactions in which there is a migration, e.g. sequential 1,2-shift, from boron to carbon and that involve a cyanoborate salt. The cyanidation reaction (reaction of trialkylboranes with sodium cyanide) leading to a facile synthesis of symmetrical and unsymmetrical ketones (frequently difficult to achieve by other methods) was developed by Pelter and coworkers[827–829].

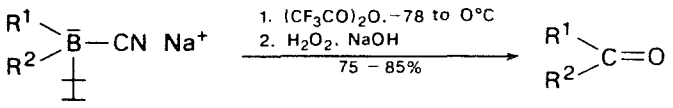
2. *Synthesis of symmetrical ketones*

Symmetrical ketones, e.g. **396**, can be prepared by conversion of trialkylboranes **(393)** into sodium trialkylcyanoborates **(394)** by reaction with sodium cyanide (the cyanidation reaction). The reaction of **394** with an electrophile (e.g. such acylating agents as imidoyl chloride, benzoyl chloride or especially, trifluoroacetic anhydride) is accompanied by migration of two alkyl groups from boron to carbon, to give an intermediate **395**, that is oxidised to a symmetrical ketone **(396)** in high yield (equation 505)[827–829]. Acetic anhydride or acetyl chloride as acylating agents afford only poor yields.



3. *Synthesis of unsymmetrical ketones*

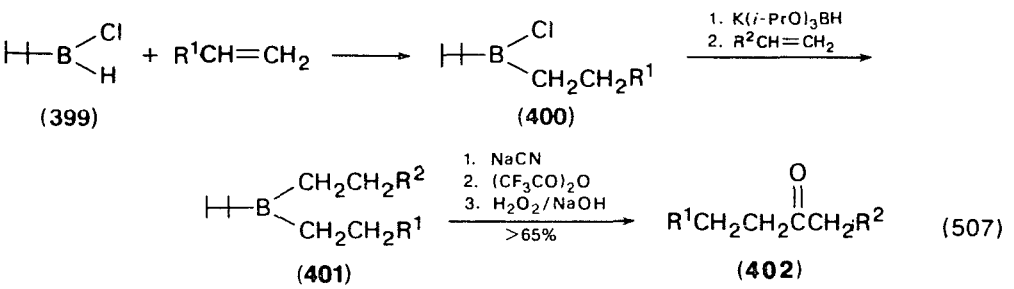
Unsymmetrical ketones, e.g. **398**, can be synthesized under the same mild conditions by use of dialkylcyanothexylborates **(397)**; thexyl (tetramethylethyl) groups are known to migrate more slowly than other alkyl groups (equation 506)[827].



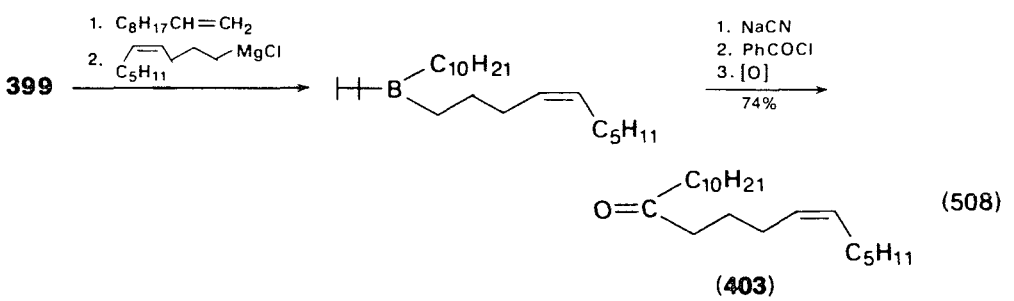
(397) (398) (506)

4. *Synthesis of ketones via sequential hydroboration*

Recently, Zweifel and Pearson[830] and Brown and coworkers[831] have independently developed a general synthesis of ketones via stepwise hydroboration with chlorothexylborane (**399**). The product, alkylchlorothexylborane (**400**), is reduced and the resulting alkylthexylborane readily hydroborates a second mole of alkene, to give dialkylborane (**401**); this is converted via cyanidation[828,829] into the ketone (**402**) (equation 507)[831]. The reaction is exemplified by the synthesis of (*Z*)-6-heneicosen-11-one (**403**), the sex pheromone (equation 508)[830]. The hydroboration–alkylation sequence provides a simple approach for the synthesis of otherwise difficultly accessible, unsymmetrical (or symmetrical) ketones.



(399) (400) (401) (402) (507)



(403) (508)

5. *Additional applications of the cyanoboration reaction*

The cyanoboration reaction has been applied in the synthesis of ketones from 1-methylcyclopentene[828], (+)-limonene[829] and 1-chlorocyclohexene[832]. Similarly, unsymmetrical ketones have been synthesized from the following alkene pairs: 1-heptene–1-pentene (62%), 1-dodecene–1-octene (72%) and styrene–methyl-1-pentene (62%)[831]; the procedure is also successful in the stereospecific synthesis of allylamides[833]. In addition, the use of trialkylboranes for the preparation of saturated[834] and unsaturated[835] nitriles has been reported. The reaction of trialkylboranes with diazoacetonitrile leads to the corresponding, homologated nitriles in good yields (equation 509)[836].

$$\begin{matrix} R \\ R \\ R \end{matrix}\!\!>\!B + N_2CH{-}CN \longrightarrow R{-}CH_2{-}CN \qquad (509)$$

$$R = n\text{-}C_6H_{13},\ n\text{-}C_8H_{17},\ c\text{-}C_5H_9$$

F. Palladium Dichloride–Nitrile Complexes

The *substitution* of alkenes is difficult, because the π-electron cloud between the carbon–carbon double bond disfavours the nucleophilic *addition*. However, the coordination of alkenes to palladium makes it possible for hydroxyl, alkoxyl or acetate ions to give the corresponding substituted alkenes.

Reaction of benzene with acrylonitrile in the presence of palladium(II) gives *trans*-β-cyanostyrene (17%) and the *cis* isomer (8%); the low yield of the product is due to the coordination of Pd(II) with the lone-electron pair of the acrylonitrile nitrogen atom, thus hindering the aromatic substitution of the alkene[838].

Palladium complexes in organic chemistry have been reviewed[837–841] and discussed[842–844].

1. *Bis(benzonitrile)palladium(II) dichloride*, $PdCl_2(PhCN)_2$ or $Pd(PhCN)_2Cl_2$ (BBPD)*

This transition-metal catalyst[845] is a versatile reagent for many syntheses conducted in nonpolar solvents such as benzene, chloroform or THF. The major synthetic uses of $PdCl_2(PhCN)_2$ (BBPD) are summarized next.

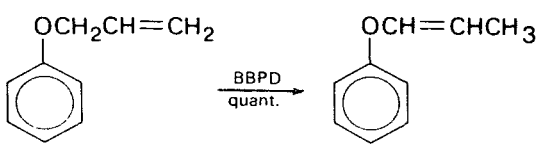
2. *Alkene dimerization*

This is exemplified by the preparation of hexenes in high yields (equation 510)[846].

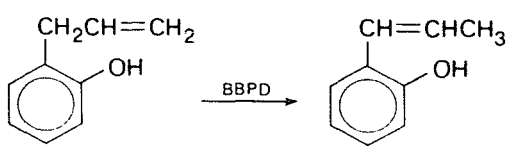
$$2\ MeCH{=}CH_2 \xrightarrow{BBPD} \underset{92\%}{n\text{-Hexenes}} \qquad (510)$$

3. *Isomerization of alkyl phenyl ethers and allylphenols*

Allyl phenyl ether (**404**) in refluxing benzene, with BBPD as the catalyst, is isomerized quantitatively to the 1-propenyl ether (**405**) (30% *trans* and 70% *cis*) (equation 511). Similarly, 2-allylphenol (**406**) is isomerized to 2-(2-propenyl)phenol (**407**) (equation 512)[847].



(404) (405) (511)

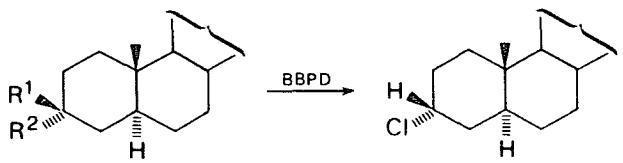


(406) (407) (512)

*Also known as dichlorobis(benzonitrile)palladium(II) or dibenzonitriledichloropalladium(II), i.e. $(PhCN)_2\ PdCl_2$.

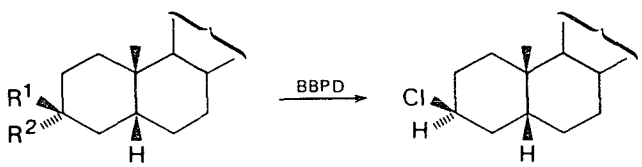
4. Stereospecific chlorination of steroids

BBPD reacts stereospecifically with 5α- or 5β-cholestan-3-ols (**408–411**) to give the 3-chloro derivatives in high yield (equations 513 and 514)[848]. The stereochemistry of the reaction is very different from that observed with other common chlorinating agents, such as thionyl chloride (retention) and phosphorus pentachloride (inversion). With BBPD configurational inversion occurs when the OH group is equatorial, as in **408** and **411**, and retention when the OH group is axial, as in **409** and **410** (equations 513 and 514).



(513)

(**408**) R^1 = OH, R^2 = H
(**409**) R^1 = H, R^2 = OH

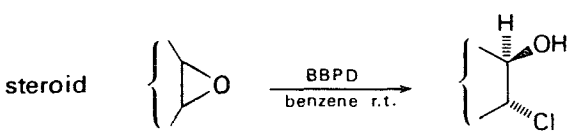


(514)

(**410**) R^1 = OH, R^2 = H
(**411**) R^1 = H, R^2 = OH

5. Ring-opening of steroid epoxides

Oxidocholestanes may be readily converted into the corresponding chlorohydrin derivatives by using BBPD (equation 515)[849].



(515)

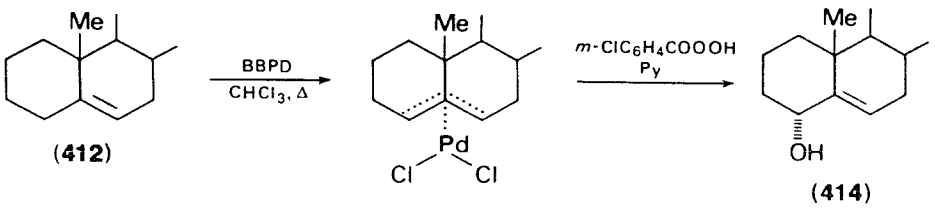
(*trans* diaxial opening)
~90%

6. π-Allylpalladium chloride complexes → allylic alcohols

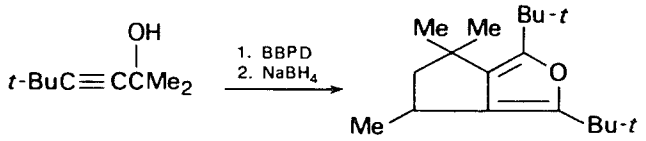
Steroidal alkenes (**412**) are efficiently converted into π-allylpalladium complexes (**413**) by treatment with BBPD. Oxidation of these complexes proceeds regio- and stereo-selectively to allylic alcohols. Thus, **413** gives 4α-hydroxy-Δ^5-cholestene (**414**) (equation 516)[850].

7. Cyclization reactions

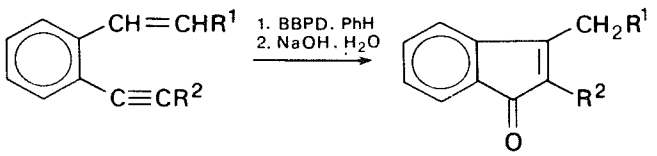
BBPD is an efficient catalyst for many cyclization reactions, including the copolymerization of acetylenes (equations 517–522)[851–855].



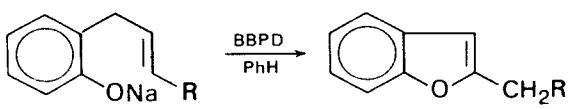
(**412**) (**413**) 71% (**414**) 66% (516)



(Ref. 851) (517)

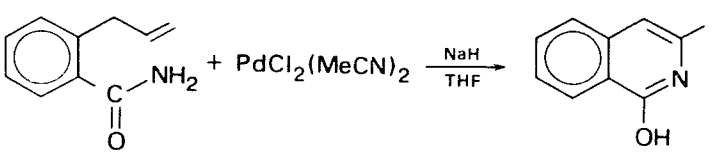


54% (Ref. 852) (518)

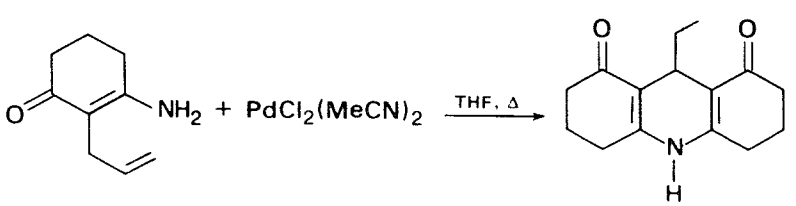


R = H, Ph 31% (Ref. 853) (519)

22–53% (Ref. 854) (520)



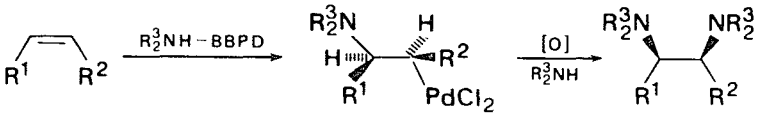
(Ref. 855a) (521)



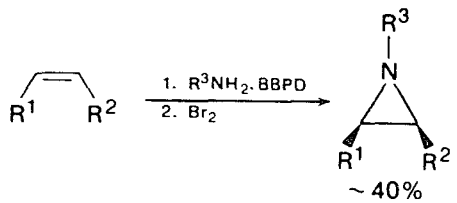
26% (Ref. 855b) (522)

8. cis-*Addition of amines to alkenes*

In the presence of BBPD and an oxidizing agent, amines stereospecifically add *cis* to alkenes (**415**), leading to the diamines (**417**) in good yield (equation 523)[857]. The reaction initially gives the adduct **416**, which is then oxidized *in situ* using *m*-chloroperoxybenzoic acid in the presence of a second molecule of amine to give the product **417**. For terminal alkenes, yields are ~70%, but, for internal alkenes, the yields are lower. However, a similar, catalytic amination of alkenes, also stereospecific, in the presence of bromine as the oxidizing agent, gives the cyclic product depicted in equation (524)[856].



(**415**) (**416**) (**417**) (523)



(524)

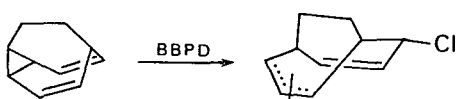
R^1, R^2, R^3 = H, alkyl, Ph

9. *Rearrangements*

Palladium(II) salts in nonpolar solvents catalyse many rearrangements, including the Cope rearrangement[858], allylic rearrangement of allyl acetates[859], formation of π-allylpalladium complexes[860] and polyhetero-Claisen rearrangements[861]. Complexes such as BBPD or $PdCl_2(MeCN)_2$ have been found to be effective for many novel rearrangements.

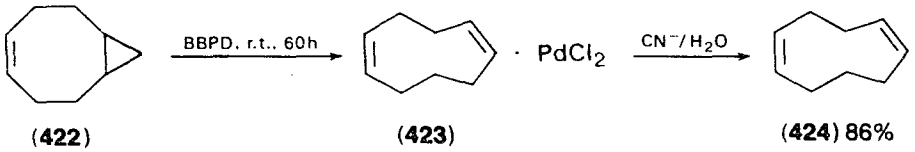
a. Rearrangement of cyclic polyenes. A homotropilidene such as dihydrobullvalene (**418**) reacts with BBPD in dichloromethane to give the bicyclic product **419** formed by addition of palladium dichloride across a vinylcyclopropane unit (equation 525). Similarly, bullvalene (**420**), in the presence of a catalyst, rearranges at 0°C to bicyclo[4.2.2]deca-2,4,7,9-tetraene (**421**) (equation 526)[862].

Bicyclo[6.1.0]non-4-ene (**422**) readily rearranges in benzene to give *cis*, *cis*-1,5-cyclononadiene (**424**). The reaction is quenched by addition of aqueous cyanide, and the intermediate palladium dichloride complex (**423**) is not isolated (equation 527)[863].



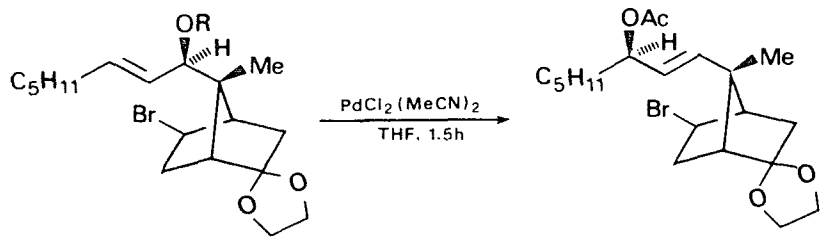
(**418**) (**419**) (525)

(**420**) (**421**) (526)



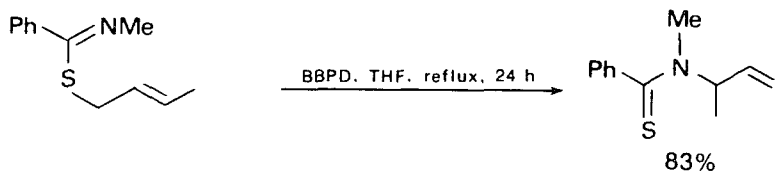
(422) (423) (424) 86% (527)

b. Stereospecific rearrangement of allylic alcohol in the presence of bis(acetonitrile)palladium(II) dichloride. Complete transfer of chirality in the [3,3]sigmatropic rearrangement of the allylic acetate (e.g. **425** → **426**), catalysed by $PdCl_2(CH_3CN)_2$, has been reported by Griego and coworkers (equation 528)[864].

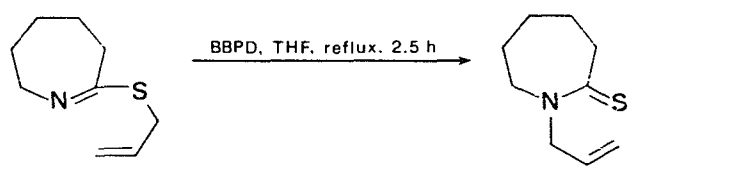


(425) R = Ac (426) 93% (528)

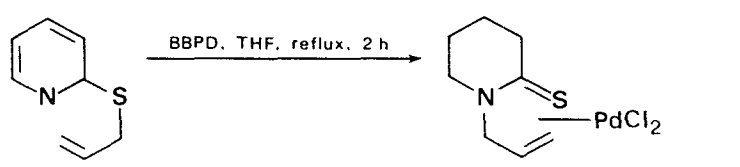
c. Palladium-catalysed polyhetero-Claisen rearrangement. Yoshida and coworkers[865] have found that Pd(II), e.g. BBPD, readily catalyses the S → N allyl-group migration of *S*-allylthioimidates to give *N*-allylthioamides (equations 529–531). The suggested mechanism does not involve the intermediacy of π-allylpalladium species. The rare S → N allylic rearrangement constitutes a novel approach to the thioamide group, a useful synthon in organic synthesis[866]; it is also one of the least studied of polyhetero-Claisen rearrangements[861].



83% (529)

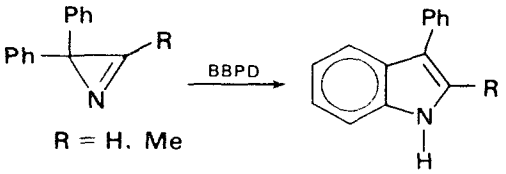


91% (530)



100% (531)

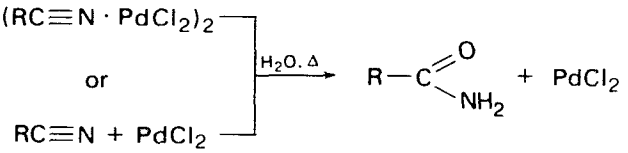
d. Ring-enlargement via rearrangement. A new Pd(II)-catalysed synthesis of indole derivatives has been reported (equation 532)[867]. In a series of analogous catalysts, bis(acrylonitrile)nickel(0) has been found to be effective in the isomerization of quadricycle to norbornadiene[868].



(532)

10. Synthesis of amides from $PdCl_2$–nitrile complexes

The partial hydrolysis of palladium(II)–nitrile complexes, either neat or in solution (prepared *in situ* from $PdCl_2$ and an excess of nitrile) leads to amides in 30–85% yield (equation 533)[869].



(533)

11. Transition-metal–cyanide complexes

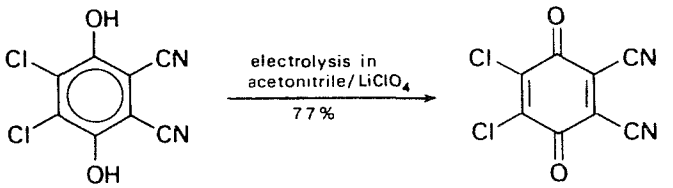
The chemistry of the cyano complexes of the transition metals has been reviewed[870]; cobalt(II) cyanide complexes[871,872] and organonitrile complexes of ruthenium[873] have been discussed.

G. 2,3-Dicyano-5,6-dichloro-1,4-benzoquinone (DDQ)

The high potential quinone, 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ), is a powerful dehydrogenating agent that has found extensive application in synthetic organic chemistry[874–878]; in many cases, it is more efficient than its analogues, e.g. 2,3-dicyanobenzoquinone or chloranil. The first half-wave potential (in acetonitrile vs. SEC) of DDQ is 0.51 V; a second electron is added at − 0.30 V[879]. For the selective oxidation of allylic alcohols, or the aromatization of dihydroaromatic compounds, DDQ is often the reagent of choice. Although it is stable in solutions of strong mineral acids[880], it decomposes in water; DDQ is generally employed under anhydrous conditions (often, in refluxing benzene, toluene, 1,4-dioxane or glacial acetic acid) and in large excess. In many cases, methanol or ethanol is used, especially at room temperature. For example, benzylic oxidation of 4-alkyl-substituted phenols by DDQ in methanol is known to proceed readily, and has been explained in terms of phenol oxidation[877,881,882]. However, the oxidation reaction conducted in refluxing methanol or ethanol can often cause displacement of the electron-attracting groups from the DDQ nucleus by alkoxyl groups. The recent highlights of DDQ oxidations are summarized next.

1. Synthesis of DDQ

The quinone can be conveniently prepared in a single-step synthesis from 2,3-dicyanohydroquinone, using hydrochloric acid and nitric acid, in 90% yield[880]. Recovered 2,3-dicyano-5,6-dichloro-*p*-hydroquinone ($DDQH_2$) (**427**) is conveniently reoxidized to DDQ (**428**), either by nitric acid[880] or by anodic oxidation (equation 534)[883].



(534)

(**427**) (**428**)

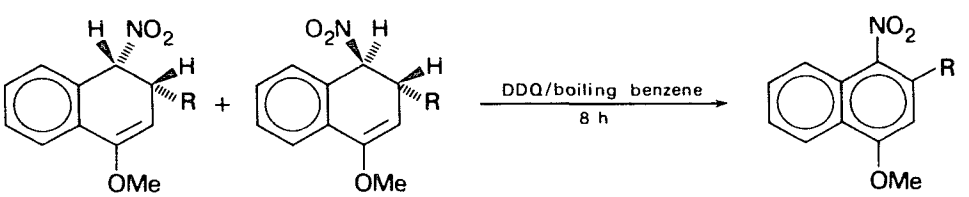
2. Mechanism of DDQ oxidations

The DDQ-induced dehydrogenation of 1,3-dihydrobenzene has been interpreted[884] as a two-step, ionic process, involving transfer of a hydride to the quinone, to give a cyclohexadienyl cation which then rapidly loses a proton, to give the aromatic product. Subsequent studies[885,886], however, support a cyclic, concerted elimination[885] or a synchronous loss of both hydrogen atoms[886]. Stable free radicals, as well as cations, can be prepared by the reaction with DDQ[887] and it is a particularly efficient one electron oxidant[877,881]. A kinetic study [888] of the dehydrogenation of 1,4-dihydrobenzenes and 1,4-dihydronaphthalenes by DDQ favours a two-step, ionic mechanism involving a positively charged intermediate which is formed as an ion pair in an intial, rate-determining hydride transfer to DDQ, i.e. a stepwise transfer of a first hydride, followed by a proton, to give the aromatic product.

For the dehydrogenation of alcohols by DDQ recent kinetic investigations[889] are in agreement with a sequence in which hydride-ion transfer from the α carbon atom of the alcohol is the rate determining step.

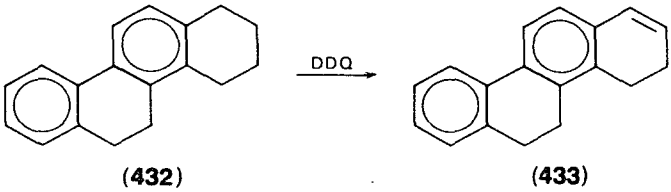
3. Dehydrogenation and benzylic oxidation

a. Hydroaromatic compounds. Certain hydroaromatic compounds are readily dihydrogenated with DDQ; e.g. a mixture of *cis*- and *trans*-2-alkyl-1,2-dihydro-4-methoxy-1-nitro- naphthalenes, **429** and **430**, is quantitatively converted into 2-alkyl-4-methoxy-1-nitronaphthalene (**431**) (equation 535)[890]. Hexahydrochrysene

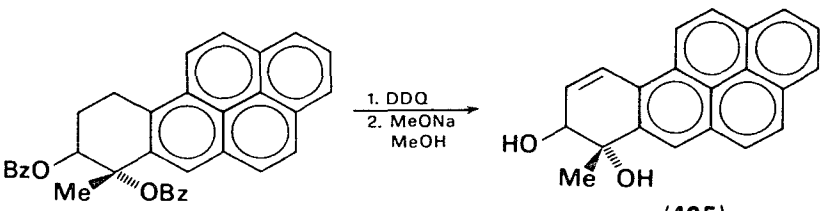


(**429**) (**430**) (**431**) (535)

(**432**) can be dehydrogenated by DDQ to 3,4,5,6-tetrahydrochrysene (**433**) (equation 536)[891], and *trans*-bis(benzoyloxy)-7,8,9,10-tetrahydro-7-methylbenzo[*a*]pyrene (**434**) is converted, after hydrolysis, into the *trans*-7,8-dihydrodiol **435** (equation

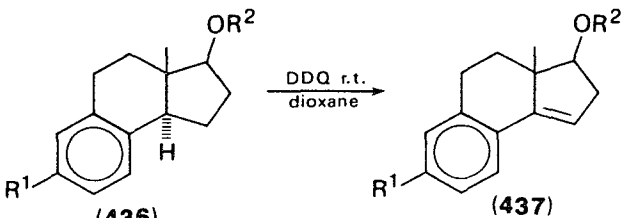


(432) (433) (536)



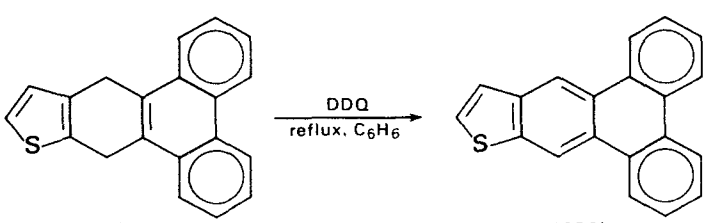
(434) (435) (537)

537)[892], which is a metabolite, in rat liver, of the carcinogen 7-methylbenzo[*a*]pyrene. The high-potential quinones have been applied in the benzylic oxidation of *A*- and *B*-aromatic steroids[893], and of some phenol de-*A*-steroids[894]. Thus, dehydrogenation of 5-methoxy-de-*A*-estra-5,7,9-trienes (**436**) with DDQ produces the styrene **437** (equation 538)[894] and **438** gives the aromatic derivative **439**[895] (equation 539).



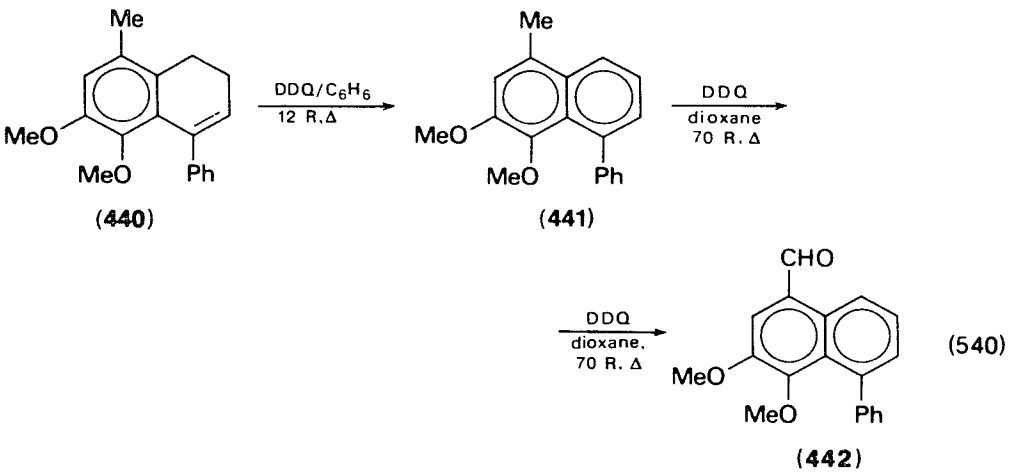
(436) (437) (538)

R^1 = OMe, R^2 = H
R^1 = OMe, R^2 = Ac
85%



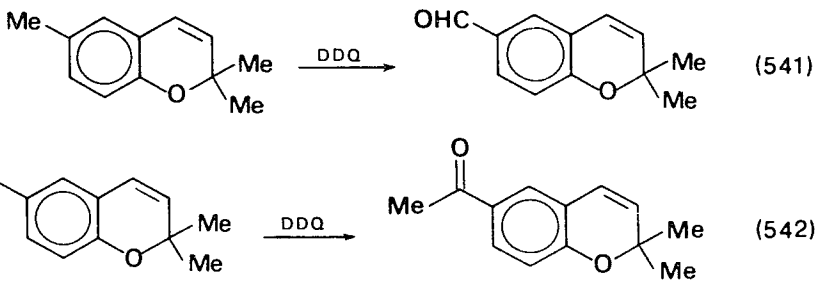
(438) (439) (539)
88%

b. Oxidative dehydrogenation of alkyl groups. The application of DDQ leading to the convenient preparation of *p*-methoxyphenylcarbonyl synthons via oxidative dehydrogenations[877,881] has recently been reported. Thus, the reaction of 3,4-dihydro-7,8-dimethoxy-5-methyl-1-phenylnaphthalene (**440**) with DDQ leads to the naphthalene derivative **441**. However, **440** readily undergoes oxidative dehydrogenation to the formylnapthalene **442** in one step with DDQ (equation 540)[896]. Here, the activa-



(440) (441) (442) (540)

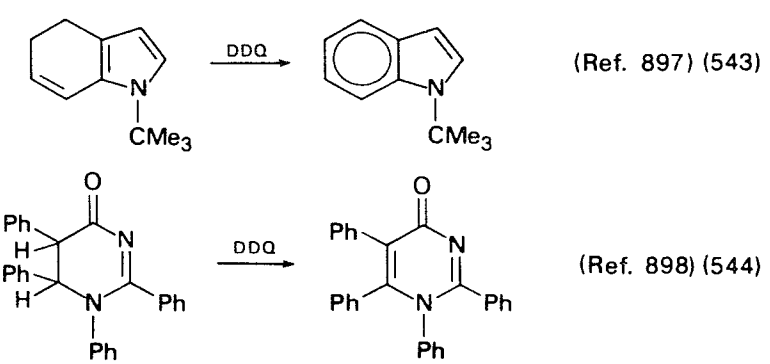
tion of the alkyl group (methyl or ethyl) by a *para*-alkoxyl group is necessary to undergo oxidative attack by DDQ. Similar oxidations with DDQ[896] at the benzylic site are effected in the 2,2,6-trimethylchromene (equation 541) and 6-ethyl-2,2-dimethylchromene (equation 542).



(541) (542)

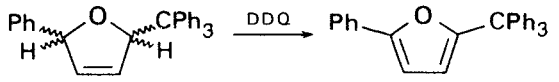
4. Dehydrogenation of nitrogen and oxygen heterocycles

Allylic and benzylic activation is frequently required for efficient oxidation of nitrogen, and, particularly, oxygen heterocyclic compounds by DDQ. The use of 1,4-dioxane (or other suitable solvent) at the reflux temperature frequently provides sufficient activation for hydrogen abstraction. Several recent examples of dehydrogenation and aromatization of some dihydroheterocyclics are depicted in equations(543)–(546)[897–901].

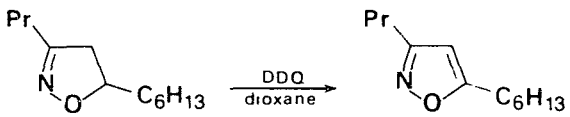


(Ref. 897) (543)

(Ref. 898) (544)



(Ref. 900) (545)

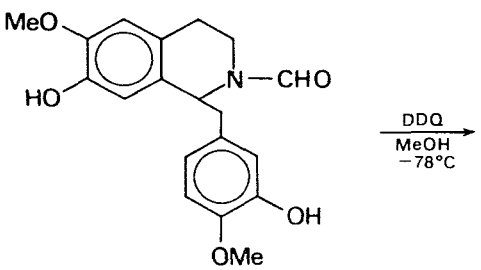


90%

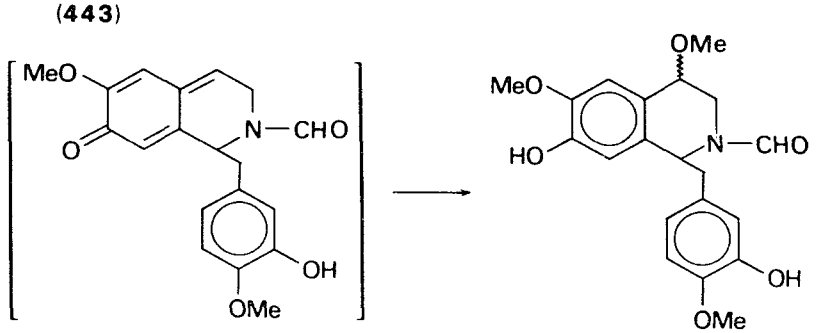
(Ref. 901) (546)

5. *Benzylic oxidation through addition of methanol*

A rare example of the benzylic oxidation of the alkaloid **443** with DDQ in methanol at low temperature affords the *N*-formyl derivative **445**, which appears to result from 1,6-addition of methanol to an intermediate quinone methide (**444**) (equation 547)[902]; the addition of nucleophiles other than methanol to analogous quinone methides can be useful synthetic procedures. Indeed, a valuable, preparative method of 2- and 4-(hydroxyphenyl)acetonitriles that seems to involve addition of a cyanide ion to a quinone methide has been reported[903].



(**443**)

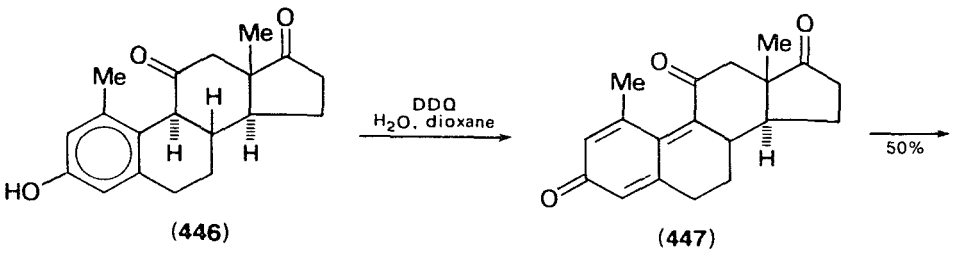


(**444**) (**445**) (547)

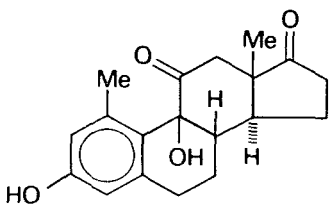
6. *Benzylic hydroxylation*

The 11-oxoestrone **446** is oxidized by DDQ to the ketol **448**. The hydroxyl group has been shown to originate from water. The oxidation is considered to involve an intermediate quinone methide (**447**) (equation 548)[904]. The oxidation of guaiacylacetone (**449**) to give **450** is similar (equation 549).

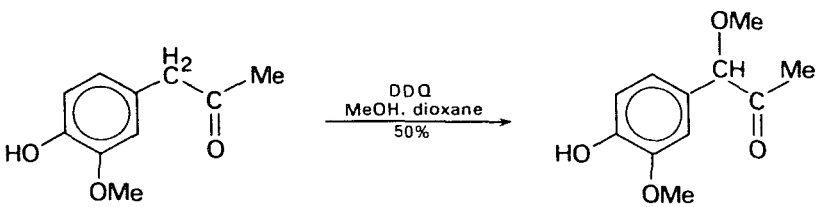
A few benzylic oxidations of substituted 1,2,3,4-tetrahydronaphthalenes to ketones with DDQ in methanol may have been described earlier[905].



(446) (447)



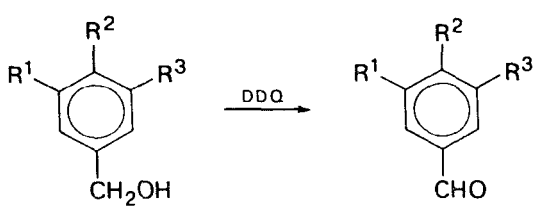
(448) (548)



(449) (450) (549)

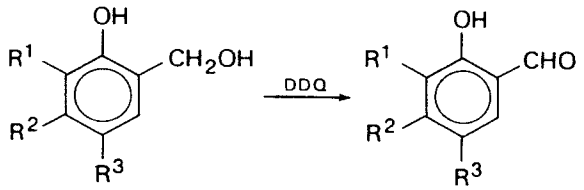
7. *Oxidation of benzylic alcohols*

The dehydrogenation of primary and secondary, aryl-substituted alcohols with DDQ under mild conditions in 1,4-dioxane solution gives the corresponding carbonyl compounds (equation 550)[882]. In contrast to other oxidants, DDQ can be applied for the oxidation of hydroxyaryl-substituted alcohols (equation 551) or diarylcarbinols. Oxidation of hydroxyaryl-substituted alcohols by DDQ in methanol solution results in the formation of benzoquinone by loss of the hydroxylalkyl side-chain (equation 552).

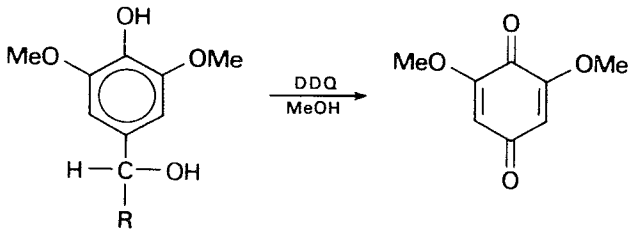


(550)

R^1	R^2	R^3	Yield (%)
H	H	H	80
H	Me	H	93

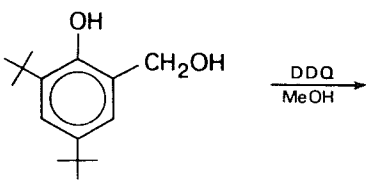


(551)

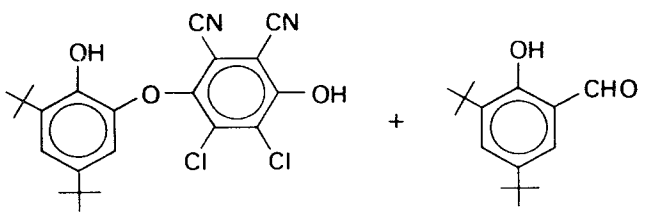


(552)

An example of oxidative coupling in methanol solution is found in the reaction of DDQ with 3,5-di-*t*-butylsalicyl alcohol (**451**), which gives the substituted diphenyl ether **452** (54% yield) and salicylaldehyde (**453**) (35% yield) (equation 553)[882]. The



(**451**)



(**452**) (**453**)

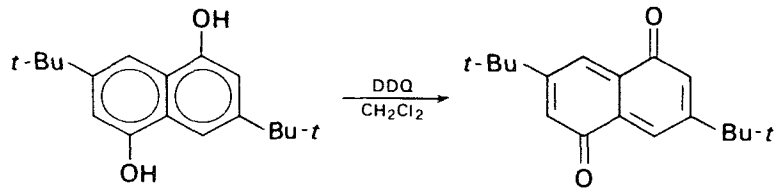
(553)

mechanism of the dehydrogenation of alcohols by DDQ is in agreement with an initial hydride-ion transfer from the α carbon atom of the alcohol. Benzylic oxidation of 4-alkyl-substituted phenols by DDQ in methanol can be explained in terms of phenol oxidation[881].

The choice of oxidant in the oxidation of *p*-alkoxyphenols is generally substrate-dependent; often, ferric chloride, thallium(III) nitrate and DDQ complement each other as successful oxidants[906].

8. *Synthesis of 1,5-naphthoquinone*

The only recorded preparation of a 1,5-naphthoquinone (**455**) involves the quantitative dehydrogenation of 3,7-di-*t*-butyl-1,5-naphthalene-diol (**454**) with DDQ (equation 554)[907].

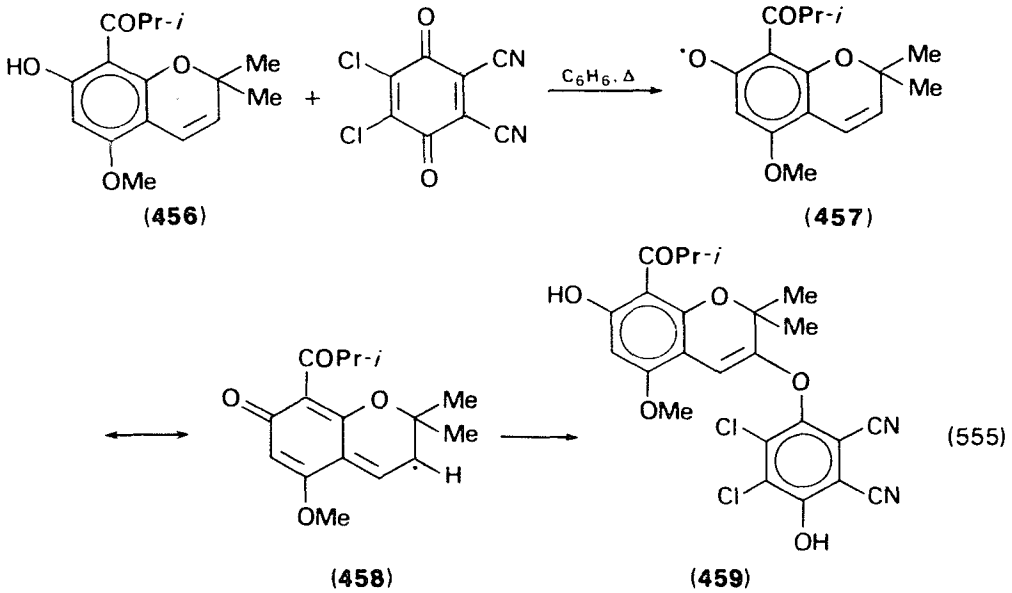


(554)

(454) (455)

9. Oxidation of hydroxychromens to ethers

DDQ is known to effect the oxidative coupling of phenols. For example, 7-hydroxy-2,2-dimethyl-2*H*-chromen (**456**) reacts with DDQ to give the 3-(2,3-dichloro-5,6-dicyano-4-hydroxyphenyl ether, **459**) (equation 555)[908]. The formation of the ether **459** via intermediates **457** and **458** and the DDQH·semiquinone radical agrees with the one-electron process proposed for the oxidation of phenols[881], and cannot be explained by an alternative ionic mechanism[909].

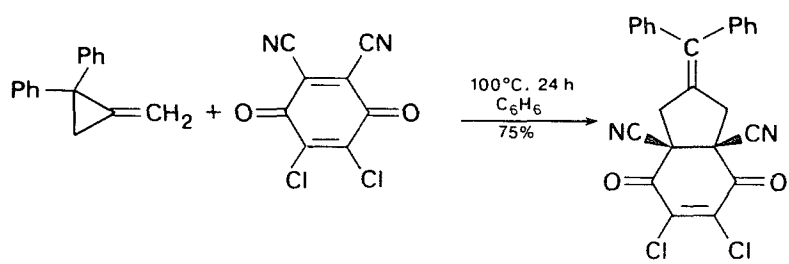


(555)

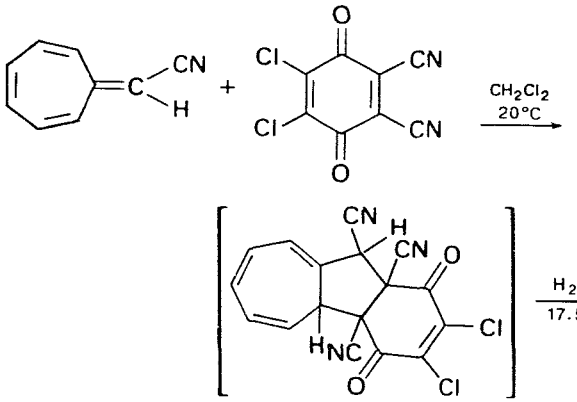
(458) (459)

10. Cycloaddition reactions

Cycloaddition reactions of DDQ are known (equations 556 and 557)[910,911].



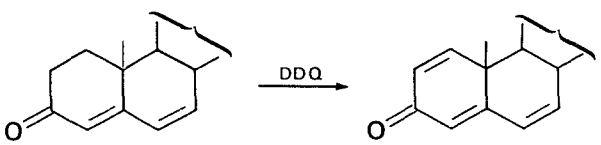
(556)



(557)

11. Dehydrogenation of ketones

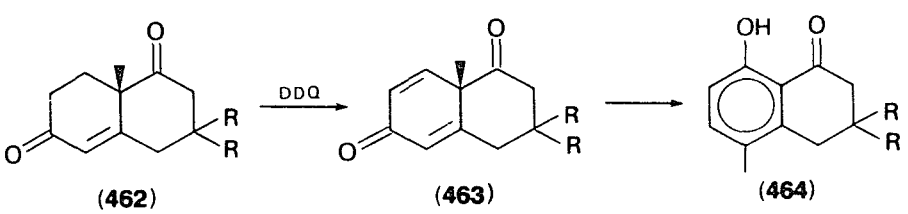
Wide application of DDQ in the steroid field followed the discovery that the common 4-en-3-one grouping **460** is converted into the 1,4-dien-3-one system (**461**) (equation 558)[912]. On heating the DDQ in benzene with the ketone **462** (R = H) or its



(558)

(460) **(461)**

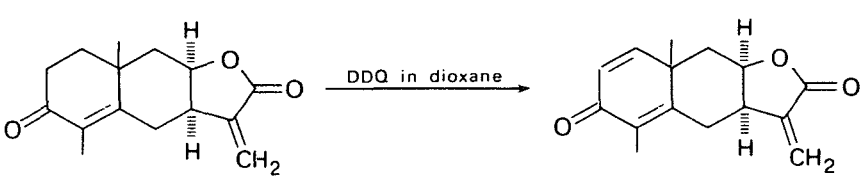
analogue **462** (R = Me) gives only the phenol **464**, presumably by dienone–phenol rearrangement of the intermediate **463** (equation 559)[913]. Oxidation of the naturally occurring ketone **465** with DDQ converts it into the cross-conjugated dienone *d,l*-yomogin (**466**) (equation 560)[914]. Ketone **467** is readily dehydrogenated to give the acid-labile enone **468** (equation 561)[915]. Oxidation of 5-hydroxytropolone (**469**) gives 3,6-cycloheptadiene-1,2,5-trione (**470**) (equation 562)[916].



(559)

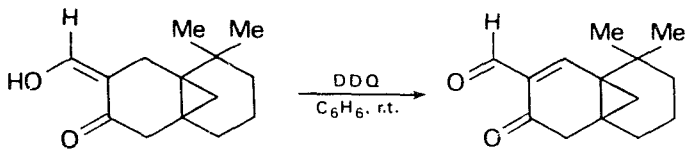
(462) **(463)** **(464)**

R = H, Me



(560)

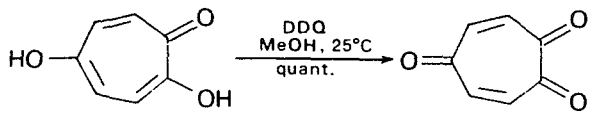
(465) **(466)**



(467) (468)

75%

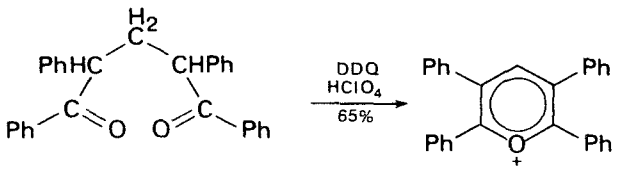
(561)



(469) (470)

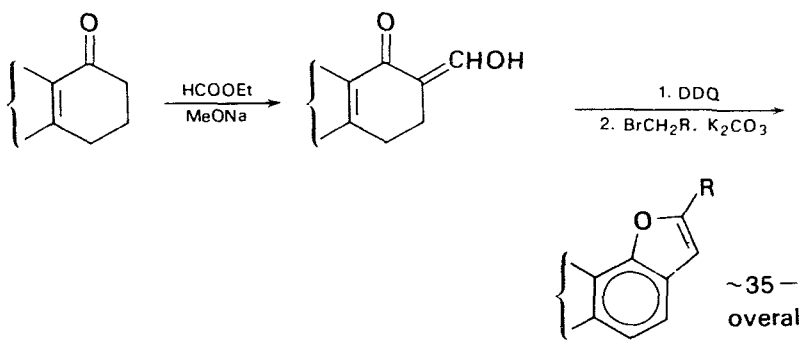
(562)

The dehydration of, for example, the 1,5-diketone **471** with DDQ in acetic acid containing perchloric acid gives the pyrylium salt **472** (equation 563)[917]; the cyclization of a conjugated ketone by DDQ has also been reported (equation 564)[918].



(471) (472)

(563)



(564)

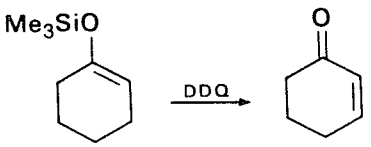
R = COR, COOR, CN, NO_2, etc.

12. Oxidation of silyl enol ethers to α,β-unsaturated ketones

For the introduction of α,β-unsaturation into saturated ketones direct hydrogenation of ketones by quinones is one of the attractive approaches, and it has already found extensive application with steroidal ketones[877,878,919].

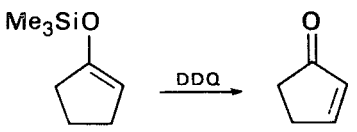
In a new method ketones[920–922], not easily enolizable, for example, cyclohexanone[921], are first converted into an enol silyl ether, and this is then oxidized with DDQ. Thus, the reaction of 1-trimethylsilyloxycyclohexene (**473**) with DDQ at 15°C in 1,4-dioxane (or benzene[920]) gives the enone **474** (equation 565)[921]. Similarly, enol

silyl ethers of cyclopentenone (equation 566)[920], of an acyclic ketone (equation 567)[920] and of cholestan-3-one (equation 568)[922] are converted into the corresponding α,β-unsaturated ketones. Also, the enol ether **475** is converted into the methoxydienone **476** (equation 569)[923]; however, **477** is aromatized with DDQ to the phenol **478** (equation 570)[923].



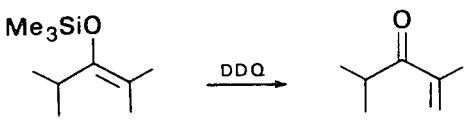
(565)

(**473**) (**474**)
60%



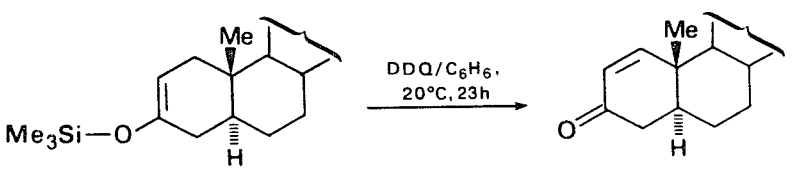
(566)

50%



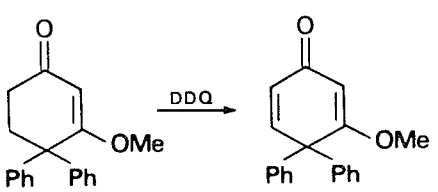
(567)

45%



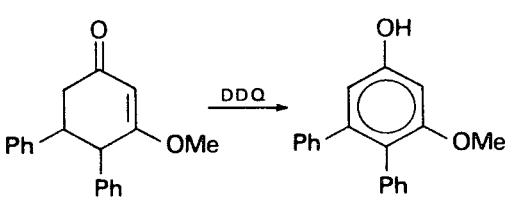
(568)

70%



(569)

(**475**) (**476**)

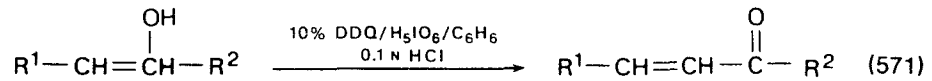


(570)

(**477**) (**478**)

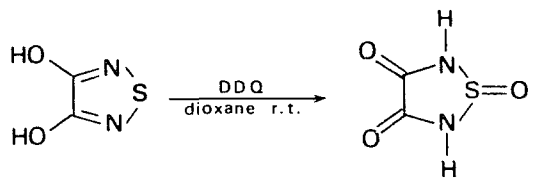
13. Oxidation of allylic alcohols in a two-phase system

A new, selective oxidation of allylic alcohols employs only a catalytic amount of DDQ in a slightly acidic two-phase system benzene–water, in the presence of periodic acid, with $DDQH_2$ as the oxidizing agent; in this way, allyl alcohols can be oxidized to the corresponding α,β-unsaturated ketones (equation 571)[924]. An interesting oxidation of 3,4-dihydroxy-1,2,5-thiadiazole (**479**) to 3,4-dioxo-1,2,5-thiadiazolidine-1-oxide (**480**) was reported earlier (equation 572)[925].



(571)

R^1	R^2	Yield (%)
Ph	H	91
Ph	Ph	86
Ph	Me	80



(572)

(**479**) (**480**)

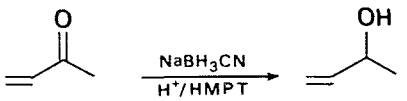
H. Sodium Cyanoborohydride

Sodium cyanoborohydride ($NaBH_3CN$)* is a highly selective reducing agent for a variety of organic functional groups; the topic has been reviewed by Lane[926] and by Hutchins and Natale[927]. As compared to sodium borohydride, $NaBH_4$, modification of the activity of the borohydride in sodium cyanoborohydride (by introduction of the strongly electron-withdrawing cyanide group) increases the Lewis acidity, and improves stability towards protic solvents; moreover, the chemoselectivity of the reagent can often be controlled by controlling the pH. The use of sodium cyanoborohydride includes (*i*) reduction of polar π bonds and (*ii*) reductive displacement by hydride of σ-bonded leaving groups via S_N2 or S_N1 mechanisms. Groups unaffected by the reagent include alkenes, amides, carboxylic acids, esters, lactones, nitrates and nitriles. Except for iminium ions, π bonds are almost inert towards sodium cyanoborohydride, unless activated by protonation or complexation.

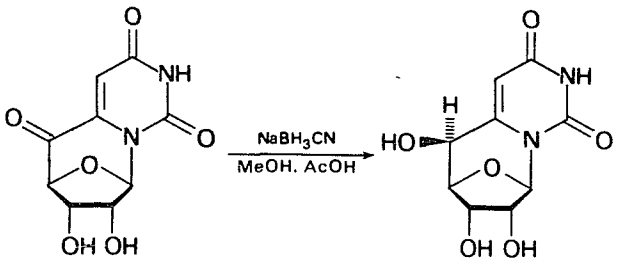
1. Reduction of α,β-unsaturated aldehydes and ketones.

Satisfactory yields of allylic alcohols can be obtained by reduction of a conjugated ketone in HMPT (equation 573)[928], acidic aqueous methanol[929] or acetic acid–methanol (equation 574)[930]. Reduction of α,β-unsaturated esters, nitriles and nitro compounds[931] and the reductive amination of α-formyllactones[932] have been reported.

*Two structures for sodium cyanoborohydride are now in use, i.e. $NaBH_3CN$ and $NaCNBH_3$; the former has, however, a larger appeal.



15–90% isolated (573)



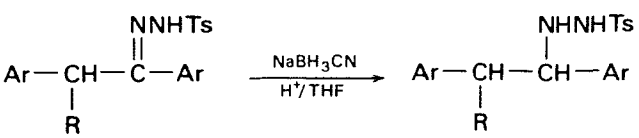
96% (574)

2. Deoxygenation of α,β-unsaturated carbonyl compounds via tosylhydrazones

Tosylhydrazones of aliphatic aldehydes or ketones are reduced to hydrocarbons[933] or alkenes[934,935] by $NaBH_3CN$ in acidic DMF[934], acidic methanol[935] or acidic 1:1 DMF–sulpholane[933]; reduction of α,β-unsaturated tosylhydrazones leads to alkenes with migration of a double bond (equation 575)[933]. However, some tosylhydrazones are reduced to the hydrazino derivatives (equation 576)[936]. Further examples of

$$PhCH{=}CHCH{=}NNHTs \xrightarrow{NaBH_3CN} PhCH_2CH{=}CH_2 \quad (575)$$

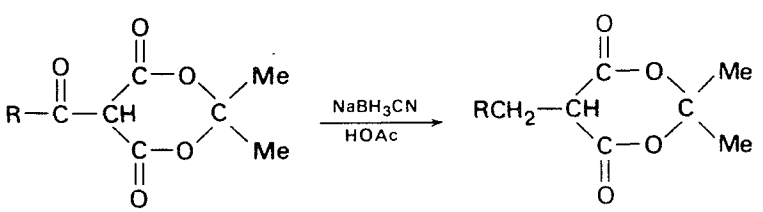
98%



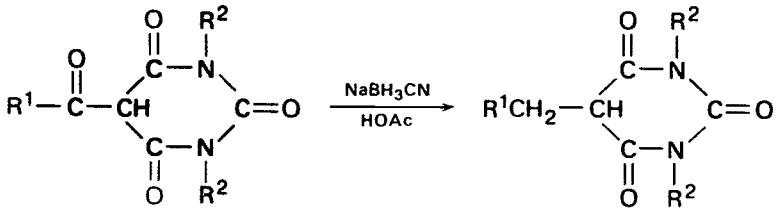
~80–90% (576)

R = Me, Et, OH, OMe, OEt

direct reductive deoxygenation of the acyl carbonyl group have recently been reported; for example, isopropylideneacylmalonate (equation 577), 5-acylbarbituric acid (equation 578) and 3-acyl-4-hydroxycoumarin (equation 579) are reduced to the corresponding alkyl derivatives in good yields[937].

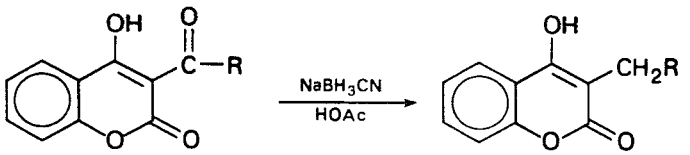


R = Et (577)



(578)

$R^1 = n\text{-Pr}$, $R^2 = H$

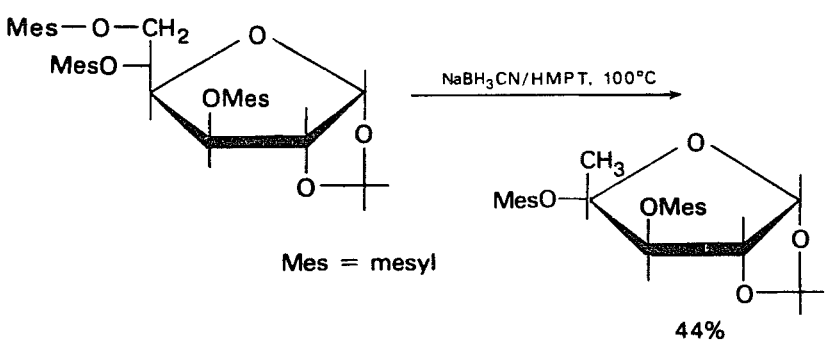


(579)

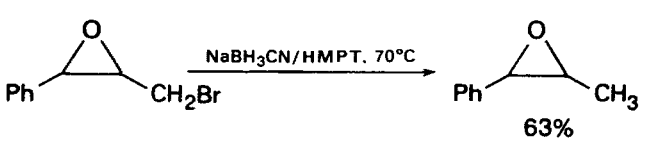
R = Et

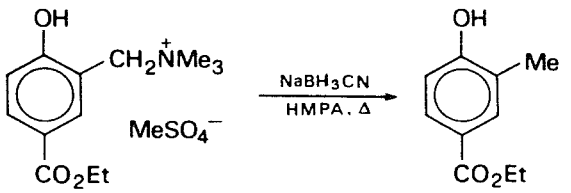
3. *Other selective reactions*

Sodium cyanoborohydride has been applied to selective reductive displacement of alkyl halides and sulphonic esters (equation 580)[938] and of a quaternary ammonium group (equation 581)[939], to reductive amination (equations 582[940], 583[941], and 584[942]), to a reduction of acetals (equation 585)[943] and to an epoxide ring-opening (equation 568)[944]. Oximes[945,946] and nitrones[945] are readily reduced by sodium cyanoborohydride to *N*-(monoalkyl)hydroxylamines (equation 587)[945] and *N,N*-dialkylhydroxylamines (equation 588)[945], respectively. The reagent reduces enamines[947] and imines[944]; it can also be used for methylation (and demethylation) of primary amines (equation 589)[948] stereospecific reduction of an iminium salt (equation 590)[949] and the reductive ring-enlargement of a polyamide alkaloid (equation 591)[950]. The difference between catalytic reduction and reduction with the $NaBH_3CN$–formic acid reagent of the alkaloid periphylline (equation 592)[950] should be noted.

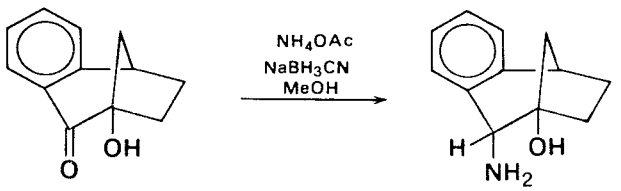


(580)

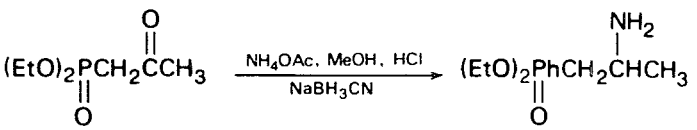




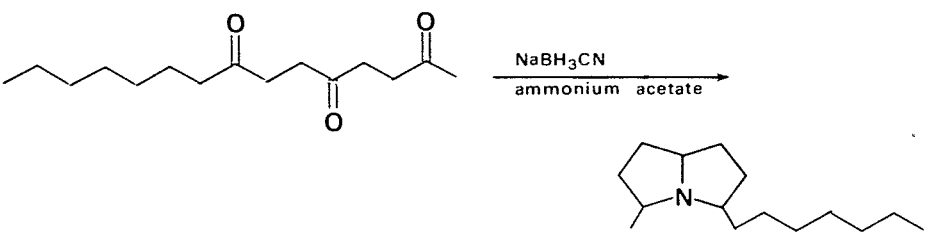
91% (581)



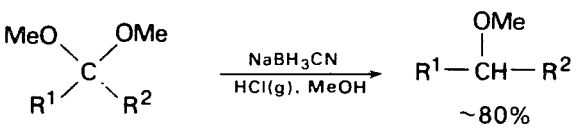
(582)



86% (583)

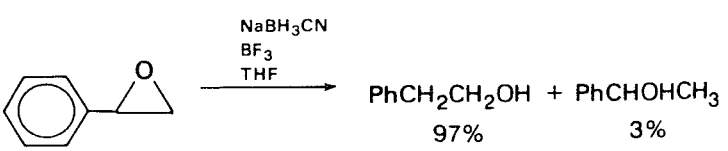


(584)



~80% (585)

R^1, R^2 = H, Ph, alkyl, cyclic



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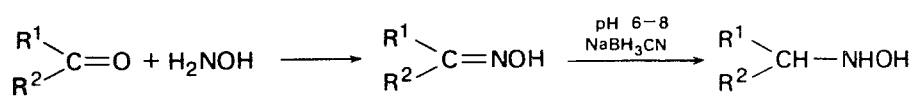

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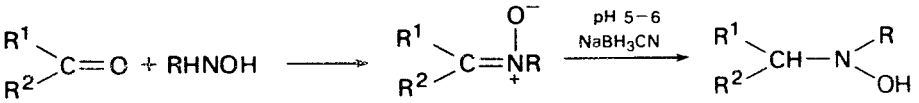

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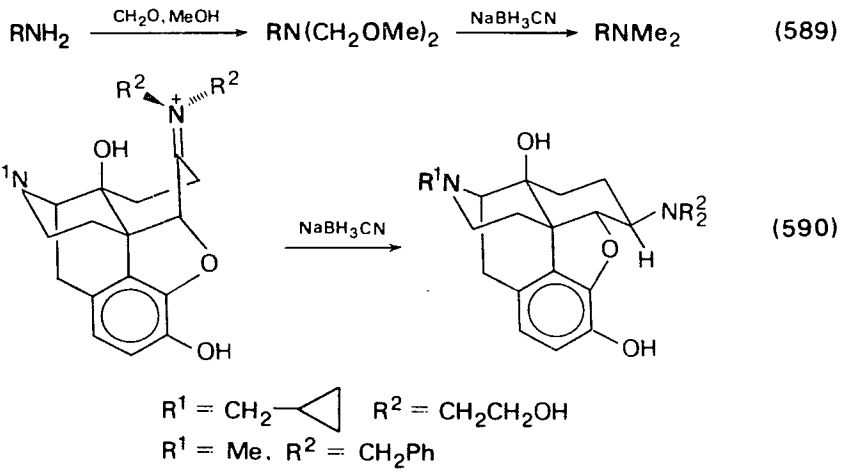
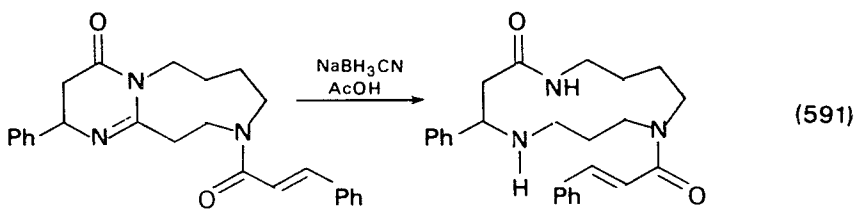
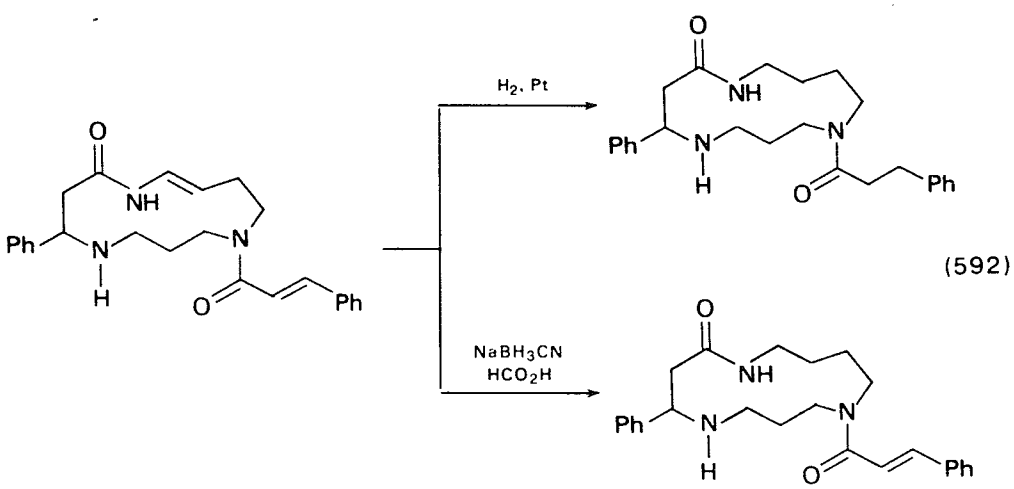


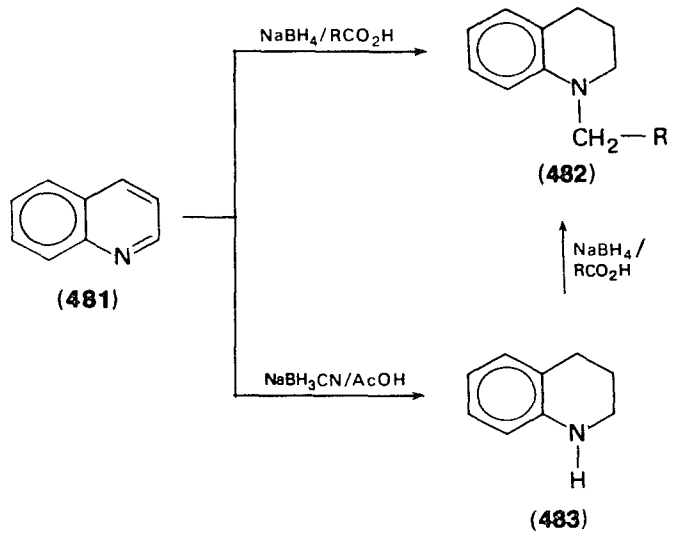




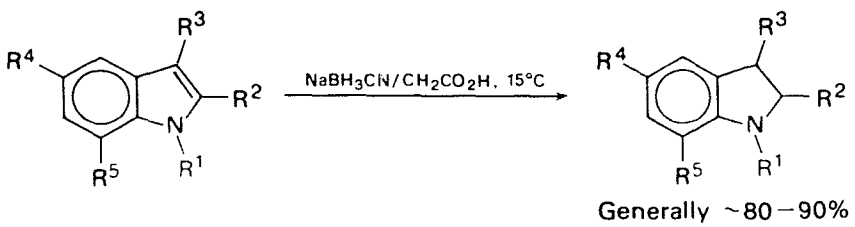
4. Different behaviour of indole and quinoline towards sodium borohydride and sodium cyanoborohydride

Sodium borohydride in carboxylic acid media sequentially reduces and alkylates quinoline (**481**) to give the corresponding *N*-alkyl-1,2,3,4-tetrahydroquinoline (**482**). However, sodium cyanoborohydride effects the reduction of quinoline (**481**) without *N*-alkylation, to provide a simple preparation of 1,2,3,4-tetrahydroquinoline (**483**)

(equation 593)[951]. Similar behaviour of both reducing agents towards indoles[952] was observed earlier. Substituted indoles give indolines in excellent yield (equation 594)[953].



(593)



R^1 = H, alkyl, Ph, Bz
R^2, R^3 = H, Me, $-(CH_2)_4-$
R^4, R^5 = H, Me, Br

(594)

5. *Reduction of α,β-diarylacrylonitriles*

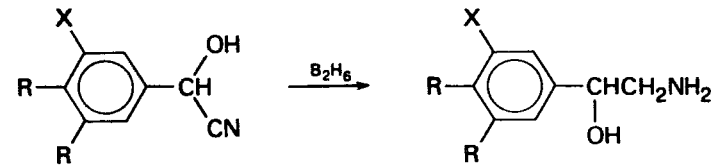
Reduction of α,β-diarylacrylonitriles by sodium borohydride in DMF provides an excellent synthesis of α,β-diarylpropanonitriles (equation 595)[954]; a similar reduction can also be achieved with sodium cyanoborohydride[931].

$$ArCHO + ArCH_2CN \xrightarrow[(-H_2O)]{OH^-} \underset{Ar}{\overset{H}{\diagdown}}C{=}C\underset{CN}{\overset{Ar}{\diagup}} \xrightarrow[DMF]{NaBH_4} ArCH_2CHArCN \quad (595)$$

6. *Special reduction of cyano compounds*

The hydrogenolysis of alkyl halides with sodium cyanoborohydride or tetrabutylammonium cyanoborohydride has been discussed[955]. Reduction of α,β-unsaturated nitriles to saturated nitriles can be performed with magnesium in methanol[956], lithium

amide[957] or a copper hydride complex[958]. Reduction of nitriles to amines can be achieved with $NaBH_3(OCOCF_3)$[959], lithium triethylborohydride[960], $NaBH_2S_3$[961] or catalytic hydrogenation with a rhodium(I)hydrido compounds, e.g., $RhH(i\text{-}Pr_3P)$ as the catalyst[962]. Reduction of saturated nitriles to aldehydes (e.g. $-CH_2CN \rightarrow -CH_2CHO$) can be performed with diisobutylaluminium[963,964]. The examples depicted show reduction of cyanohydrins to amino alcohols by diborane in tetrahydrofuran, without hydrogenolysis of the halogen substituent or the alcoholic group on the aromatic ring (equation 596)[965], reductive elimination of the cyano group (equation 597)[966] and catalytic reduction of cyano groups, followed by rearrangement (equation 598)[967].

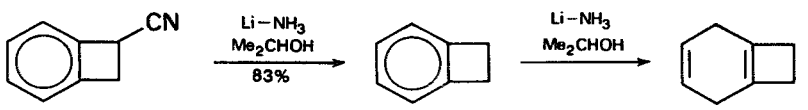


(596)

70–80%

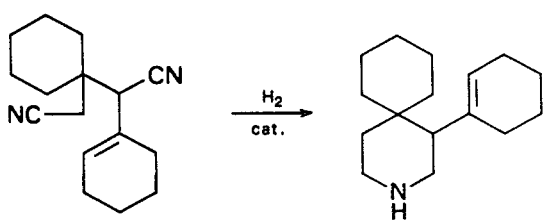
X = Cl, Br, I
R = OH or OMe

System does not hydrogenolyse halides



(597)

98%



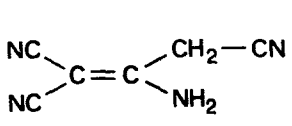
(598)

V. CYANOCARBONS AND ELECTRON ACCEPTORS

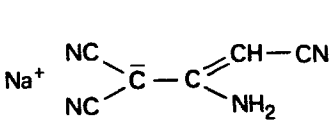
A. Malononitrile

1. General considerations

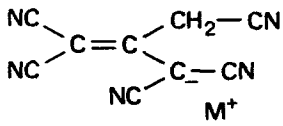
The chemistry of malononitrile has been thoroughly studied and reviewed[9–13], and will not be discussed in detail here. However, for the sake of continuity, a summary of some of the key transformations of malononitrile, and some of its pertinent reactions taken from the recent literature, will be covered. The chemical literature on malononitrile is abundant[10,11]; the reagent forms an acyclic dimer **484a** and the salt **484b**, acyclic (linear) trimers **484c–484f** and cyclic trimers (pyridine derivatives) **484g** and **484h**, and all of these are potential intermediates for synthesis[968]. The Knoevenagel reaction between malononitrile and carbonyl compounds yields ylidenemalononitriles (equation 599)[12]. This reaction is usually catalysed by weak bases. Malononitrile is an important synthon for synthesis of diverse heterocyclic systems.



(484a)

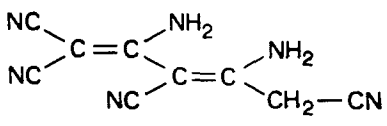


(484b)

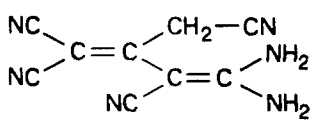


(484c)

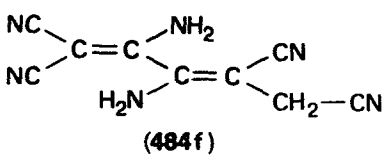
M = H, NH_4



(484d)



(484e)



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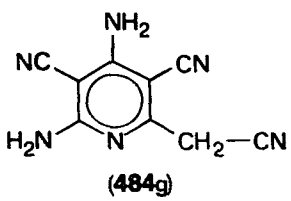

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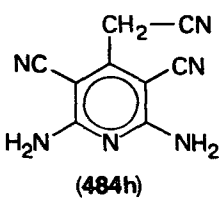
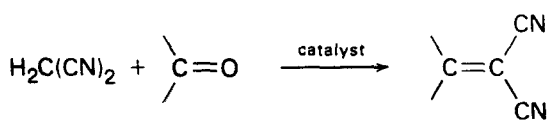


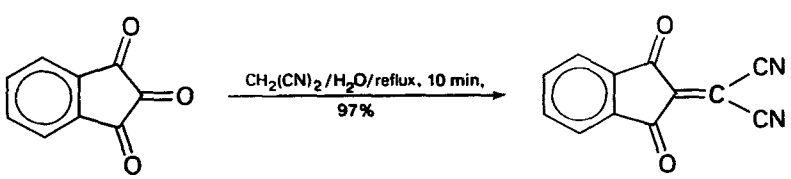
(484h)



(599)

2. *Reaction of cyclic polyketones with malononitrile*

Cyclic triketones in which the unfavourable dipolar interaction between adjacent carbonyl groups is maximal and the carbonyl groups are eclipsed (*S-cis* conformation)[969] are more reactive than others in regard to the formation of addition compounds. Thus, 1,2,3-indanetrione reacts readily with malononitrile with replacement of the most reactive 2-carbonyl oxygen atom, to give 2-(dicyanomethylidene)-1,3-indandione; the reaction proceeds readily in organic solvents[970,971] and in aqueous media (equation 600)[10].



(600)

3. *Reaction of oxocarbons with malononitrile. Bond-delocalized salts. Pseudo-oxocarbons*

The reaction of malononitrile with aromatic oxocarbons[972] is examined next. Either partial or complete replacement of the original carbonyl oxygen atoms in three-, four- or six-membered oxocarbon anions $C_nO_n^{m-}$ with such C=O equivalent, π-isoelectronic groups as dicyanomethylene $=C(CN)_2$[15] (also C=N, C=P, C=S, C=Se groups) yields a series of unusual oxocarbon analogues called pseudo-oxocarbons[973]; their chemistry has recently been reviewed[974].

In recent years, several pseudo-oxocarbon anions containing $=C(CN)_2$ groups have been synthesized and studied; the procedures used include either direct replacement of the oxygen atom in the C=O group or an indirect method. In the three- and four-membered, pseudo-oxocarbon series, these include the preparation of 1,2,3-tris(dicyanomethylene)deltate (**485**)[975], the monanion (**486**)[976], the disodium salt of 1,2-bis-(dicyanomethylene)-3-cyclobutene-3,4-dione, a new analogue of the squarate dianion **487**[977], the monoanion **488**[978] and the mixed dianion **489**[976]. The dicyanomethylene derivatives best studied to date are derivatives of croconic acid and the croconate dianions. One, two or three oxygen atoms in $C_5O_5^{2-}$ can be replaced by $=C(CN)_2$ groups[973,979]. The orange dianion **490** is obtained from dimethyl or diethyl croconate. The violet dianion **491** is prepared by treatment of dipotassium croconate with malononitrile, and the blue dianion **492** is synthesized by reaction of croconic acid with the reagent to give the parent acid, i.e. 1,2,3-tris(dicyanomethylene)-4-cyclo pentene-4,5-diol, which is converted into the potassium salt by titration with potassium methoxide in methanol. The mixed pseudo-oxocarbon croconates also include the dianion **493**[976]. The dipotassium salts **490**, **491** and **492** are semiconductors[980]; for example, the dipotassium salt of **491** has single-crystal conductivity of $2 \times 10^{-6}\ \Omega^{-1}\text{cm}^{-1}$ at room temperature, comparable to that of the dipotassium salt of the TCNQ anion radical. The crystal structure of **491**[981] shows the D_{5h} symmetry of the croconate ring. Structurally, there are columns of the cyclopentene-ring anions parallel to the cation columns, with only 3.42 Å separation between adjacent molecular sites. Hence, by virtue of its size and of partial occupancy of sites in the channel, the potassium cation is capable of some ionic conductivity; however, most of the conduction in the salt occurs through interacting cyclopentene anions.

In addition to these anions, uncharged pseudo-oxocarbons could be of considerable interest. A crystal-structure determination[982] of the 1:1 charge-transfer complex of pyrene (**494**) and 2-(dicyanomethylene)-4,5-diethoxy-4-cyclopentene-1,3-dione (DDC, **495**) has shown the existence of a 'neutral' pseudo oxocarbon in the complex. The bond distances in DDC are: Cl—C(2) 1.486 Å, C(2)—C(3) 1.483 Å, C(3)—C(4) 1.466 Å, C(4)—C(5) 1.381 Å, C(5)—C(1) 1.475 Å, C(2)—$C(CN)_2$ 1.338 Å and C—O 1.213 Å; the internal C—C—C bond angles deviate somewhat from the usual pentagonal angle of 108°, with angles of 106° and 107.5°, and larger values for the angles C(3)—C(4)—C(5) (110.5°) and C(4)—C(5)—C(6) (109.8°). Thus, DDC in the pyrene–DDC complex may be viewed as a 'neutral, internally resonance compensated' pseudo-oxocarbon (**495d**), that is, a hybrid of resonance forms (**495a** ↔ **495c**).

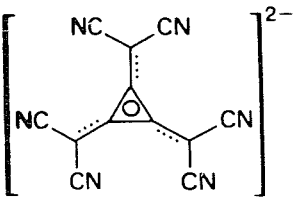
4. *Amidinoethylation. A facile synthesis of 3,3-disubstituted 1,5-pentanedicarboxamides*

As an example of the amidinoethylation reaction[983], the addition of malononitrile to the propenamidine **496** gives 3,3-disubstituted 1,5-pentanedicarboxamidines **497** (equation 601)[984]. Such non-catalysed Michael additions to electrophilic alkenes are extremely rare[985].

a. Preparation of bis(dialkylamino)malononitrile. Treatment of chloroformamidinium chloride (**498**) with a concentrated solution of potassium cyanide followed by ether extraction gives bis(dialkylamino)malononitrile (**499**). However, treatment of **498** in acetonitrile with aqueous KCN (1:1) yields the dimethylamide of cyanoformic acid (**500**) (equation 602)[986].

5. *Thermochemical behaviour of o-amino- or azido-cinnamonitriles*

Recently, the effect of two diferent geometrical arrangements around the double bond in *o*-amino- or azido-cinnamonitriles on the course of the cyclization has been



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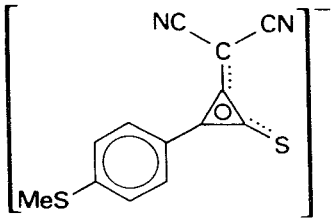

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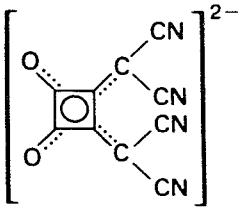

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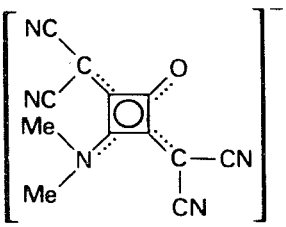

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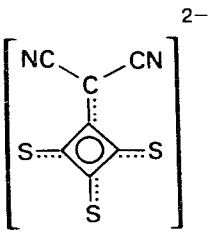

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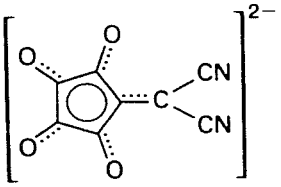

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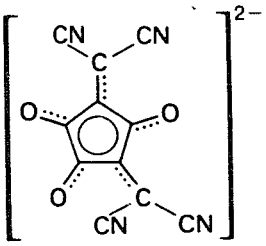

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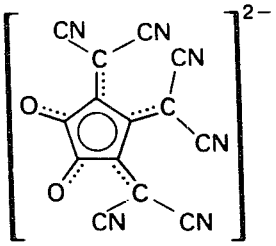

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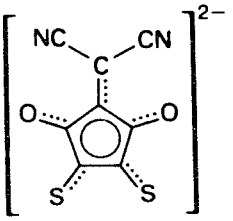

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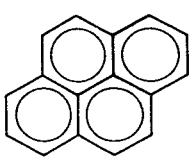

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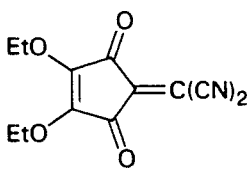

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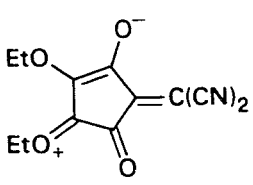

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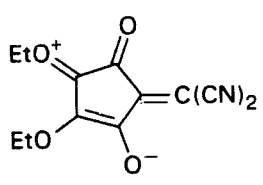
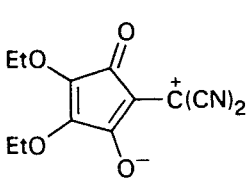
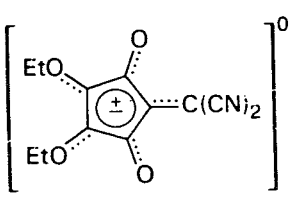


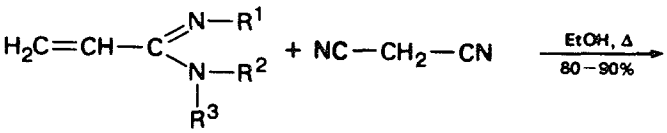
(495b)



(495c)



(495d)



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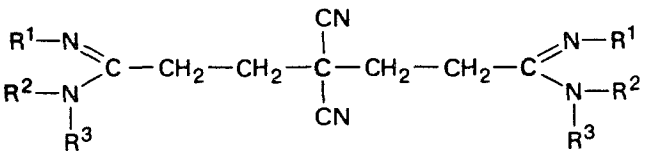
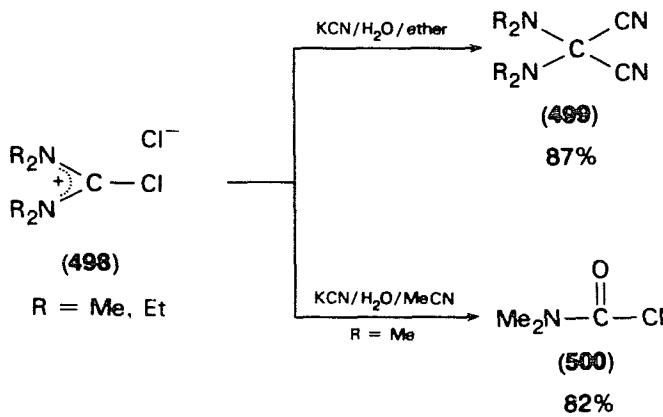


(497) (601)



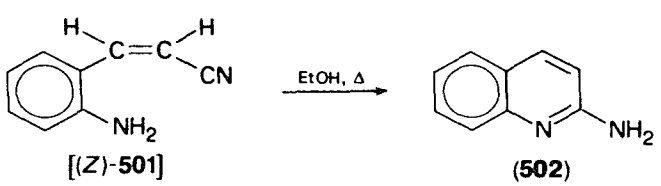
(498)

R = Me, Et

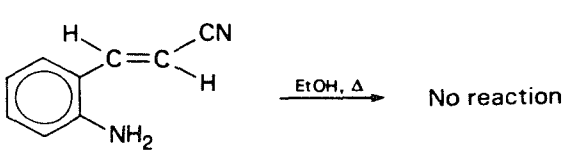
(499) 87%

(500) 82% (602)

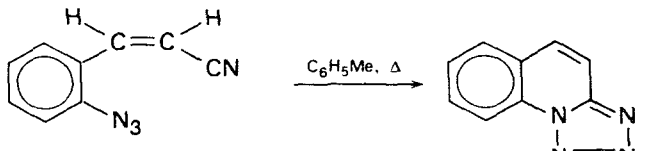
examined. Thus, (*Z*)-*o*-aminocinnamonitrile (**501**) can be converted into the quinoline **502** in refluxing ethanol (equation 603), whereas the (*E*)-isomer (**503**) gives no reaction (equation 604). Similarly the (*Z*) azide (**504**) requires lower temperatures (refluxing toluene) to yield tetrazolo[1,5-*a*]quinoline (**505**) (equation 605), than the (*E*) azide (**506**) (140°C, DMSO) does to be converted into 2-cyanoindole (**507**) (equation 606)[987]. The different reactions of azides **504** and **506** can be explained[987] by invoking a concerted mechanism that requires some degree of charge-separation in the transition state; this is consistent with the observed increase in rate on changing from toluene to dimethyl sulphoxide as the solvent.



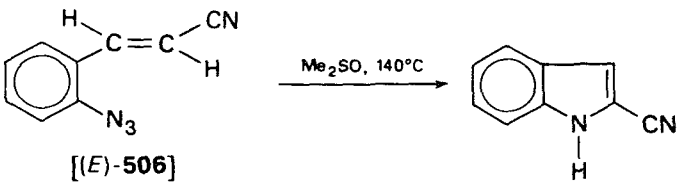
[(*Z*)-**501**] (**502**) (603)



[(*E*)-**503**] (604)



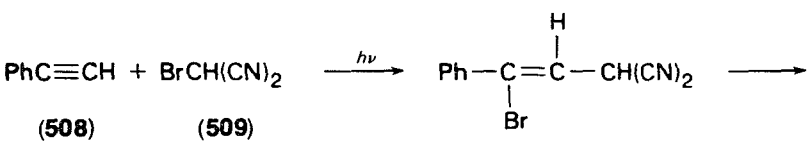
[(*Z*)-**504**] (**505**) (605)



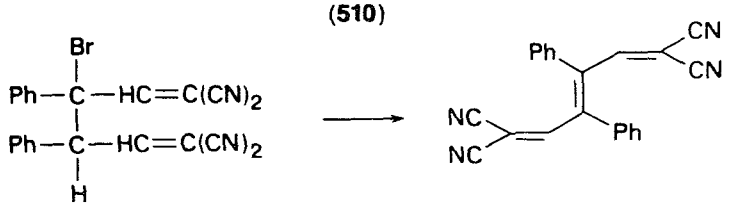
[(*E*)-**506**] (**507**) (606)

6. *Free-radical additions of bromomalononitrile to alkynes under irradiation*

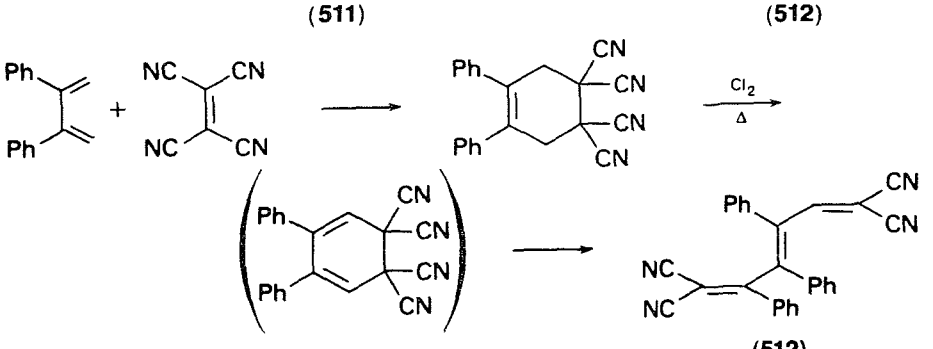
Bromomalononitrile (**509**) reacts with phenylacetylene (**508**) under irradiation to yield (*E*)-3,4-diphenyl-1,3,5-hexatriene-1,1,6,6-tetracarbonitrile (**512**) via intermediates **510** and **511** (equation 607)[988]. The preparation of **512** by an alternative route (equation 608)[988] has confirmed the structure. Light-induced reactions of bromomalononitrile with 1-hexyne yield the (*E*)/(*Z*) addition products in the ratio of 2:1. The stereoselectivity of the addition reaction is kinetically controlled. The free-radical addition of bromomalononitrile to alkenes under irradiation leads to the formation of anti-Markownikoff products; steric effects on regioselectivity have been observed[989].



(**508**) (**509**) (**510**)



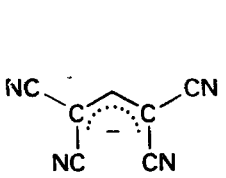
(**511**) (**512**) (607)



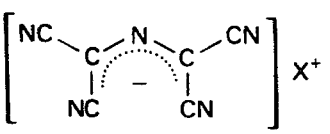
(**512**) (608)

7. Cyanocarbons and poly(cyanocarbons)

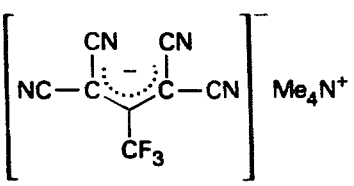
The chemistry of cyanocarbons and poly(cyanocarbons) has been actively investigated during the past thirty years, and the literature on the subject is extensive[10]; the subject has recently been summarized[990a] and thoroughly reviewed by Zefirov and Makhon'kov[990b]. A variety of cyanocarbons (neutral) or cyanocarbon acids (e.g. salts) have been prepared and studied, among them 1,1,3,3-tetracyanopropenide (**513**)[991], 1,1,3,3-tetracyano-2-azapropenide (**514**)[992], 1,1,3,3-tetracyano-2-(trifluoromethyl)propenide (**515**)[993], hexacyanobutadiene (**516**)[991,994] and a bright-red cyanocarbon anion believed to be heptacyanopentadienide (**517**)[991]; 1,1,2,4,5,5-hexacyanopentadienide salts (**518**)[995] and a yellow cyanocarbon dianion (**519**) have also been prepared.[991] This series has been extended by application of Grignard reagents for alkylation of tetracyanoethylene[995].



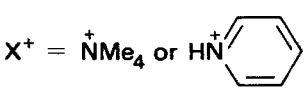
(**513**)

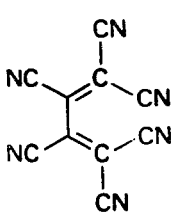


(**514**)

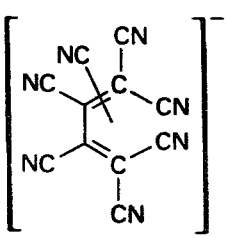


(**515**)

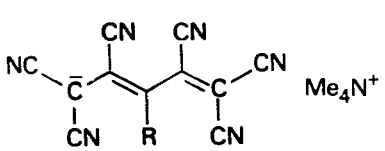




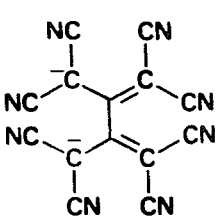
(**516**)



(**517**)



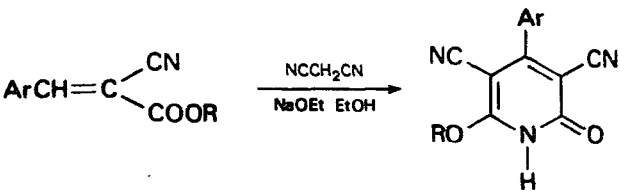
(**518**)



(**519**)

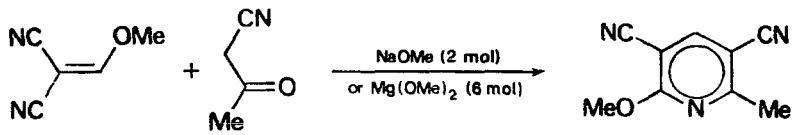
8. Selected syntheses of heterocycles via malononitrile

Synthesis of heterocycles via malononitrile selected from the recent literature are depicted in equations (609)–(618)[996–1005].

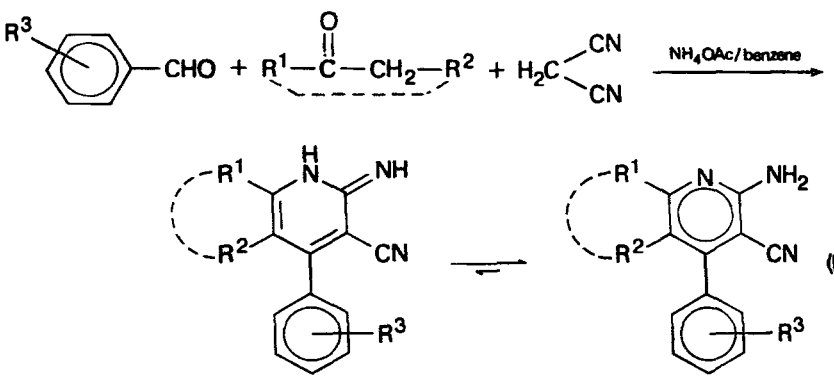


78–92%

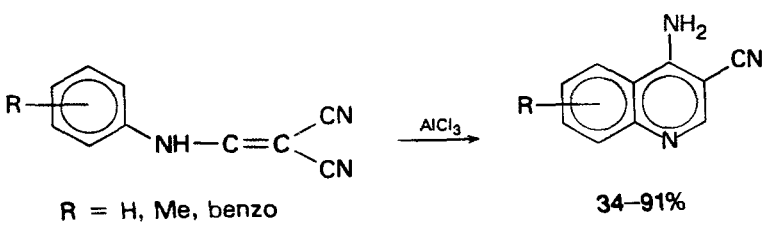
(Ref. 996) (609)



(Ref. 997) (610)



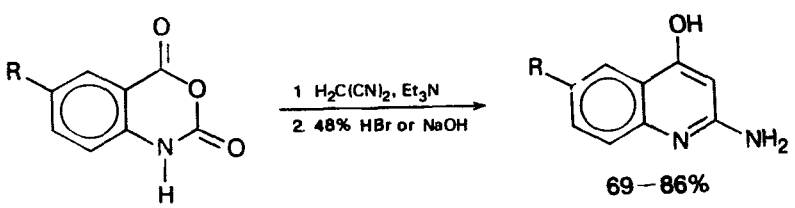
(Ref. 998) (611)



R = H, Me, benzo

34–91%

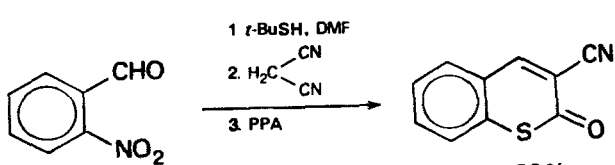
(Ref. 999) (612)



R = H, Cl, Me, MeO

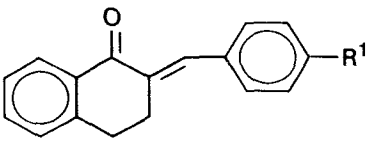
69–86%

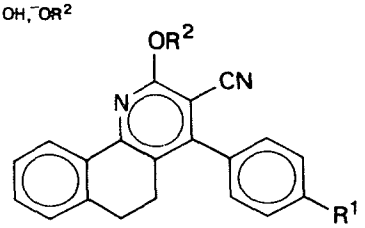
(Ref. 1000) (613)



~50–90%

(Ref. 1001) (614)



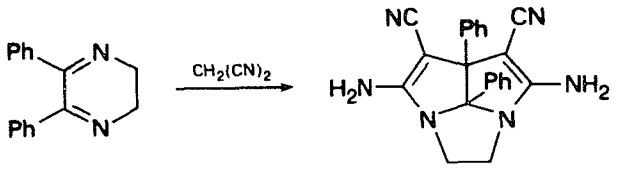


(Ref. 1002) (615)

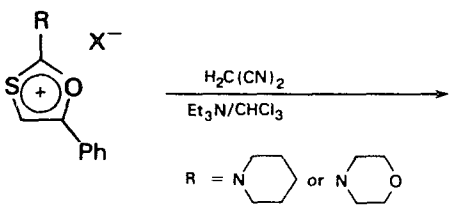
R^1 = H, Me, OMe, Cl, NO_2

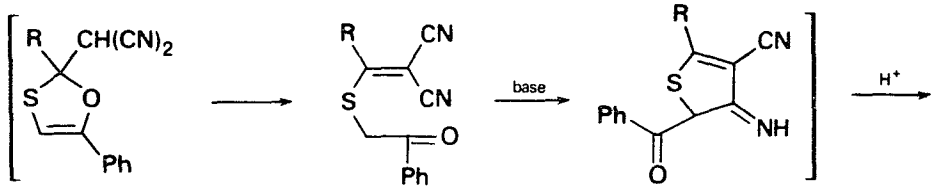
R^2 = Me, Et

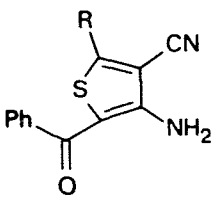
73–92%



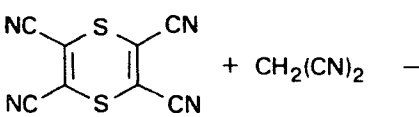
(Ref. 1003) (616)

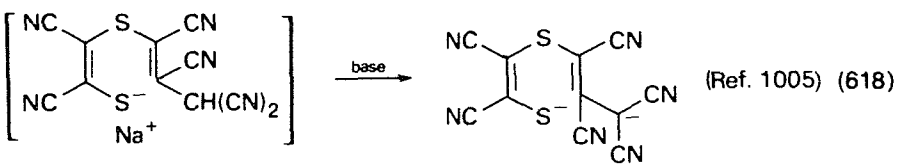






(Ref. 1004) (617)





(Ref. 1005) (618)

B. Tetracyanoethylene

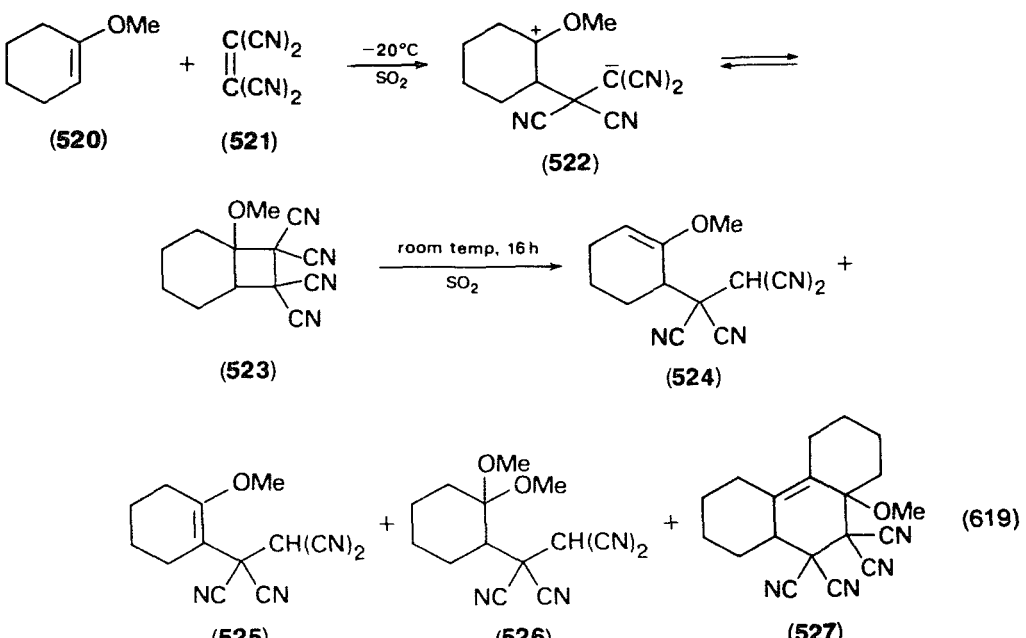
1. General considerations

Tetracyanoethylene* (TCNE) is the simplest of the percyanoalkenes (cyanocarbons). The cyano group is a powerful electron-withdrawing group, although it is a poor dipolarophile. It is, however, sufficiently small to present no important steric problems. Hence, TCNE is a highly electron-deficient and strongly electrophilic reagent. Thus it is easily attacked by electron-rich alkenes or dienes, and also reacts with other nucleophiles, such as alcohols and amines, and gives, for example, tricyanovinylation of aromatic amines. The affinity of TCNE for electrons is so great that the stable anion-radical, $TCNE^{\cdot-}$ is formed by treatment with many reducing agents, such as I^-. TCNE forms intensely coloured complexes with alkenes or aromatic hydrocarbons. The colour arises from donor–acceptor complexes, with partial transfer of a π-electron from the aromatic hydrocarbon to TCNE. TCNE is today an established reagent for testing ene, diene and *n*-ene systems of organic and metalloorganic substrates. In addition, TCNE is a useful reagent for synthesis of cyanocarbon acids, spiro compounds and novel heterocycles.

The chemistry of TCNE has been studied and reviewed[5,879,1006–1009], and will not be discussed here. The presentation here will be limited to a few recent applications of TCNE.

2. Reaction of tetracyanoethylene with nucleophilic double bonds via ene-type reactions and 1,4-dipolar intermediates

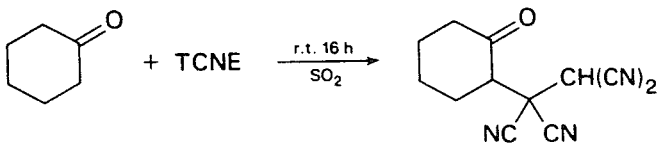
Abundant experimental evidence indicates that [2 + 2]cycloadducts from reaction of TCNE with enol ethers are formed by an intramolecular cyclization of the corresponding 1,4-dipolar ion intermediates[1010–1013]. The latter were successfully trapped by



(520) (521) (522) (523) (524) (525) (526) (527) (619)

*Also known as ethenetetracarbonitrile or cyanoethylene.

such reactive dipolarophiles[1013] as aldehydes, ketones and Schiff bases, although there was no evidence that the dipolar ion could be intercepted by the nucleophilic double bond of the enol ether itself. However, such evidence has now been provided in a recent study[1014]. Reaction of 1-methoxycyclohexene (**520**) with TCNE (**521**) gives the expected [2 + 2]cycloadduct (**523**) in quantitative yield. However, at room temperature **523** undergoes isomerization to give the open-chain adducts **524** and **525**, the ketal **526** and the cycloadduct **527** in 30, 60, 5 and 5% yields, respectively (equation 619). The experimental facts indicate that the 1,4-dipolar ion **522** is a common intermediate in all of these transformations. Hence the cycloadduct **523** is a kinetic product that exists in equilibrium with **522**. Under thermodynamic conditions, the intermediate dipolar ion undergoes an ene reaction, to give an open-chain adduct that can also react further (formation of **524** through **526**). In the reaction of cyclohexanone with TCNE in liquid sulphur dioxide, the corresponding dipolar ion does not give 'cycloadduct' at all. Instead, a proton rearrangement affords the 2-(1,1,2,2-tetracyanoethyl)cyclohexanone **528** (equation 620)[1014].



(620)

(528)

3. *Reaction of protoporphyrin with tetracyanoethylene*

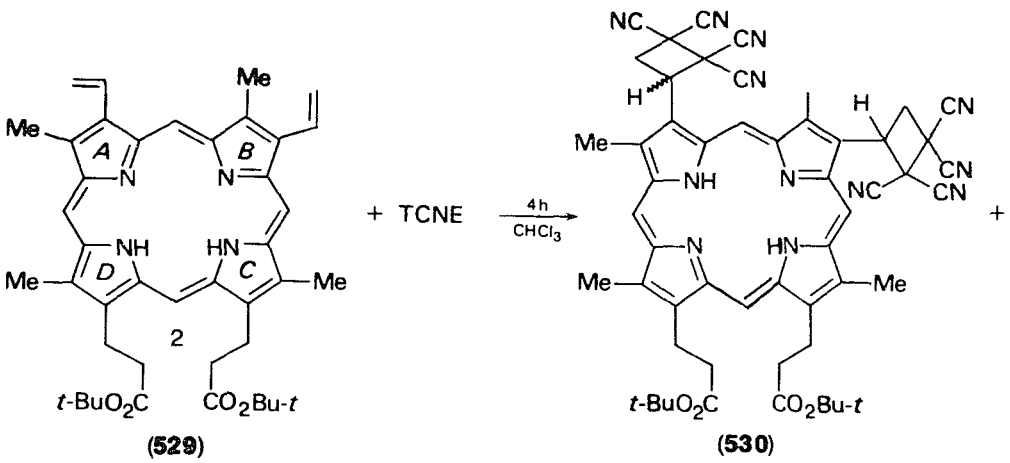
Reaction of TCNE with protoporphyrin di-*t*-butyl ester (**529**) gives three major products; one has been identified as the kinetically favoured [2 + 2]cycloadduct **530**, containing two cyclobutane rings. Two other thermodynamically more stable isomers are probably the [4 + 2]cycloadducts **531** and **532** containing a cyclobutane ring and a six-carbon ring (equation 621)[1015a].

4. *Vinylcyclobutane–cyclohexene rearrangement*

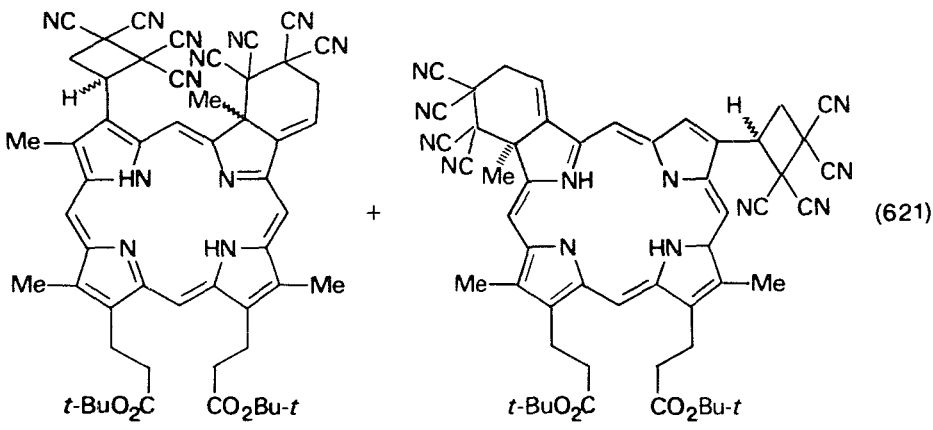
The vinylcyclobutane–cyclohexene rearrangement is known to occur at elevated temperatures, but examples that occur at room temperature are rare. However, it has been reported[1015b] that the reaction of 1,1-dicyclopropylbuta-1,3-diene with TCNE gives 1-(2′,2′-dicyclopropylvinyl)-2,2,3,3-tetracyanocyclobutane, and if allowed to react for longer periods, 3,3-dicyclopropyl-4,4,5,5-tetracyanocyclohex-1-ene (**533**) (equation 622). Although **533** is formally the product of a [4 + 2]cycloaddition, these observations can also be interpreted in terms of a vinylcyclobutane–cyclohexene rearrangement. Following solvent and substituent studies, the rearrangement has been concluded to be a heterolytic process involving a zwitterionic intermediate **534**[1015b].

5. *Facile synthesis of 2-amino-3,4,5-tricyanopyridines*

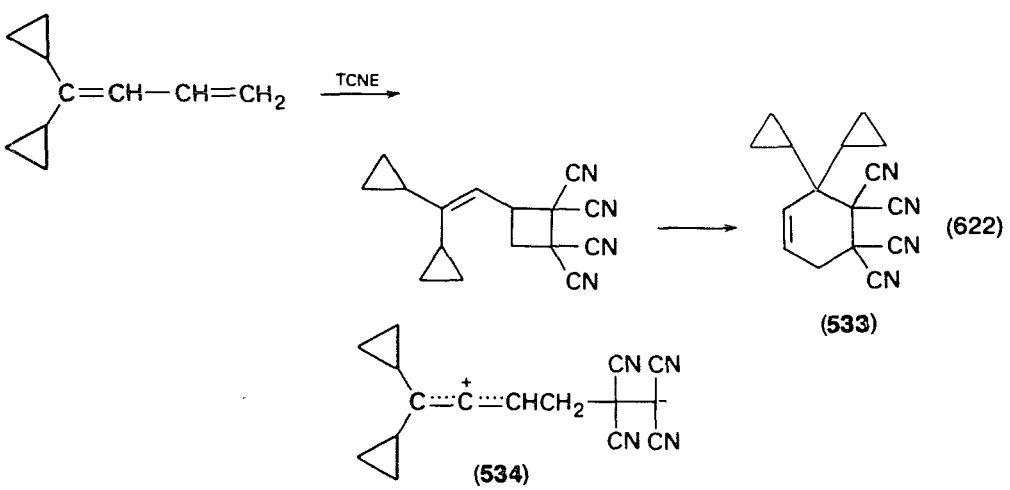
Tetracyanoethylene reacts readily with various CH-acids, leading to the synthesis of diverse heterocycles. The facile synthesis of 2-amino-3,4,5-tricyanopyridine (**535**) involves the reaction of the CH-acid 3-iminopropanonitrile (or its enaminenitrile tautomer) with TCNE, and apparently proceeds via the adduct shown (equation 623)[1016].



(529) (530)

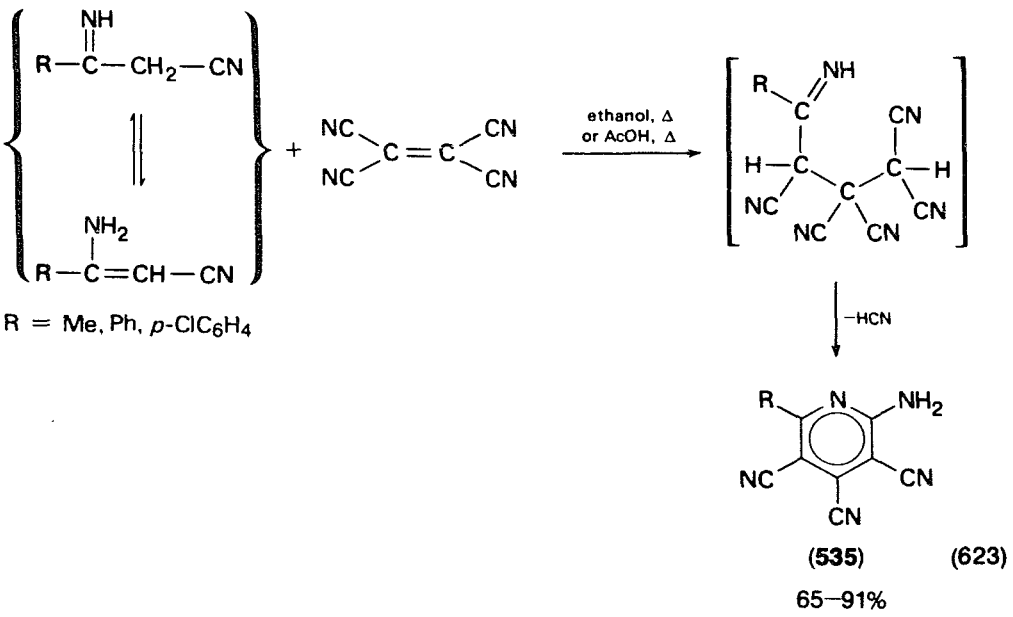


(531) (532) (621)



(533) (622)

(534)



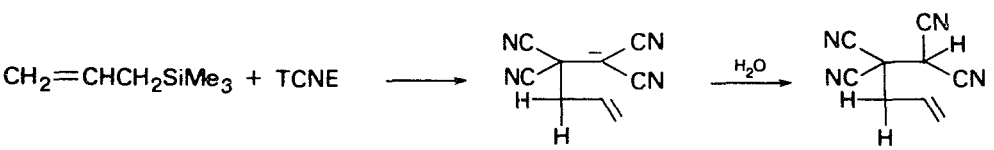
R = Me, Ph, *p*-ClC_6H_4

(535) **(623)**

65–91%

6. *Reaction of allylsilane with tetracyanoethylene*

The reaction between allylsilane and TCNE involves a 1,4-dipolar intermediate, to yield 4,4,5,5-tetracyano-1-pentene, produced by displacement of a trimethylsilyl group (equation 624)[1017].

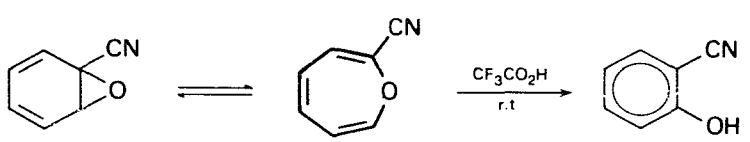


(624)

7. *Miscellaneous recent results*

The charge-transfer absorption bands resulting from the interaction of bis(homocubane) derivatives (phenylated cage compounds) with TCNE have been reported[1018a]. In a new synthesis, for example, *n*-octanenitrile is obtained in 87% yield from the copper-catalysed, gas-phase reaction of 1-octanol with ammonia at 325°C and 1 atm[1018b].

The aromatization of 1-cyanobenzene oxide in trifluoroacetic acid at room temperature is complete is 3 h; the only product formed is *o*-hydroxybenzonitrile (equation 625)[1018c].

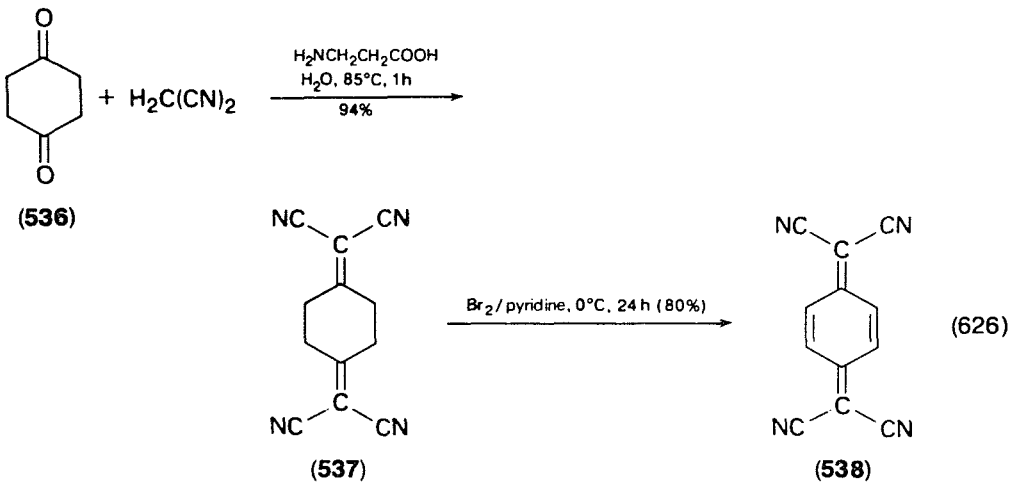


(625)

C. 7,7,8,8-Tetracyanoquinodimethane and Analogous Electron Acceptors

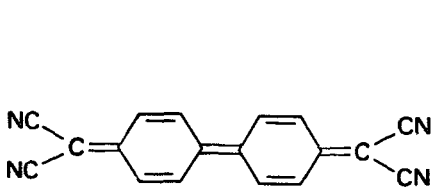
Among electron acceptors containing a malononitrile moiety, tetracyanoquinodimethane (TCNQ, **538**) has acquired a most prominent place. The chemistry[1019] and some of the properties[10,12,1020,1021] of TCNQ have been reviewed, and will not be discussed here. Polymeric donor–TCNQ complexes have been reviewed and discussed[1022].

The acceptor **538** is still best prepared by the classical procedure[1023,1024] shown in equation (626). The dehydrogenation of **537** can also be performed with manganese dioxide or with DDQ.



(626)

Recent interest in highly conducting, charge-transfer salts derived from TCNQ has promoted the design of new organic acceptors whose structures would enhance their electrical properties when complexed with donor molecules such as tetrathiafulvalene (TTF)[1025]. The quinodimethane series includes extended analogues of TCNQ, such as 13,13,14,14-tetracyanodiphenoquinodimethane (**539**, TCNDQ)[1026], 11,12,11′,12′-tetracyanonaphtho-2,6-quinodimethanide (**540**, TNAP)[1027,1028] and 13,13,14,14-tetracyanopyrene-2,7-quinodimethane (**541**, TCNP)[1029]. New heteroatom-substituted acceptors include tetracyanoquinoquinazolinoquinazoline (**542**, TCQQ)[1030], a pyridine analogue of TCNQ (**543**)[1031,1032], the sulphur analogues of TCNQ, **544**[1033] and **545**[1034] and the paramagnetic salt (radical anion) **546**[1034]. The acceptor capacity of alkyl- and halogen-substituted TCNQ has also been reported; methyl-TCNQ (MTCNQ), 2,5-dimethyl-TCNQ (DMTCNQ) and the especially effective 2,5-diethyl-TCNQ (DETCNQ)[1035,1036] acceptors have been prepared and their electrical conductivity for charge-transfer complexes with a series of donors, e.g. TTF or tetraselenafulvalene (TSF) has been measured[1036]. The preparation of monofluoro-TCNQ (FTCNQ)[1037] and of 2,5-difluoro-TCNQ(F_2TCNQ)[1038] have been reported; however, their charge-transfer complexes with TTF show the electrical conductivity at room temperature to be only in the semiconductor range; for example, for the salt TTF-2,5-F_2TCNQ, the conductivity is[1038] $2 \times 10^{-5}\ \Omega^{-1}\ cm^{-1}$. The tetrafluoro-TCNQ ($F_4$TCNQ) invariably forms insulating salts with TTF[1038,1039]. Thus, except for the acceptors TNAP[1027,1028] and DETCNQ[1035,1036], halogen-substituted TCNQ[1038,1039] and **544**[1033] form TTF salts that are insulators; other potential acceptors, such as TCNDQ[1026], TCNP[1029], TCQQ[1030] and the acceptors **543**[1031,1032] and **545**[1034] have not been tested.



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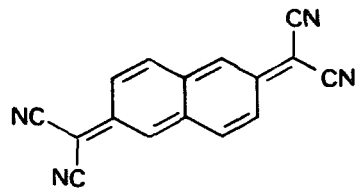

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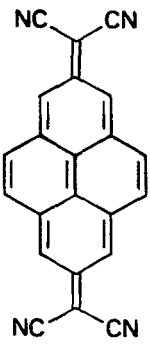

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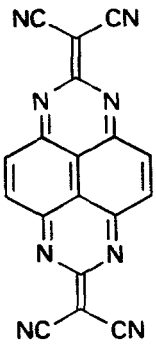

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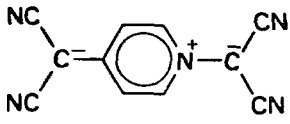

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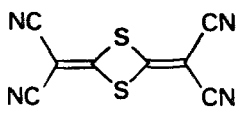

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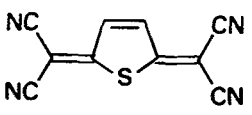

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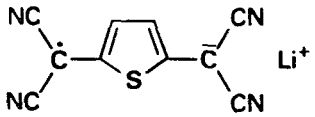
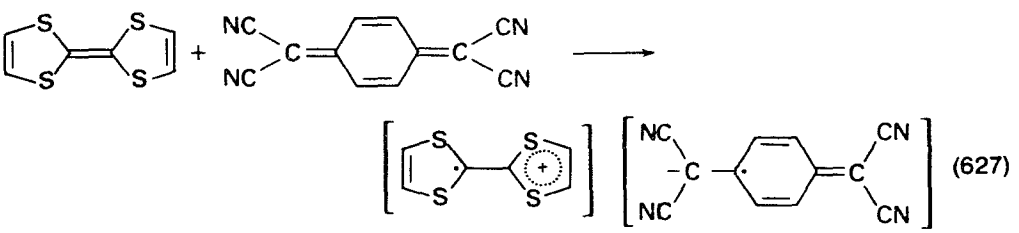


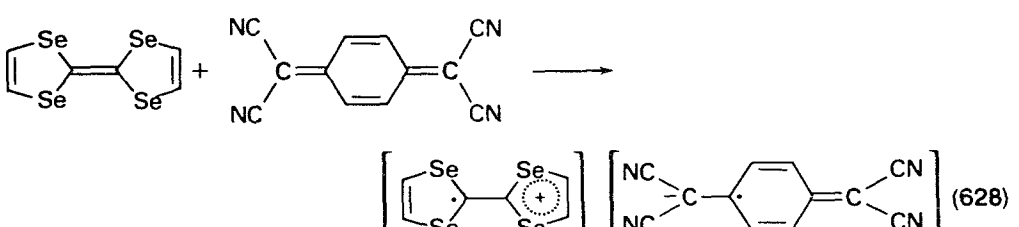
(546)

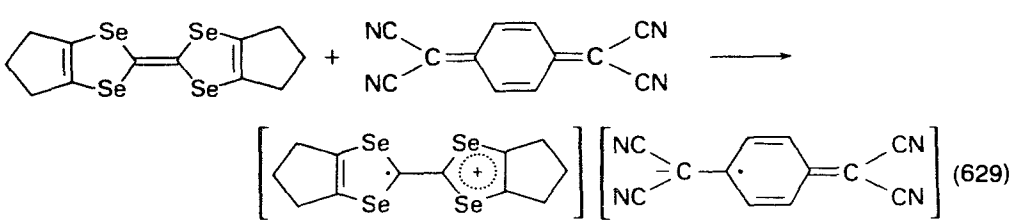
1. Organic 'metals'

Conventional molecular complexes are composed of neutral molecules held together by van der Waals' forces. Charge-transfer salts, on the other hand, have unpaired electrons on the acceptor ion, the donor ion, or both, as a result of electron transfer from donor to acceptor. Metallic behaviour results from delocalization of the unpaired electrons. Charge-transfer salts containing TCNQ as the acceptor are among those organic solids having the highest electrical conductivity. This is due to the high electron affinity of the molecule, its planar structure and high symmetry, as well as the arrangement of the molecules in the crystal lattice, which is favourable for carrier transport. Charge-transfer salt, organic conductors consist of segregated stacks of electron donors and electron acceptors, one (or both) of which is capable of existing in multiple oxidation states. High-conducting, donor–acceptor combinations are characterized by a charge transfer ranging from 0.5 to 0.8 per formula unit. The typical structural features[1040] are planarity with extended π molecular orbitals, high symmetry

and a widely spaced charge and spin distribution. The charge-transfer salts of the π donor tetrathiafulvalene (TTF)[1041,1042] (equation 627) or tetraselenafulvalene (TSF)[1043] (equation 628) with TCNQ are examples of a new class of solids, the quasi-one-dimensional organic metals; the topic is extensively studied and reviewed[1021,1040,1044–1048a]. The Crystal structure[1049] of these 'organic metals' consists of parallel columns of separately stackd TTF (or TSF) and TCNQ molecules (e.g. alternating stacks of cation and anion radicals). For conduction, the stacking must be uniform and the distance between adjacent molecular sites must be close enough to allow overlap of their π orbitals into an energy band. There must also be relatively weak electron–electron coulomb repulsion (which causes electrons to correlate their motions in order to stay apart), so that electrons are uncorrelated and can move from one molecule to another among the positive attractive potentials. The conductivity of the TTF–TCNQ complex at room temperature is σ 500 Ω^{-1} cm^{-1}, reaching its maximum of σ 1.47×10^4 Ω^{-1} cm^{-1} at 60 K, rapidly changing from metallic to nonmetallic conductivity as temperature falls below 60 K[1041,1042]. The latter transition near 60 K may be associated with a periodic distortion of the crystal lattice driven by the conducting electrons (called the Peierls instability). An even better conductor is the TSF–TCNQ complex with a conductivity of σ 800 Ω^{-1} cm^{-1} at room temperature, rising[1043] to σ 10^5 Ω^{-1} cm^{-1} at 40 K. The hexamethylenetetraselenafulvalene–TCNQ complex salt (HMTSF–TCNQ) (equation 629) subsequently described has the largest electrical conductivity of any known organic compound (σ 2000 Ω^{-1} cm^{-1} at room temperature); moreover, the conductivity remains[1049,1050] metallic down to temperatures as low as 0.045 K. Finally, the organic metals may be regarded as products of the intermolecular migration of aromaticity; the most efficient conductors contain molecules whose (*a*) radical ions form a new aromatic sextet upon one-electron oxidation or reduction, and (*b*) aromaticity can migrate by mixed-valence interaction[1048].



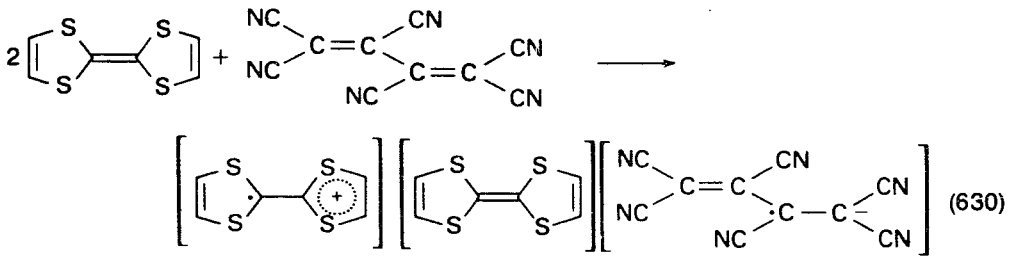




a. Structure–conductivity correlation in TTF–TCNQ charge-transfer complexes. This correlation has recently been observed. The study has shown[1048b] that steric effects in donors and acceptors are the main factor which determines the stacking mode of the molecules, the redox power influencing only the degree of charge transfer. The presence of four bands at 0.4, 0.6, 0.9 and 3.3 μm is characteristic of conducting salts, which consist of chains of donors and acceptors in segregated stacks. Three bands only at 0.4, 0.6 and 1.5 μm are observed in the cases of semiconductors or insulators in which donor and acceptor molecules alternate along the chains.

2. Other organic metals and semimetals

An unusual complex salt is formed between tetracyanomuconononitrile (TCM) and TTF; the complex contains a TTF (cation radical) a neutral TTF molecule and a TCM anion-radical (equation 630); its conductivity is σ ~3.3 Ω^{-1} cm^{-1} [1051]. A series of



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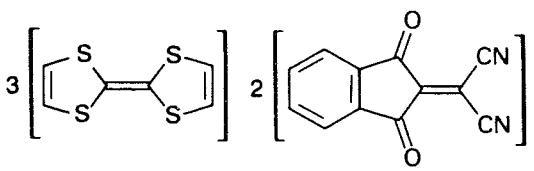

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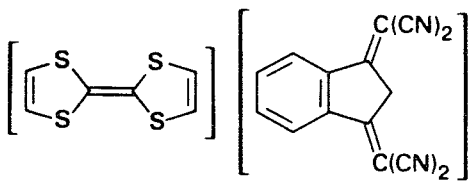

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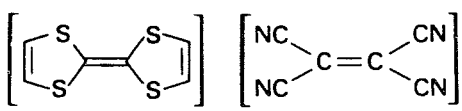
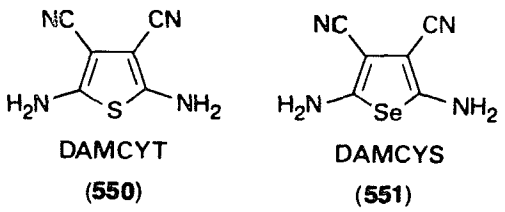
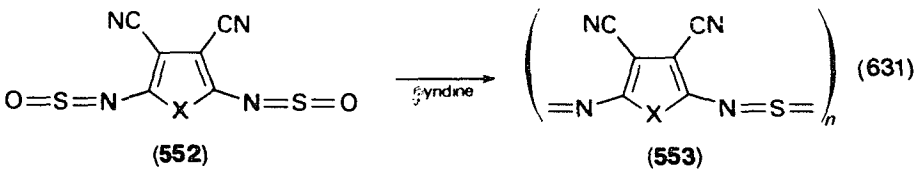


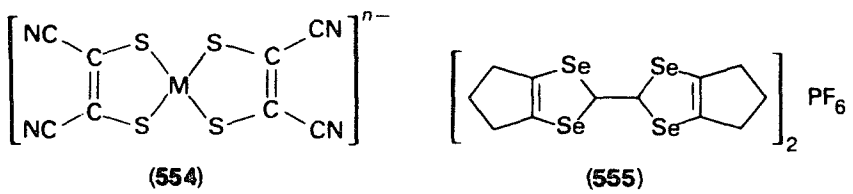
(549)

organic salts of TTF and unsymmetrical cyano acceptors have been synthesized that show all the properties of semiconductors[10]. For example, TTF, with 2-(dicyanomethylene)-1,3-indandione (DCID) as the acceptor, forms a charge-transfer salt having a stoichiometry of 3:2 (TTF):(DCID), **547** (σ 4 × 10^{-2} Ω^{-1} cm^{-1}) and the salt **548** (σ 1 × 10^{-4} Ω^{-1} cm^{-1}); with TCNE the 1:1 (TTF):(TCNE) complex is formed **(549)** (σ 4 × 10^{-2} Ω^{-1} cm^{-1})[10]. Recently, organic polymer semiconductors based on diaminodicyanothiophene (DAMCYT) **(550)** and diaminodicyanoselenophene (DAMCYS) **(551)**, with their bis(sulphinylamino) derivatives **552a** and **552b** as acceptors, have been prepared. Reaction of **552a** and **552b** with pyridine produces polymeric conducting complexes **553a** and **553b** (with σ 1.4 × 10^{-3} Ω^{-1} cm^{-1} for **553a** and σ

$3.3 \times 10^{-4}\ \Omega^{-1}\ cm^{-1}$ for **553b** (equation 631)[1052]. The synthesis and electrical conduction properties of compounds containing planar bis(dicyanoethylenedithiolato)metal anions, **554** (M = Ni, Pd or Pt), have been extensively studied[1053–1056]. However, one-dimensional metallic properties have only been established for compounds in which the organic cation and not **554**, is responsible for the high conductivities[1055,1056]. Previous studies have used bulky cations, whereas the presence of small cations in the lattice will facilitate a short intraanion separation and, hence, the possibility of 1-D metallic properties being associated with **554**[1057]. Recently, metallic behaviour in single crystals of $Pt(S_2C_4N_2)_2^{n-}$ salts, e.g. **554** (M = Pt), has been observed[1057]; here, the conduction must occur through interacting anions. The electrical conductivity for $Li_x[Pt(S_2C_4N_2)]\cdot 2H_2O$ (where x = 0.75) at room temperature is σ 96 $\Omega^{-1}\ cm^{-1}$ (an average value) The conductivity of such 1-D metallic tetracyanoplatinate complexes as $K_2[Pt(CN)_4]Br_{0.3}\cdot 3H_2O$ has been reported[1058,1059]. Recently, superconductivity has been observed for the organic conductor bis(hexamethylenetetraselenafulvalene) hexafluorophosphate, $(TMTSF)_2PF_6$ (**555**), with a transition temperature[1060] of 0.9 K at a pressure of 12 kbar.







VI. SYNTHESES OF HETEROCYCLES VIA CYANO SUBSTRATES

A. Introduction and General Considerations

The nucleophilic and electrophilic character of the cyano group[636] allows the creation of a variety of heterocyclic structures. The nitrile group often acts as an electrophile in heterocyclic syntheses, i.e. only the carbon atom is incorporated into the ring-system, with formation of aminosubstituted heterocycles[1061–1063]. Ring-closure reactions entailing incorporation of the entire nitrile group are normally preceded by the conversion of this group into an imidic ester or a carboxamide group[636,1064,1065]. The

nitrile group is only weakly nucleophilic. Thus, the presence of Lewis acids is necessary for the formation of alkyl- and acyl-nitrilium salts[1066]. Only very reactive acyl halides, such as malonyl chloride, react directly with nitriles to afford heterocycles[1065,1067].

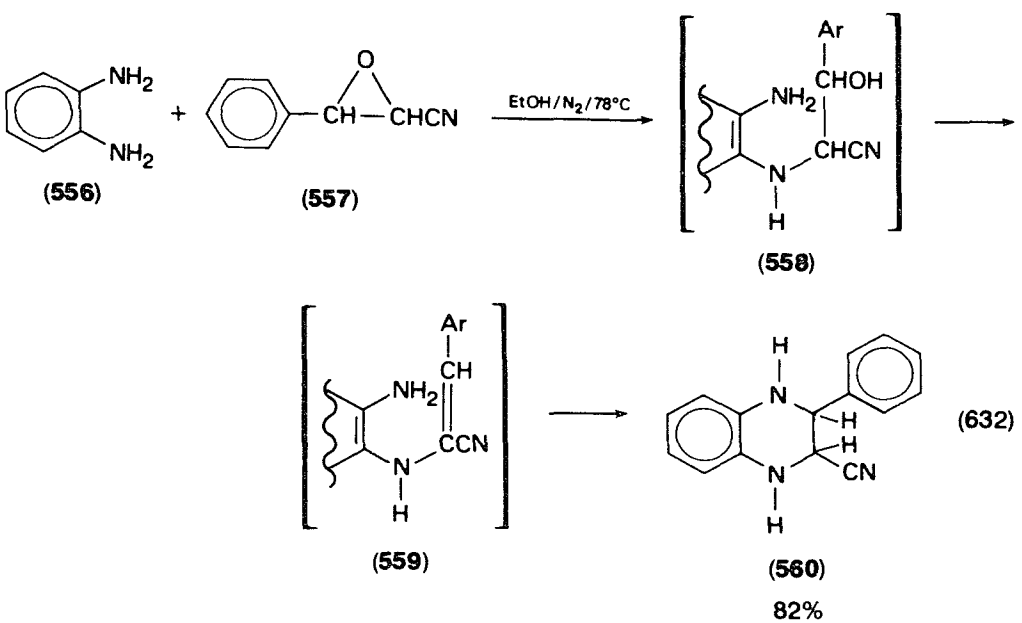
Developments in the past 10–15 years have involved a multitude of new reactions and methods for syntheses of heterocycles from nitriles. These include 1,3-dipolar cycloadditions[636], 1,3-dipolar addition of diazocarbonyl acompounds to nitriles[1068,1069], 1,3-dipolar cycloaddition of nitrile sulphides to 1,4-quinones[1070] and the 1,3-dipolar reaction of dicyanomethylids with phenyl vinyl sulphoxides[1071]. The syntheses of heteroarenes can also be achieved on the basis of nitrilium salts[1065,1072] by intramolecular acylation of nitrile–hydrogen halide adducts[1073] or by the use of the Reissert compounds[1074,1075]. An interesting recent application is the use of isoxazoles (from 1,3-dipolar cycloaddition of acetylenes to nitrile oxides) in the synthesis of corpins and corins (related to vitamin B_{12})[1076,1077].

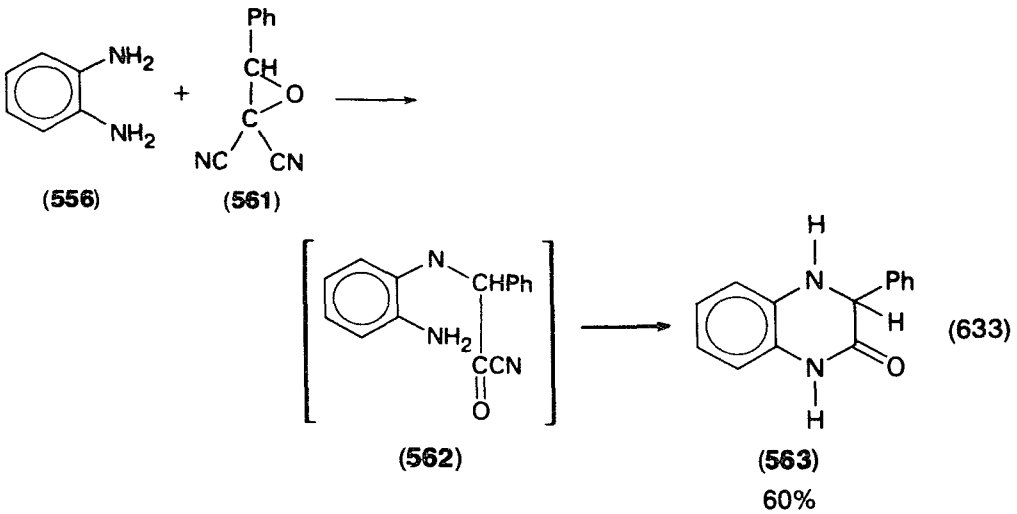
Meyers and coworkers[1078] have developed oxazolines and dihydro-1,3-oxazolines as useful masked enolates (for a series of useful carbon–carbon bond-formation reactions); the topic has been reviewed[1079,1080]. The use of acyl nitrile oxides generated *in situ* from diacylfuroxans has recently been initiated[1081]. Thus, the use of heterocyclic synthons (derived from nitriles) or nitrile synthons[1070] (generated from heterocyclics) is a new tool in synthetic methodology. The literature on the synthesis of heterocycles from nitriles is vast; this discussion will be restricted to a few, selected syntheses from the most recent literature.

B. Selected Syntheses of Heterocycles

1. *Synthesis of tetrahydroxyquinoxalines via heterocyclization with cyanoepoxides*

Continuing interest in new methods for the construction of heterocycles has led to the utilization of α-cyanoepoxides as bifunctional two-carbon synthons. Thus, a new





heterocyclization method developed by Taylor and coworkers[1082] involves the reaction of α-cyanoepoxides with *o*-phenylenediamine to give quinoxaline derivatives[1083]. The required α-cyanoepoxides (**557**) have been prepared as described by Makosza and coworkers[437] from chloroacetonitriles with various benzaldehydes.

Thus, condensation of 2-aryl-1-cyanooxirane (**557**) with *o*-phenylenediamine (**556**) affords 3-aryl-2-cyano-1,2,3,4-tetrahydroquinoxaline (**560**). The mechanism apparently involves nucleophilic attack on **557** and, via epoxide ring-opening, the benzylic alcohol **558**; dehydration to **559** is then followed by intramolecular conjugate addition, to give **560** (equation 632)[1082]. The tetrahydro derivatives are converted into 3-aryl-3-cyanoquinoxalines or 2-(carboxamido)-3-phenylquinoxalines.

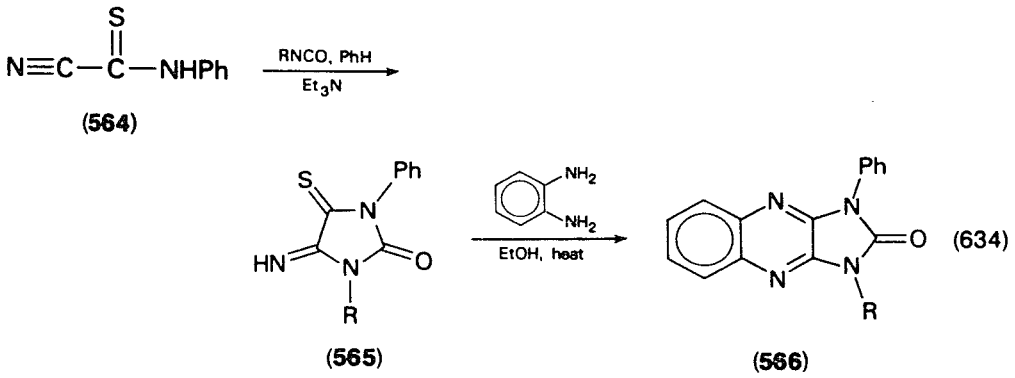
An additional cyano group at C-1 in α-cyanoepoxides can lead to exclusive ring-opening at C-2. Thus, 1,1-dicyano-2-phenyloxirane (**561**)[1084,1085] condenses with **556** to give 1,2,3,4-tetrahydro-3-phenyl-2-quinoxalinone (**563**) via intermediate **562** (equation 633)[1082]. Applications of these reactions to the synthesis of pyrrolopyrimidines and pteridines can be envisaged. The condensation of **561** with thiourea and with thioamides to give thiazole derivatives has been reported[1086].

2. *Reactions of isocyanates with 1-cyanothioformanilide*

Nitriles containing an appropriately situated nucleophilic group undergo cyclization with isocyanates, to afford imino or amino heterocycles. Typical examples are the formation of aminooxazoles from α-aminonitriles[1087], tetrahydroiminoquinazolines from anthranilonitrile[1088,1089] and iminooxazolidinones from iminodiacetonitrile[1090]. Recent work[1091] has described the expected analogous reaction between isocyanates and 1-cyanothioformanilide (**564**)[1092] to form 1-substituted 5-imino-3-phenyl-4-thioxo-2-imidazolines (**565**) in 90–95% yield; these react with *o*-phenylenediamine to yield 1,3-disubstituted 1*H*-imidazo[4,5-*b*]quinoxalin-2(3*H*)-ones (**566**) (60–70% yield) (equation 634)[1091].

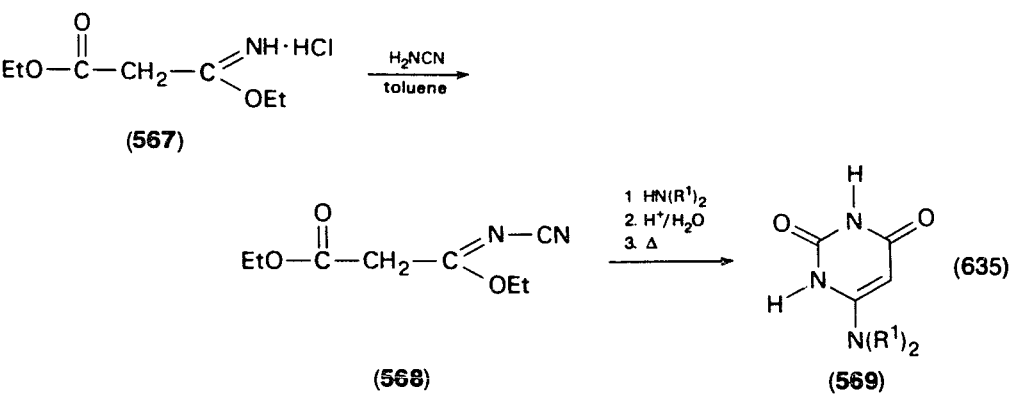
3. *New synthesis of pyrimidinones and pyrimidinediones*

The application of cyanoimines in the synthesis of pyrimidinones and pyrimidinediones has been reported[1093]. A new route to these important heterocycles



(564) (565) (566) (634)

involves the reaction of **567** with cyanamide to yield ethyl 3-(*N*-cyanoimino)-3-ethoxypropanoate (**568**). Further treatment with piperidine (or morpholine), and acid hydrolysis followed by thermal cyclization, yields 6-amino-2,4-(1*H*, 3*H*)-pyrimidinediones (**569**) (equation 635)[1094]. Similarly, starting from **570** the intermediate **571** has been obtained, which cyclizes *in situ* to the pyrimidinone **572** (equation 636)[1094].



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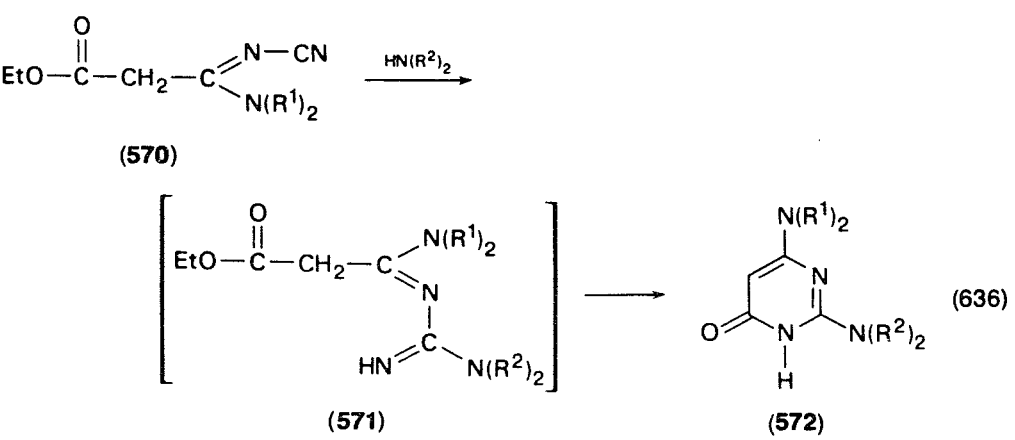

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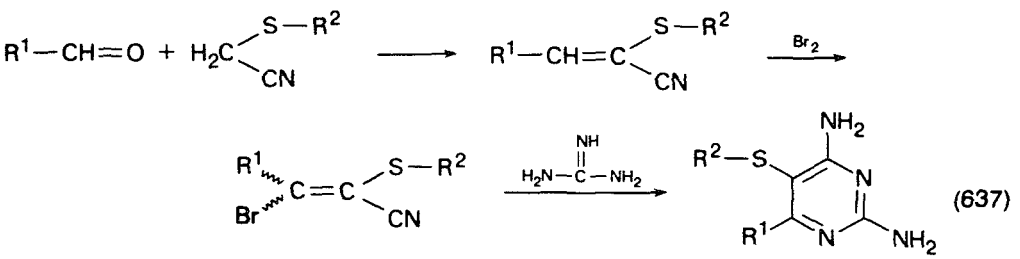
A facile synthesis of 5-substituted 5-[alkyl(or aryl)thio]-2,4-diaminopyrimidines[1095] (antimalarial agents) uses the condensation of guanidine with bromoacrylonitrile (equation 637).



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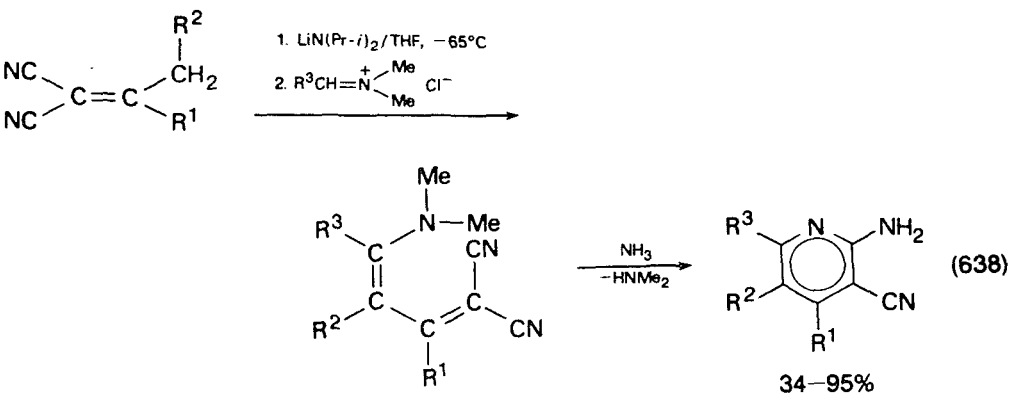
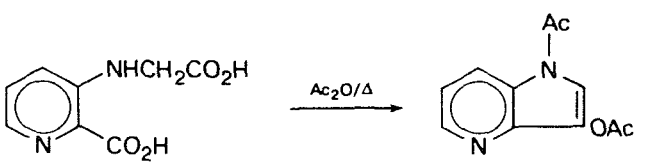
4. Additional syntheses via cyclization

Cobalt-catalysed pyridine syntheses from alkynes and nitriles have been reviewed[1096]. Cyclization occurs in syntheses of substituted pyridines (equation 638)[1097], 3-acetoxy-1-acetylpyrrolo[3,2-*b*]pyridine (equation 639)[1098], 2,4,4-trialkyl-substituted imidazolines (equation 640)[1099], 2,4-diphenylquinoline and dibenzodiazocine (equation 641)[1100], 2-cyanoindole (equation 642)[1101] and 2-cyano-1-hydroxyindole (equation 643)[1101], and in the self-condensation of an unsaturated thioamide (to form a dihydrothiopyran by a regio- and stereo-controlled reaction) (equation 644)[1102]. The thermal decomposition of 2-azidopyridine-1-oxides and 2-azidopyrazine-1-oxides leads to the formation of 2-cyano-1-hydroxypyrroles and 2-cyano-1-hydroxyimidazoles, respectively[1103].

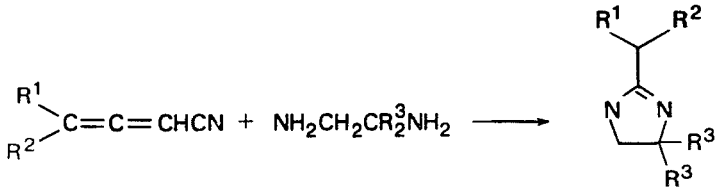


(638)

R^1 = Ph, Me, Bz
R^2 = H, Me, Ph
R^3 = H, Ph, SMe



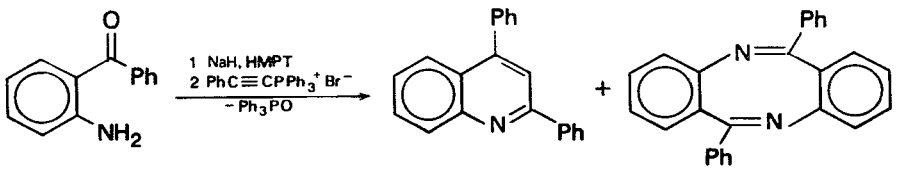
(639)



68–85%

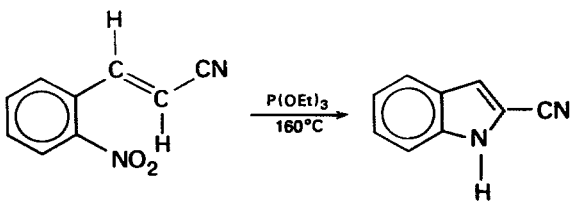
$R^1, R^2 = H, Me, Et, Pr$
$R^3 = H, Me$

(640)

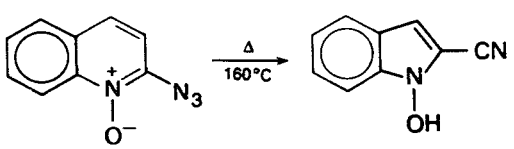


16%

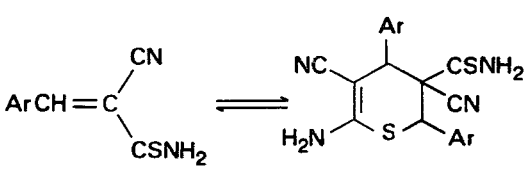
(641)



(642)



(643)

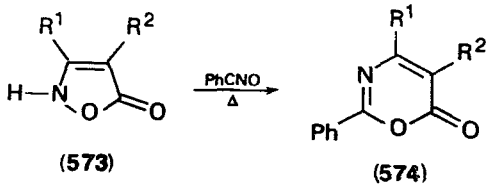


(644)

5. *Synthesis of heterocycles via a ring-enlargement*

a. Ring-enlargement of 2-isoxazolin-5-ones (573) to 1,3-oxazin-6-ones (574). **(573)** reacts with benzonitrile oxide to give **574** with loss of HNO_2 and formation of PhCN (equation 645)[1104].

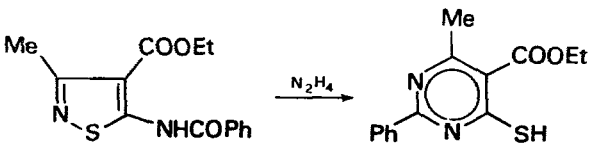
b. Ring-expansion in the isothiazole and 1,2,5-thiadiazole ring-systems. This is exemplified by the transformation of 5-(benzamido)-4-(ethoxycarbonyl-3-methyl-isothiazole **(575)** to the pyrimidine derivative **576** on treatment with hydrazine (equation 646)[1105]. In a new approach[1106] isothiazole and 1,2,5-thiadiazole compounds have been treated with nucleophiles, e.g. CN^- (equation 647) or the methyl propiolate ion (equation 648), to form novel heterocyclic ring-systems.



(573) (574)

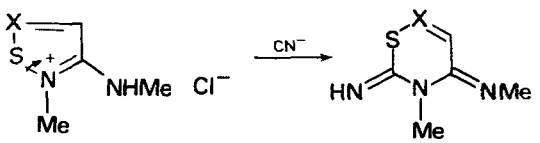
30–85%

(645)



(575) (576)

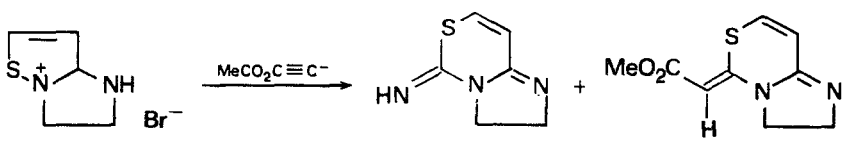
(646)



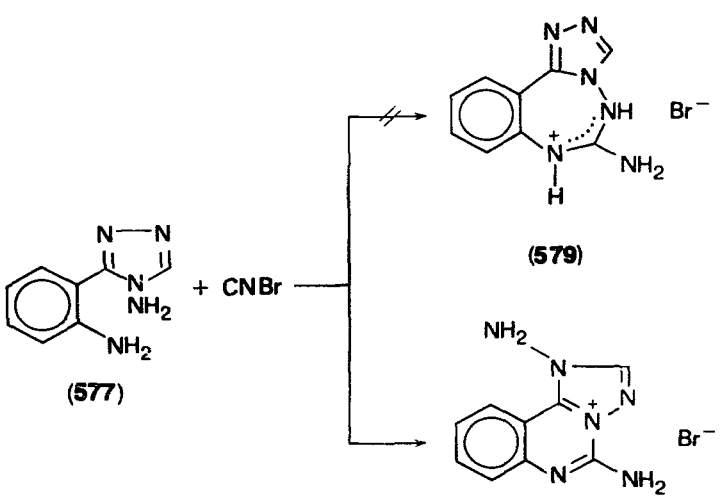
X = CN
X = N

X = CN
X = N

(647)



(648)



(577) (579) (578)

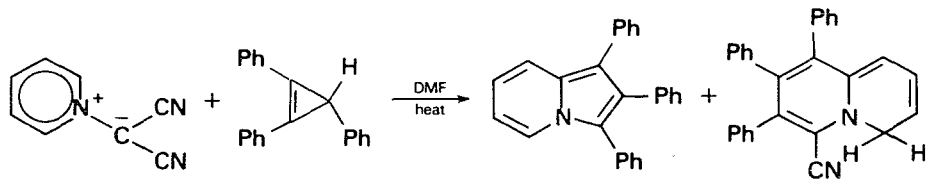
(649)

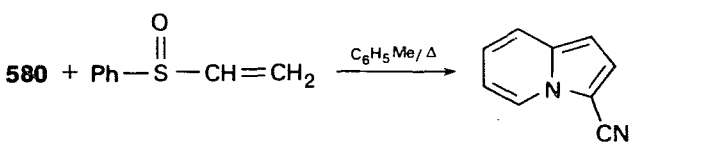
c. No ring-enlargement in the triazole series. The reaction of cyanogen bromide with the triazole **577** gives 1,5-diamino-1*H*-*S*-triazolo[1,5-*c*]quinazolinium bromide (**578**), and not the expected triazepine (**579**) (equation 649)[1107].

6. Cycloaddition of cycloimmonium ylids with triphenylcyclopropene

Reaction of pyridinium dicyanomethylide (**580**) with triphenylcyclopropene (**581**) (a dipolarophile) gives 1,2,3-triphenylindolizine (**582**) and 6-cyano-7,8,9-triphenyl-4*H*-quinolizine (**583**) (equation 650)[1108,1109]. This is an example of a π [4 + 2]cycloaddition–extrusion reaction that provides a new route to indolizines and quinolizines.

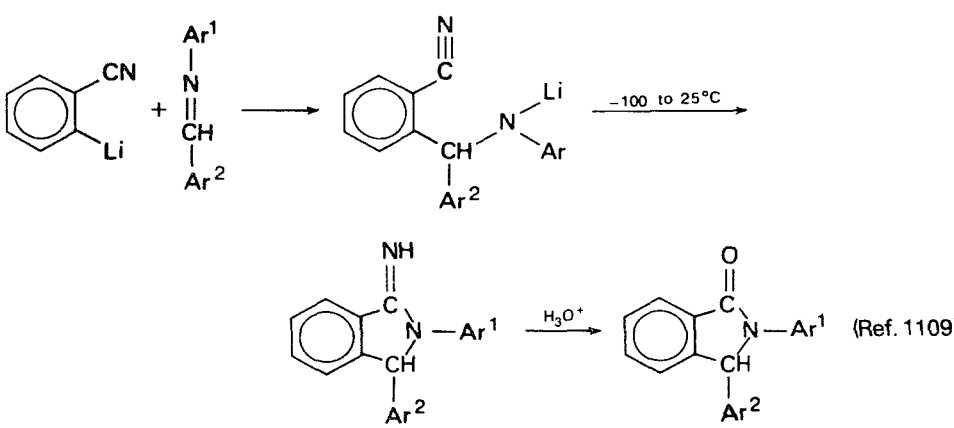
The cycloaddition–extrusion reaction can be extended to the synthesis of 3-cyanoindolizines (**583**) by heating **580** with phenyl vinyl sulphoxide (**584**) (equation 651)[1071].

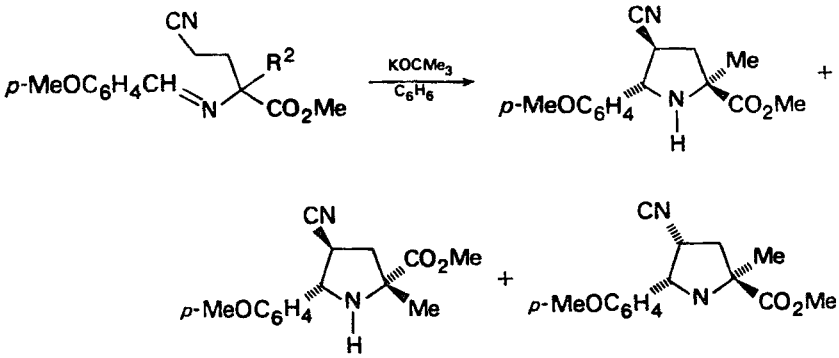




7. Additional syntheses of heterocycles

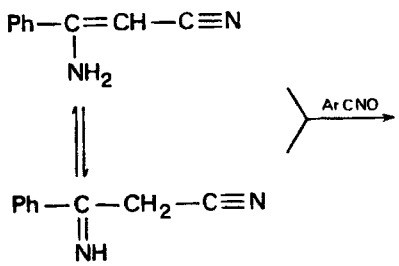
Some additional, recent syntheses of heterocycles are depicted in equations (652)–(663)[1068,1070,1074,1080,1109–1116].

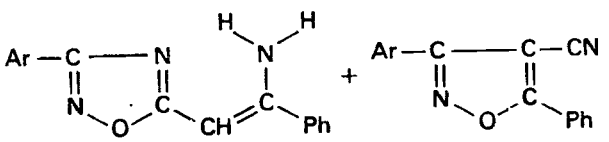




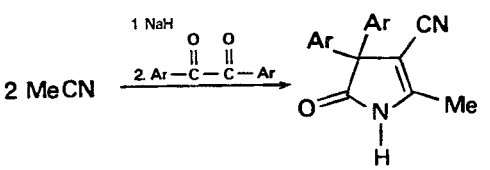
(Ref. 1110) (653)

3:1:1·2 mixture of pyrrolidines

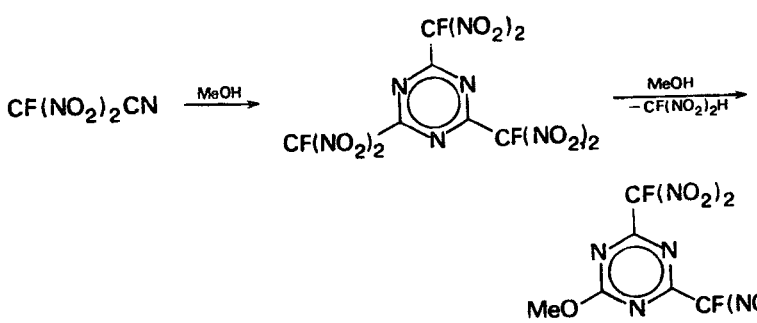




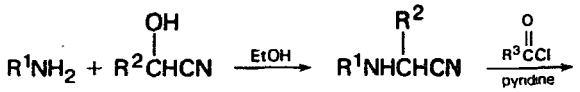
(Ref. 1111) (654)

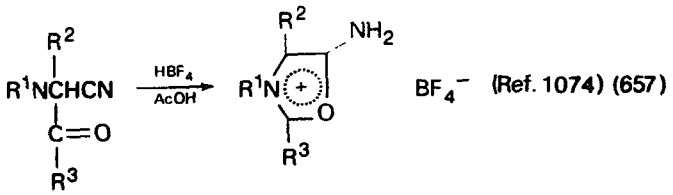


(Ref.1112) (655)

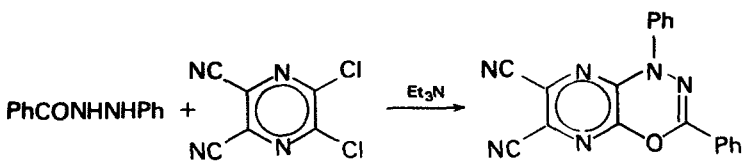


(Ref. 1113) (656)

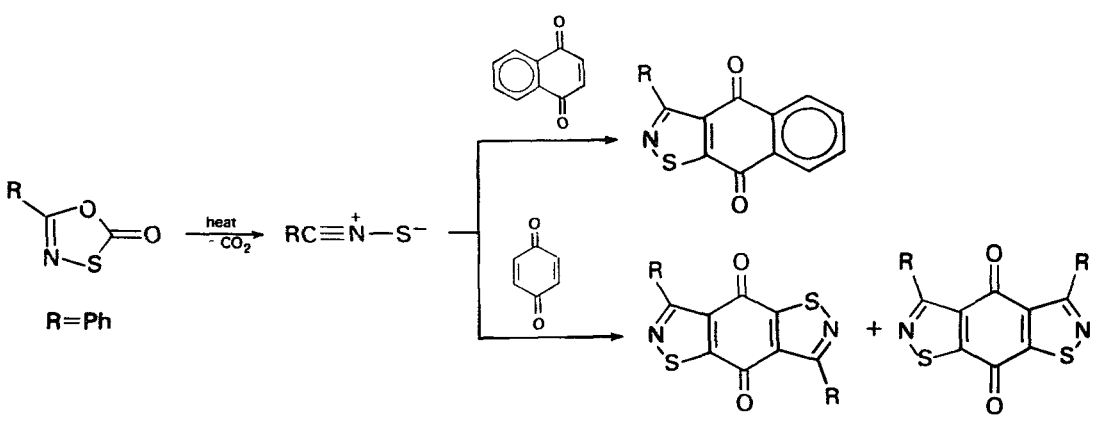




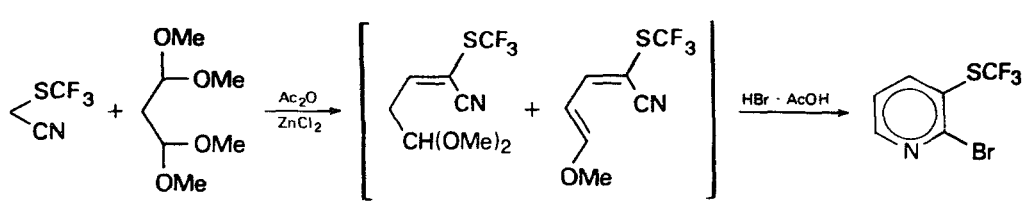
(Ref. 1074) (657)



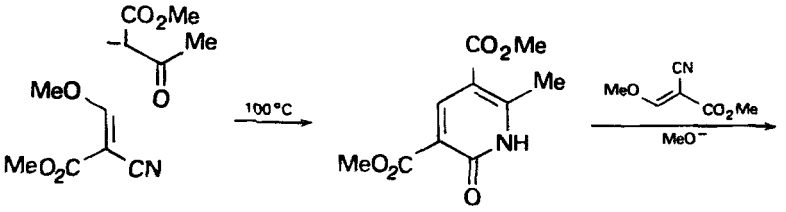
(Ref. 1114) (658)

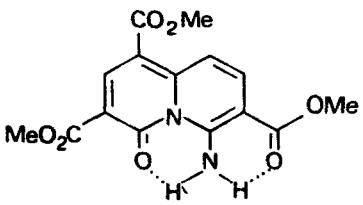


(Ref. 1070) (659)

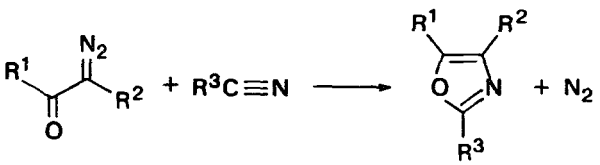


(Ref. 1115) (660)

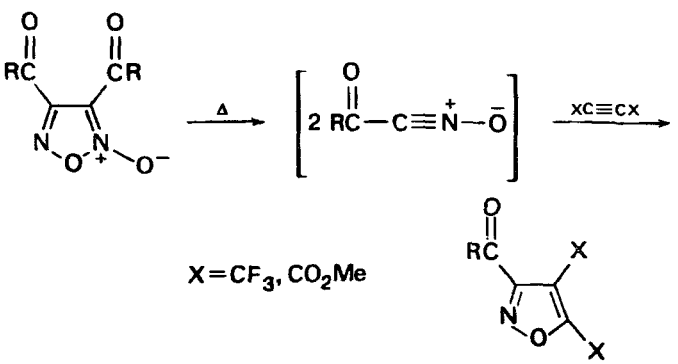




(Ref.1116) (661)



(Ref. 1068) (662)



(Ref. 1080) (663)

VII. ADDENDA

A. Miscellaneous Recent Results

Polymerization of nitrile monomers, e.g. acrylonitrile, methacrylonitrile, cinnamonitrile, crotononitrile, fumaronitrile, vinylidene cyanide, etc., has been reviewed[1117].

Photoadditions of 1- and 2-naphthols to acrylonitrile have recently been studied[1118].

$PdCl_2(MeCN)_2$ has recently been used for the *N*-alkylation of indoles[1119] and amination of electron-deficient alkenes[1120]; the catalyst also facilitates cyclization of allylated enamines to form acridines in a one-step synthesis[1121].

$PdCl_2(PhCN)_2$ is reportedly[1122,1123] an efficient catalyst for the Cope rearrangement of acyclic 1,5-dienes.

A new method for the conversion of primary alcohols into nitriles having one extra carbon atom has been described[1124].

A phase-transfer-catalysed oxidative decyanation of α-secondary nitriles (to give aromatic ketones) has been reported[1125].

A silver(I)-photocatalysed addition of acetonitrile to norbonene has recently been achieved[1126].

Symmetric cyanohydrin syntheses catalysed by synthetic peptides are of much recent interest, in connection with the high stereospecificity of enzymic reactions[1127,1128].

Recent applications of synthetic cyano reagents involve the preparation of β-iminosulphones (by addition of sulphones to nitriles)[1129], 1,3-thiazole derivatives [via $(NC)_2C$ = NOTs][1130], benzodiazepins[1131], cyclopropa[*c*]cinnolines (via nitrilimines)[1132], 4*H*-pyrano[2,3-*c*]pyrazoles (via malononitrile)[1133] and 3-cyano-2-azetidinones (via thermolysis or photolysis of 4-azido-2-pyrrolinones)[1134].

The mechanism of polymer-supported, phase-transfer catalysis in the reaction of 1-bromooctane or benzyl bromide with aqueous sodium cyanide has recently been studied[1135].

The thermolysis of α-azidosulphones has been studied; for example, α-azidobenzyl phenyl sulphone in refluxing chlorobenzene generates benzonitrile, in addition to other products[1136a], and 3-*H*-isoxazoles on thermolysis give α-carbonylacetonitrile[1136b].

Iodoacetonitrile (ICH_2CN) has been used as a potential alkylating agent in the synthesis of *C*-nucleosides[1137].

The mechanism of the photochemical conversion of 1-amino-2-cyanoethylene into imidazole that involves a nitrile → isocyanide rearrangement (e.g. NCCCN → NCCNC reorganization) and an azirine intermediate has recently been presented[1138].

Alcohols are converted into nitriles in good to excellent yields by treatment with 2 equiv. of NaCN–Me_3SiCl and a catalytic amount of NaI in DMF–MeCN[1139].

Condensation of malononitrile with trimethoxymethane and aniline affords 3-anilino-2-cyanoacrylonitrile, which on treatment with hydrazine gives 3-amino-1*H*-pyrazole-4-carbonitrile, in a one-vessel synthesis[1140].

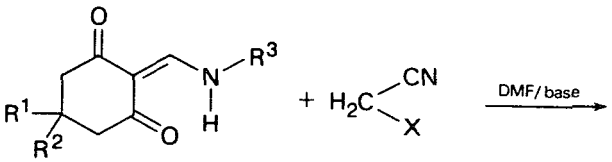
Increased reactivity of coordinated nitriles has been observed in a series of organometallic reactions[1141].

The chemical equivalence of the carbonyl oxygen atom and the $C(CN)_2$ group as proposed by Wallenfels[15] has now been confirmed experimentally by the electrochemical oxidation of the croconate and dicyanomethylene-substituted croconate salts. It has been found[1142] that the first oxidation wave shows a linear increase in potential of 100 mV with the addition of each dicyanomethylene group in the series $C{=}O \rightarrow C(CN)_2$, $2\ C{=}O \rightarrow 2\ C(CN)_2$ and $3\ C{=}O \rightarrow 3\ C(CN)_2$.

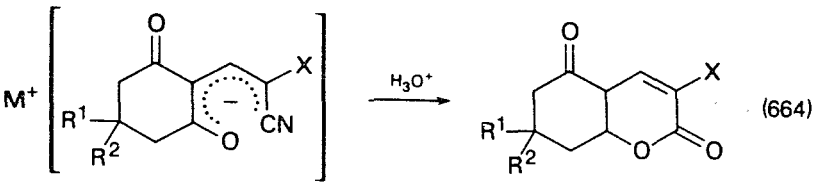
Condensation of a cyclohexane-1,3-dione with triethoxyethane and various ureas affords the 2-ureidomethylenecyclohexane-1,3-diones; these on reaction with activated acetonitriles (e.g. $PhCH_2CN$) in the presence of a strong base, benzyltrimethylammonium hydroxide (Triton B) or potassium *t*-butoxide, give, after aqueous work-up, the 5-oxo-5,6,7,8-tetrahydrocoumarins (50–80% yield) (equation 664)[1143].

Lithiated nitriles are useful intermediates for the synthesis of a variety of organic compounds[1144] and it has been recognized that terpenoids bearing a nitrile group may have wide utility in fragrances[1145]. A recent publication[1146] has described the base-catalysed self-dimerization of 3-methyl-3-butenenitrile to give the cyclodimer selectively. The same group[1147] have extended this study and reported a convenient synthesis of 3-amino-4-cyano-1,5,5-trimethylhexa-1,3-diene (37%) (having the ferulol skeleton), from the reaction of lithiated 3-methyl-3-butenenitrile with 3-methyl-2-butenenitrile and its conversion into 4-cyano-1,5,5-trimethylcyclohexa-1,3-diene (53%) (equation 665).

The lithiated *O*-(trimethylsilyl)-cyanohydrin derived from benzonitrile reacts with α,β-unsaturated ketones in highly coordinating solvents or in the presence of crown ethers in a 1,2-addition reaction affording allylic alcohols or ketones. However, when the reaction is conducted in ether an exclusive 1,4-addition ensues to yield 1,4-diketone, followed by acid hydrolysis of the adduct formed (equation 666)[1148].

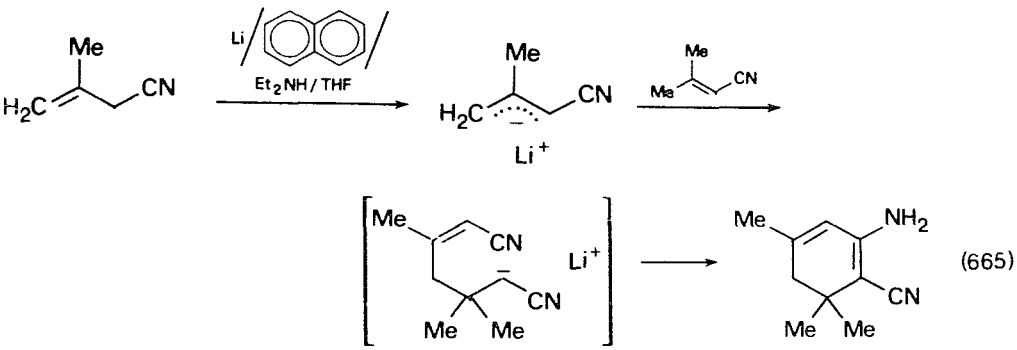


X = COOMe, COOEt, Ph



(664)

R^1	R^2	X
H	H	COOMe
Me	Me	COOMe
Me	Me	COOEt



(665)

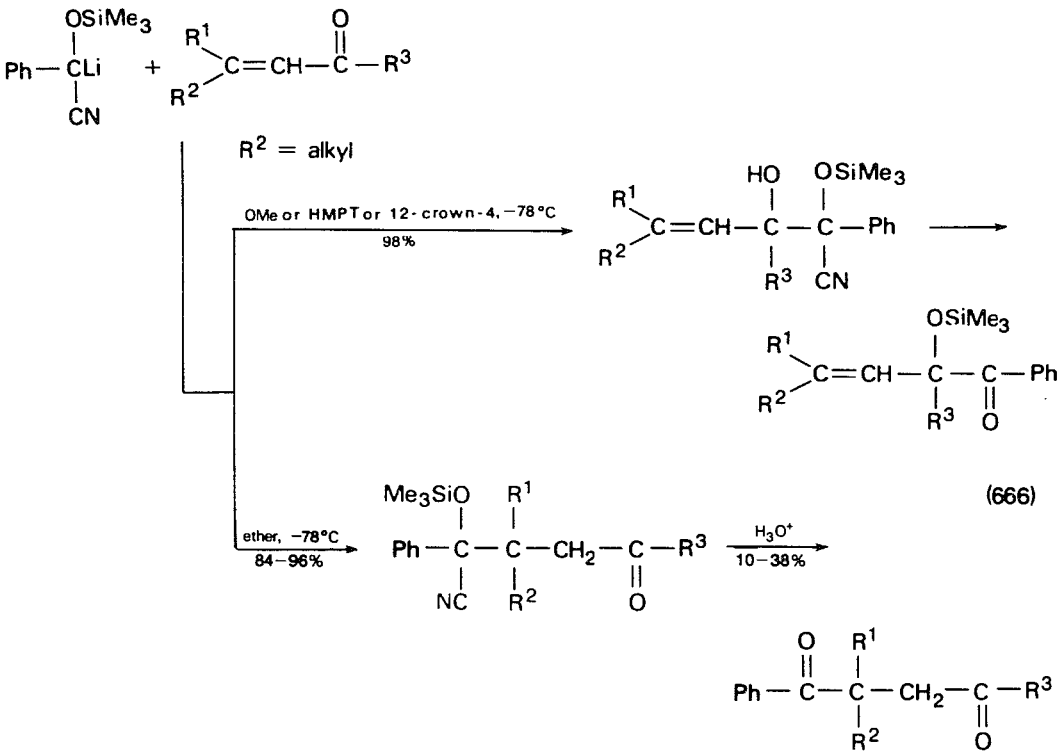
Lithiated 2-aminoalkenenitriles, prepared by metalation of the nitrile with lithium diisopropylamide in tetrahydrofuran, react as ambient nucleophiles with ketones in the presence of zinc chloride to give the 3-oxocyclopentenes (equation 667)[1149].

A new synthesis of β-amino alcohols requires a double addition of an organometallic reagent (RLi) to a cyano function of *O*-silylated cyanohydrins leading to 2-trimethylsiloxyalkanemines and, by desilylation, to β-amino alcohols in good yields (73–90%) (equation 668)[1150].

α-Hydroxyketones may be prepared by addition of 2-lithiated 2-(*N*,*N*-dialkylamino)-alkanenitriles to carbonyl compounds and subsequent hydrolysis (equation 669)[1151].

One step conversion of aldehydes into nitriles allows the reaction of metalated tosylmethyl isocyanide to commence at −80 to −60°C, followed by careful addition of methanol only after complete formation of the intermediate (in order to avoid the irreversible formation of 1,3-oxazole by-products (equation 670)[1152a]. A selective reduction of nitriles to aldehydes has been reported[1152b].

The reaction of an α-metalated secondary nitrile with an oxirane generates an intermediate, this on addition of −78°C to dry ammonium chloride allows the isolation of the pure γ-hydroxyalkanenitriles $(R^1R^2)(CN)CHCH(OH)R^3$[1153].



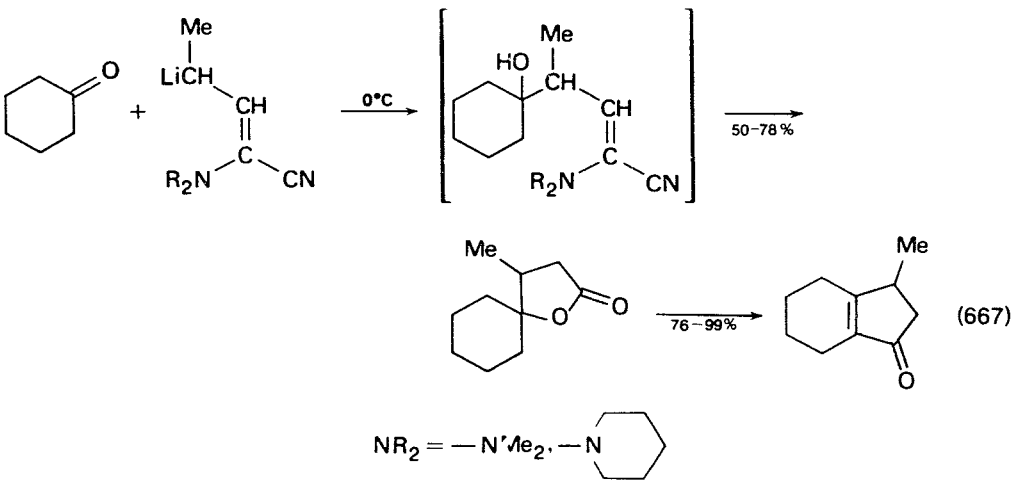
(666)

R^1 = Me, Ph

R^2 = H, Me, OEt, Br, Cl

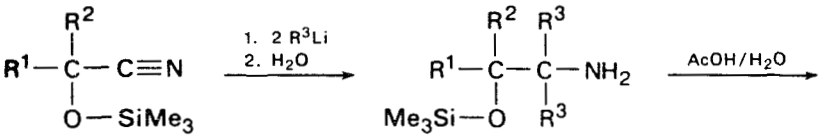
R^3 = Me, OMe, OEt

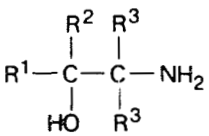
R^1, R^2 and R^3 may form alicyclic systems



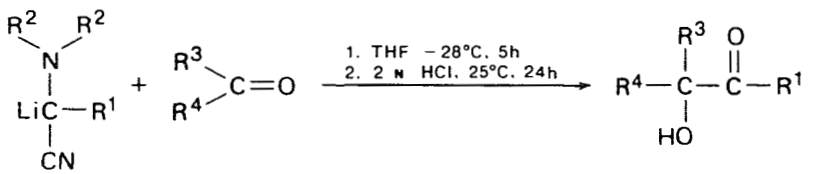
(667)

NR_2 = —NMe_2, —N⟨ ⟩



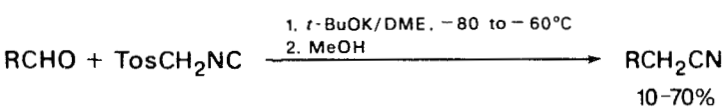


(668)



(669)

R^1, R^2=Me, Et
R^3 = H
R^4 = C_nH_{2n+1} (n = 5 − 7, 13)

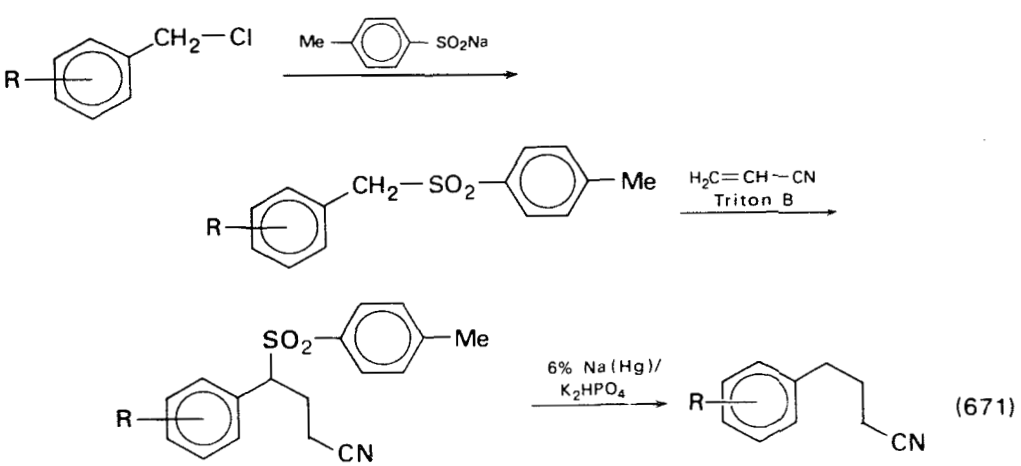


(670)

R = n-Pr, $Me_2C{=}CH(CH_2)_2C(Me){=}CH{-}$, aryl

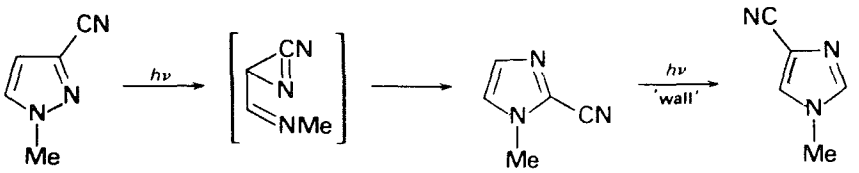
The synthesis of 4-arylbutanenitriles is based on the reductive desulphonylation (6% Na–Hg/K_2HPO_4) of α-cyanoethylated benzyl 4-tolyl sulphones (readily prepared from the corresponding benzyl chlorides) (equation 671)[1154].

Cyano-substituted pyrazoles transpose photochemically into imidazoles by two concurrent paths: (*i*) 1,5-interchange, probably by a 5-bonding to a diazobicyclopentene which isomerizes by nitrogen 'walk' before rearomatization, and (*ii*) 2,3-interchange,



(671)

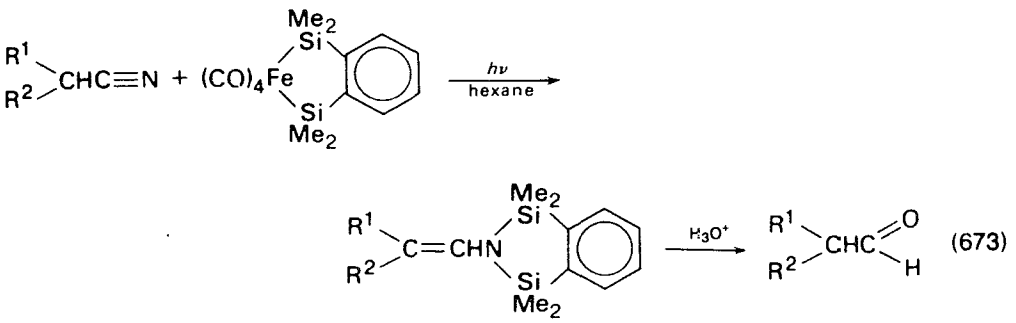
probably via an intermediate azirine. For example, irradiation of 3-cyano-1-methylpyrazole in acetonitrile gives 2-cyano-1-methylimidazole (25%) and 4-cyano-1-methylimidazole (11%) (equation 672) [1155].



(672)

A recent method[1156] has described the general synthesis of allyl heterocyclic bases by a photoinduced substitution reaction of cyanoheterocyclic bases with certain alkenes. Thus, irradiation of a solution of 4-pyridinecarbonitrile in 2,3-dimethyl-2-butene leads to the formation of two isomeric 4-allylpyridines. However, under similar conditions carbocyclic systems such as benzene yield instead photocycloaddition products[1157].

Still another method for conversion of nitriles into aldehydes has recently been described. Thus, exposing a hexane solution of equimolecular amounts of nitrile and a readily available disilylated iron carbonyl complex to UV light for several hours affords the disilylated enamines in good yields; these on hydrolysis with dilute HCl led to the corresponding aldehydes in 65–84% yield (equation 673)[1158].



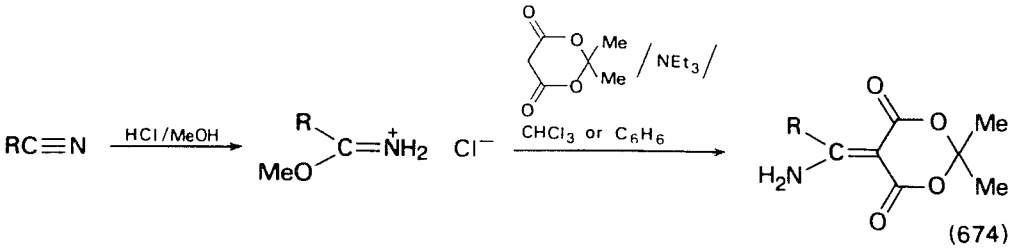
(673)

The utility of gaseous plasmas formed from atoms is well established, and the utility of plasmas from complex molecules[1159] and plasma synthesis are only now being developed. In a recent report[1160], a unique method for the production of unsaturated nitriles from inexpensive alkenes and alkynes has been described. When cyanogen (C_2N_2) and ethylene are passed through a glass reactor (a copper coil + a rf generator, 136 MHz) for 10 min at 30 W, acrylonitrile is produced in 67% yield. Similarly, cyanogen with propylene gives acrylonitrile in 64% yield, and the reaction of cyanogen with 2-butyne results in 1-cyanopropyne (68% yield) via cyanodemethylation.

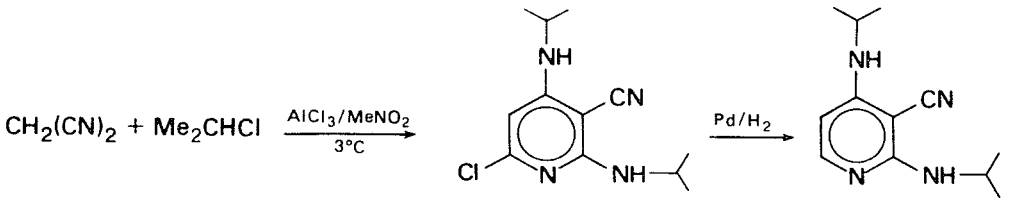
Trimethylsilyl cyanide has been used in syntheses of 2-alkenenitriles from ketones[1161] and 2-butene-4-olides from conjugated enals[1162].

A general method[1163] for the synthesis of β-enamino esters, β-keto esters and methyl ketones is based on the reactivity of Meldrum's acid[1164] with imidates[1165], prepared from nitriles (equation 674).

A one-step synthesis of 2,4-bis(*s*-alkylamino)-6-halo-3-pyridinecarbonitriles involves the $AlCl_3$-catalysed reaction of malononitrile with *s*-alkyl halides (except the alkyl fluorides) at room temperature. From these the corresponding 2,4-bis(*s*-



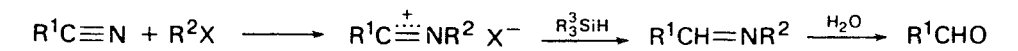
(674)



(675)

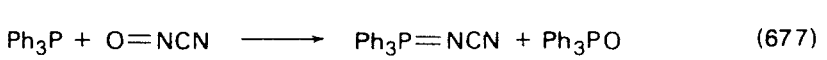
alkylamino)pyridines may be conveniently prepared via catalytic hydrogenation (equation 675)[1166].

Nitrilium ions are becoming recognized as being important not only because of the role they play as intermediates in a rather large number of chemical reactions[1167] but also because of the stereospecific manner in which they react[1168,1169]. *N*-Alkyl nitrilium ions can be prepared by the direct alkylation of nitriles with either triethyloxonium tetrafluoroborate or isopropyl chloride–iron(III) chloride[1170]. As recently demonstrated[1171] they can be reduced by trialkylorganosilicon hydride to *N*-alkylimines that yield aldehydes upon hydrolysis (equation 676).



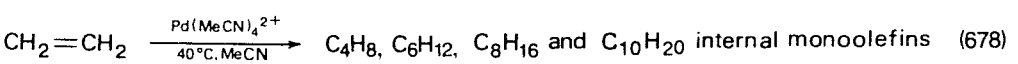
(676)

Nitrosyl cyanide (ONCN, prepared from nitrosyl chloride and silver cyanide)[678] and 9,10-dimethylantracene (DMA) react at −25°C to form the crystalline cycloadduct DMA–ONCN. Triphenylphosphine also reacts readily with nitrosyl cyanide to give phosphinimide (equation 677)[1172].



(677)

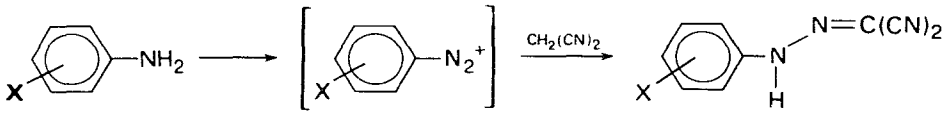
Novel catalytic transformation of alkenes by tetrakis(acetonitrile)palladium ditetrafluoroborate have recently been reported. Thus the catalytic properties of $[Pd(CH_3CN)_4](BF_4)_2$ and $[Pd(CH_3CN)(PPh_3)_3](BF_4)_2$ have been found[1173] to differ very significantly from those observed with analogous neutral Pd(II) compounds, such as $Pd(PhCN)_2Cl_2$, $PdCl_2$ and $Pd(OAc)_2$. Dropwise addition of styrene to an acetonitrile solution of $Pd(CH_3CN)_4^{2+}$ results in the immediate and quantitative precipitation of polystyrene; the compound also catalyses the oligomerization of unactivated olefins such as ethylene (equation 678).



(678)

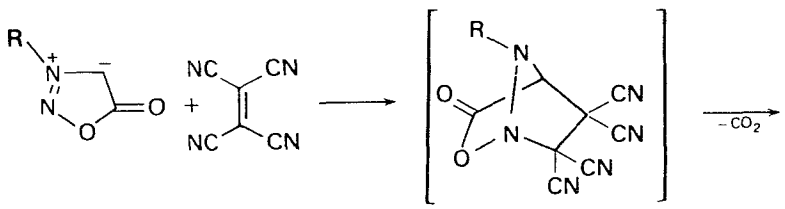
Coloration of polyacrylonitrile on heating is generally attributed to the production of a polyimine by cyclization of adjacent nitrile groups. Both anionic and free-radical mechanisms have been suggested for this cyclization[1174,1175]. In a recent study[1176] the evidence for the radical polymerization of nitrile groups in polyacrylonitrile has been sought using model compounds. No evidence for the cycloaddition of iminyl to nitrile has been obtained but nucleophilic addition occurs readily (via an intramolecular addition to nitrile groups). Thus, 1,8-dicyanonaphthalene reacts with hydroxylamine to give naphthalimide dioxime; however, adamantyl radicals do not attack the nitrile functions.

Carbonyl cyanide phenylhydrazone is well known as an uncoupler of oxidative phosphorylation in mitochondrial systems[1177]. A large number of phenyl-substituted carbonyl cyanide phenylhydrazones have been prepared by the general route involving diazotization of the aniline and coupling of the resulting diazonium ion with malononitrile (equation 679)[10,1178].

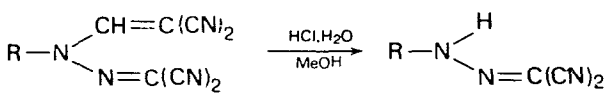


(679)

A new synthesis of carbonyl cyanide alkylhydrazones involves the reaction of *N*-butylsydnone with tetracyanoethylene followed by acid hydrolysis of the adduct (equation 680)[1179].



R = $Me(CH_2)_3$—, $MeO(CH_2)_3$—



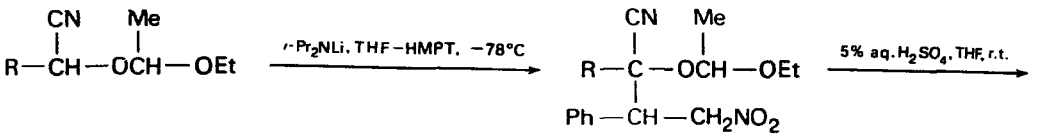
(680)

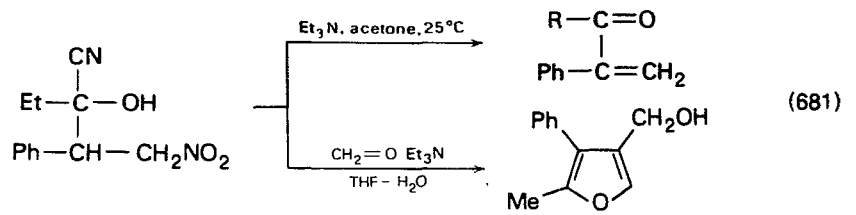
The conjugate addition of anions of protected cyanohydrins to β-nitrostyrene gives adducts in good yields (55–85%). A mild hydrolysis of these adducts yields nitrocyanohydrins; these can be converted into α-methylene ketones (50–82%) or into furan derivatives (40%) (equation 681)[1180].

Chloromethylene iminium salts (Vilsmeier reagents) have a long history and thoroughly investigated chemistry[1181]. The reagent can be recommended for a rapid and efficient dehydration of primary amides to nitriles, particularly for the preparation of acrylonitrile derivatives (equation 682)[1182].

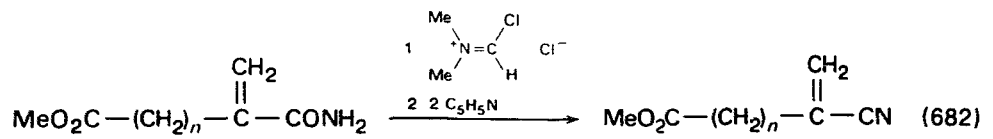
The reductive decyanation of nitriles using alkali fusion is an important synthetic method, for example, in the preparation of certain amines (e.g. antihistamines, chlorpheniramine, etc.). Table 2 summarizes a series of nitriles which have been successfully decyanated, the reaction conditions employed and the yield of the corresponding decyanated compounds[1183].

Cyanotri-*n*-butylstannate [$(n\text{-Bu})_3SnCN$] is readily prepared from chlorotri-*n*-butylstannate and KCN in the presence of 18-crown-6; a further reaction with various acyl chlorides gives a high yield of acyl cyanides[1184].





(681)



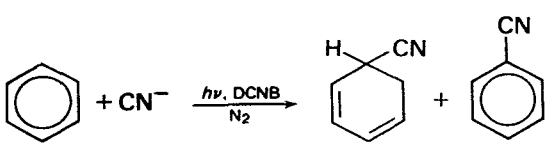
(682)

The α-cyanation of tertiary amines (and a series of sensitive amines) can be carried out under mild conditions and in good overall yields by sequential treatment of the amine with 30% aqueous H_2O_2 in methanol, esterification of the resulting *N*-oxide with trifluoroacetic anhydride in CH_2Cl_2 at room temperature and, finally, treatment with excess aqueous KCN at room temperature[1185].

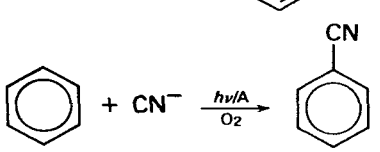
The alkylation of anions on solid inorganic supports (Al_2O_3, SiO_2 etc.) impregnated with KCN leading to the synthesis of nitriles has been described; thus, 1,3-dibromopropane is converted into glutaronitrile (97% yield) and 1-bromooctane into 1-cyanooctane (54–95% yield)[1186].

The polymer-supported synthesis of *N,N*-disubstituted *N*-cyanoguanidines (compounds of specific biological activity) has been reported[1187].

A direct photocyanation of aromatic hydrocarbons (e.g. phenanthrene, anthracene, naphthalene and 2,3-dimethylnaphthalene) in 9:1 acetonitrile–water with sodium cyanide in the presence of electron acceptors (A), e.g. *p*-dicyanobenzene (DCNB), has been reported. Photocyanation under nitrogen gives both the corresponding hydrocyanation products and aromatic nitriles (equation 683)[511,1188,1189], while irradiation under oxygen yields aromatic nitriles (equation 684)[1189]. Cyanation of naphthalene derivatives gives 1-cyanonaphthalene compounds whereas phenanthrene and anthracene are cyanated at C-9.



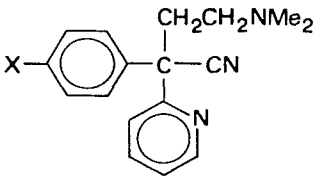
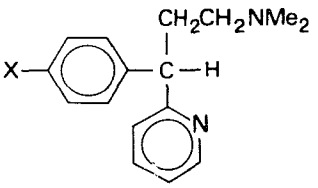
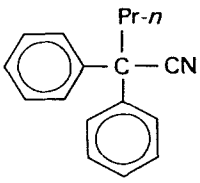
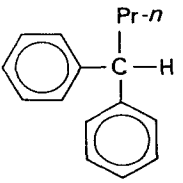
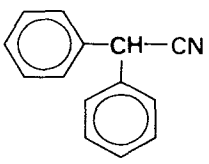
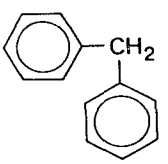
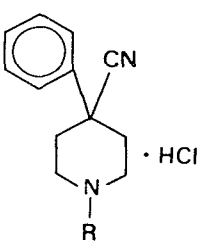
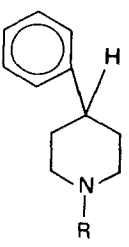
(683)

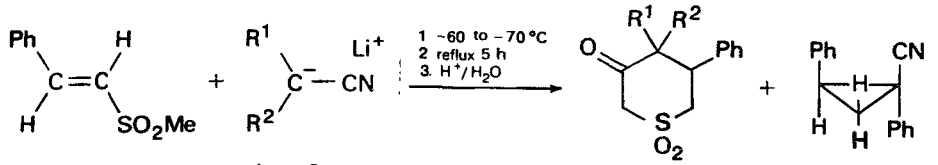


(684)

Vinyl sulphones when subjected to nucleophilic addition by 2-lithionitriles give cyclized products, 3-oxothian 1,1-dioxides or cyclopropane derivatives, according to the substituents on the reagent (equation 685)[1190].

TABLE 2. Reductive decyanation of nitriles by alkali fusion[1183]

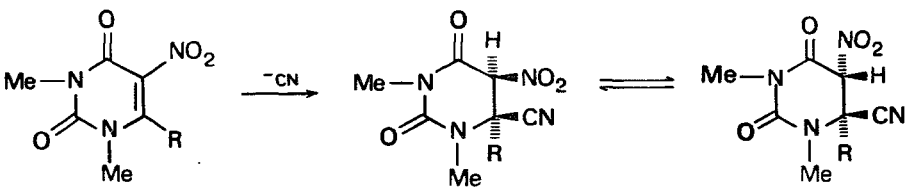
Nitrile	Reaction conditions	Product (Isolated yield %)
 X = Cl X = Br	4 equiv. KOH, 4 h, 150°C	 X = Cl (95) X = Br (75)
	4 equiv. KOH, 26 h, 150°C	 (80)
	4 equiv. KOH, 2 h, 150°C	 (80)
 R = H R = CH_2Ph	10 equiv. KOH, 4 h, 150°C	 R = H (92) R = CH_2Ph (55)



(685)

$R^1 = R^2 = H$	51%
$R^1 = H, R^2 = Me$	76%
$R^1 = R^2 = Me$	80%
$R^1 = H, R^2 = Et$	89%
$R^1 = H, R^2 = Ph$	68%

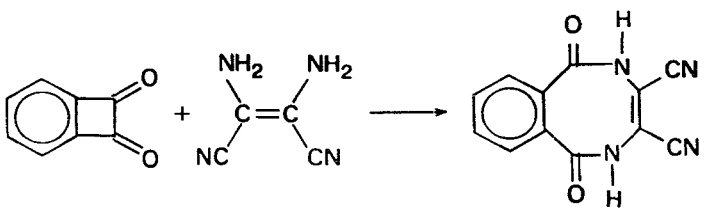
6-Substituted 1,3-dimethyl-5-nitrouracils react with potassium cyanide to give stereospecifically the 6-cyano-5-nitro-5,6-dihydrouracils (nucleophilic addition occurs across the 5,6-double bond of uracils) (equation 686)[1191].



(686)

R = Me, Et, CH=CHPh

The reaction of benzocyclobutene-1,2-dione with diaminomaleonitrile yields benzodiazocine (equation 687)[1192].



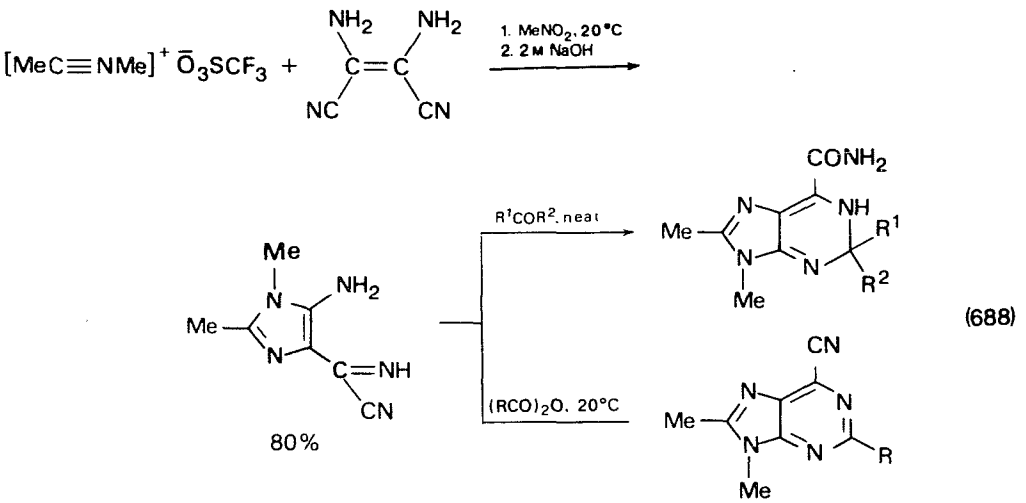
(687)

Diaminomaleonitrile reacts with *N*-methylacetonitrilium trifluoromethanesulphonate to give, after base treatment, the 5-amino-4-(cyanoformimidoyl)imidazole which forms 6-cyanopurins with carboxylic acid anhydrides, and with aldehydes or ketones gives 6-carbamoyl-1,2-dihydropurine derivatives (equation 688)[1193].

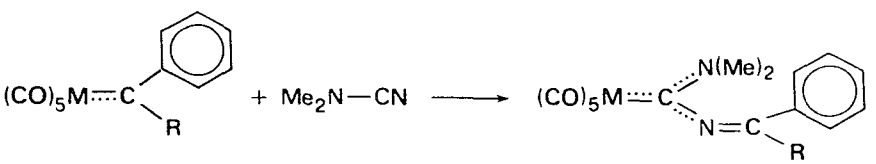
An insertion of the polar CN group into the metal–carbene carbon bond has recently been achieved. Thus, the complexes, e.g. arylcarbene(pentacarbonyl)-chromium(0) and -tungsten(0) react readily in polar and nonpolar solvents at room temperature with dimethylcyanamide to give the corresponding insertion compounds (equation 689)[1194].

A recent medical study[1195] has shown that the occupational (plant) exposure to dimethylaminopropionitrile (DMAPN) may cause neurologic abnormalities (e.g. bladder neuropathy) in humans.

Aromatic cyanomethylation can be accomplished by the photolysis of chloroacetonitrile in the presence of aromatics by way of electron transfer followed by radical coupling (equation 690)[1196].

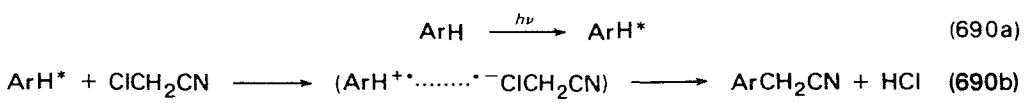


(688)



(689)

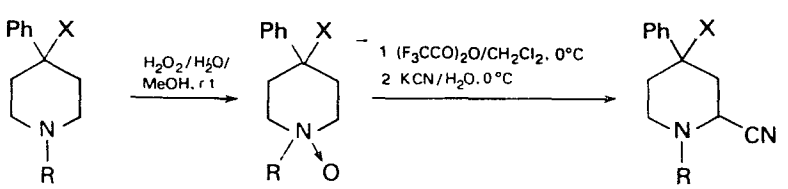
M	Cr	W	W	W
R	OMe	OMe	Ph	*p*-MeC_6H_4



(690a)

(690b)

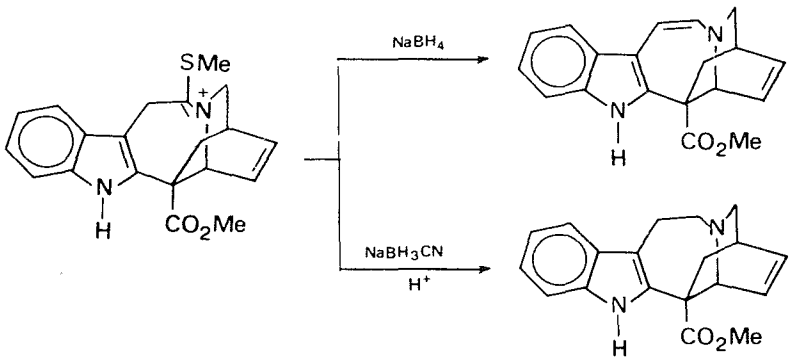
The α-cyanation of sensitive tertiary amines may be performed by the following three-step procedure under mild conditions. The amine is first treated with hydrogen peroxide to give the corresponding *N*-oxide. Esterification of the latter compound with trifluoroacetic anhydride, followed by treatment with aqueous KCN, affords the α-cyanoamine (equation 691). The three-step process can be carried out without isolation of the intermediates, the cyanation occurring at the endocyclic position in all cases investigated. α-Cyanoamines which cannot be obtained via a mercury(II) acetate oxidation are prepared in good yields by this new method[1197].



(691)

X = —COOEt, —OCOEt, —COEt
R = Me, $PhCH_2CH_2$

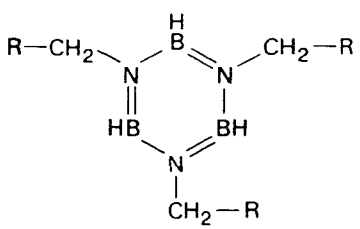
Different behaviour in borohydride and cyanoborohydride reduction of a bridgehead thiolactam deethylcatharanthine (thioimonium salt) has recently been observed[1198]. Whereas $NaBH_4$ reduction (basic solution) yields an enamine, $NaBH_3CN$ (under acidic conditions) gives complete reduction to the amine (equation 692).



(692)

An improved method for reduction of nitriles has recently been developed by Brown and coworkers[1199]. The procedure involves heating of nitriles (e.g. benzonitrile) with borane–dimethyl sulphide reagent (three moles of hydride per nitrile group) in tetrahydrofuran to give a borazine derivative. Hydrolysis of the borazine with hydrochloric acid (or $MeOH + HCl \rightarrow Me_3B$), followed by neutralization with sodium hydroxide, produces amines (e.g. benzylamine) in essentially quantitative yields (equations 693 and 694).

$$3\,RC{\equiv}N + 3\,H_3B \cdot SMe_2 \longrightarrow$$



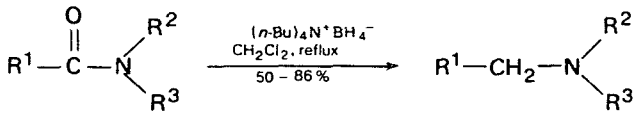
$$\xrightarrow[72-88\%]{\text{1 HCl/H}_2\text{O or MeOH; 2 NaOH}} RCH_2NH_2 \qquad (693)$$

$$N{\equiv}C-(CH_2)_4-C{\equiv}N \xrightarrow[61\%]{\text{1 } H_3B \cdot SMe_2;\ \text{2 HCl/H}_2\text{O};\ \text{3 NaOH}} H_2N-(CH_2)_6-NH_2 \qquad (694)$$

Tetra-*n*-butylammonium borohydride reduces nitriles or amides selectively to give the corresponding amines (equations 695 and 696). In contrast to complex metal hydride reagents, the new reagent is soluble in dichloromethane. The reagent has a high chemospecifity toward the cyano and amido functionality; esters, nitro or halogen groups attached to aromatic rings are not effected under the reaction conditions[1200].

$$RC{\equiv}N \xrightarrow[53-87\%]{(n\text{-Bu})_4N^+BH_4^-,\ CH_2Cl_2,\ \text{reflux}} RCH_2NH_2 \qquad (695)$$

R = aryl, aralkyl



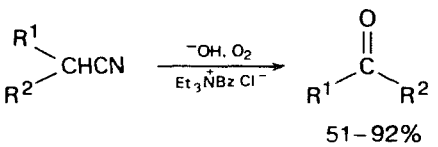
(696)

R^1 = Me, Ph, $PhCH_2$, C_6H_4COOEt

B. Additional Recent Results

Additional recent examples involving selected reactions of cyano compounds or synthesis via cyano intermediates are summarized below.

(a) Oxidation of cyano compounds (equation 697) and oxidation by DDQ (equations 698–701).

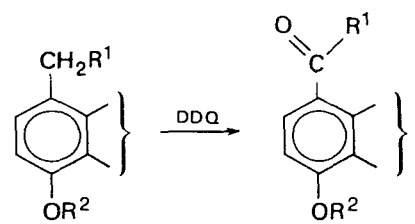


51–92%

(Ref. 1201) (697)

R^1 = Ph, naphthyl

R^2 = alkyl, Ph, pyridyl, etc.

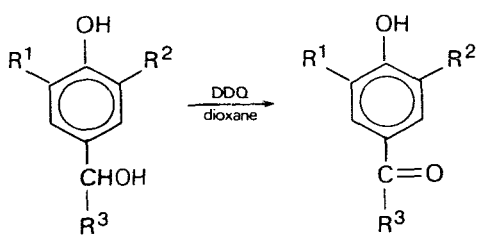


60–85%

(Ref. 1202) (698)

R^1 = H, Me

R^2 = Me, cyclic etc.

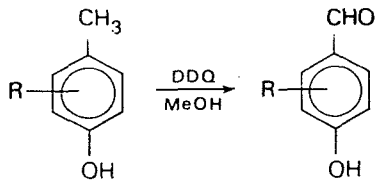


~70–90%

(Ref. 1203) (699)

R^1, R^2 = H, alkyl, Cl, OMe

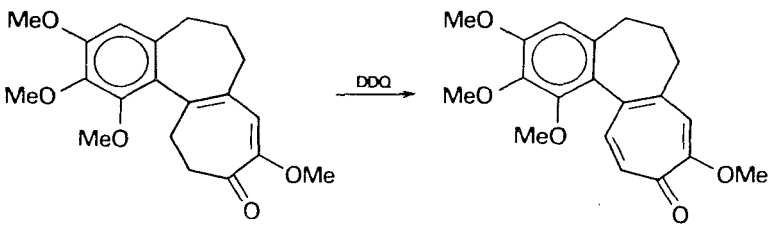
R^3 = H, Bz, Et



(Ref. 1204) (700)

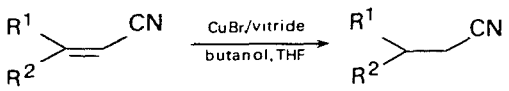
71–84%

R = Me, Br, $-OR^1$, $-\overset{O}{\overset{\|}{C}}-R^1$



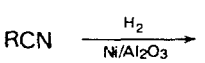
(Ref. 1205) (701)

(b) Reduction of conjugated nitriles (equation 702) and the cyano group (equations 703 and 704).



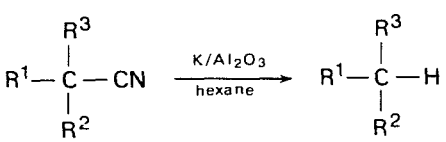
(Ref. 1206) (702)

R^1, R^2 = H, alkyl, aryl, furyl



(Ref. 1207) (703)

R = subst. Ph, alkyl Widely varying yields

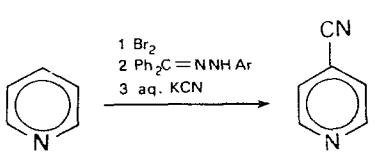


(Ref. 1208) (704)

70–91%

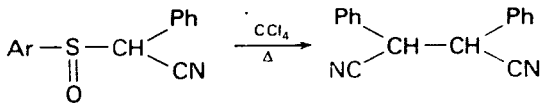
R^1, R^2, R^3 = H, alkyl, vinyl

(c) Cyanation methods (equations 705–709).



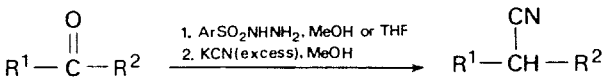
(Ref. 1209) (705)

73%



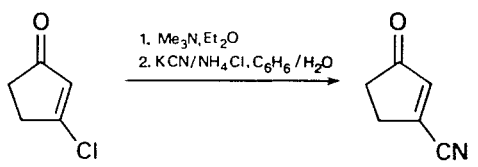
90%

(Ref. 1210) (706)



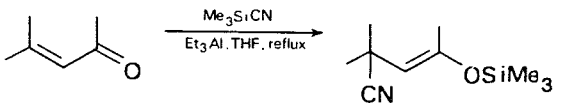
60 - 77%

(Ref. 1211) (707)



71%

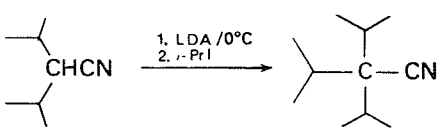
(Ref. 1212) (708)



87%

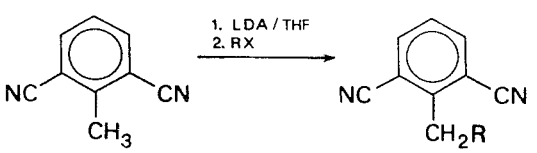
(Ref. 1213) (709)

(d) Alkylation of nitriles (equations 710 and 711).



70%

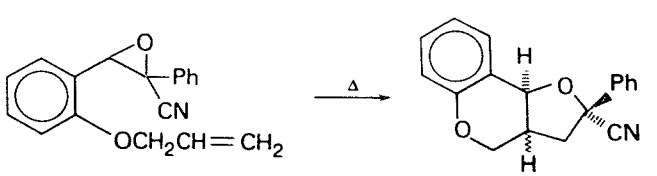
(Ref. 1214) (710)



48 - 84%

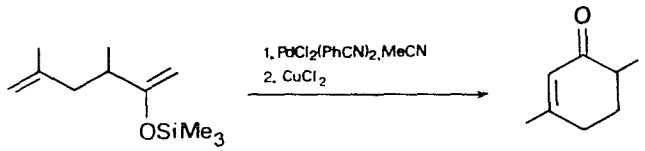
(Ref. 1215) (711)

(e) Rearrangements (equations 712 and 713).



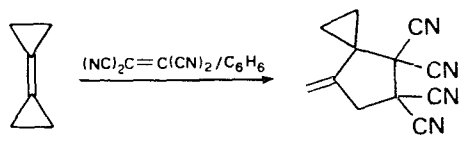
75%

(Ref. 1216) (712)

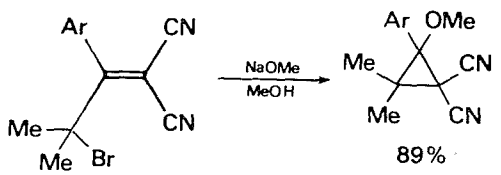


82% (Ref. 1217) (713)

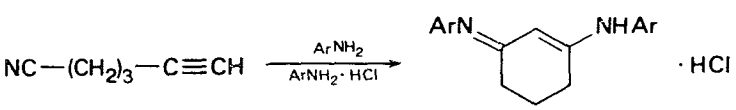
(f) Synthesis of carbocyclic compounds (equations 714–720).



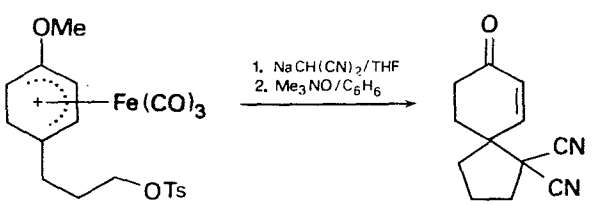
56% (Ref. 1218) (714)



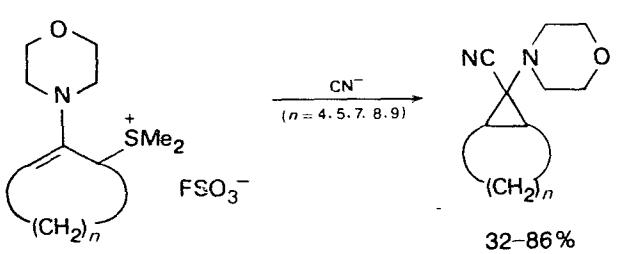
89% (Ref. 1219) (715)



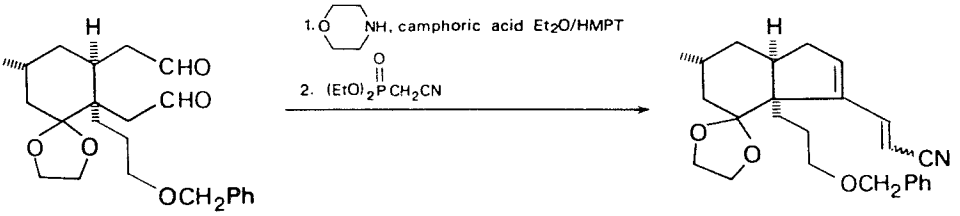
15–52% (Ref. 1220) (716)



< 59% (Ref. 1221) (717)

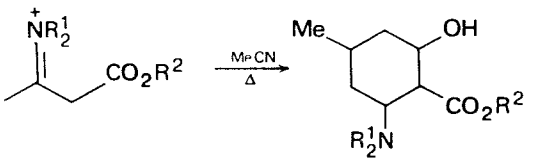


32–86% (Ref. 1222) (718)



46%

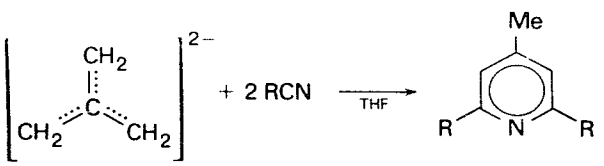
(Ref. 1223) (719)



35–90%

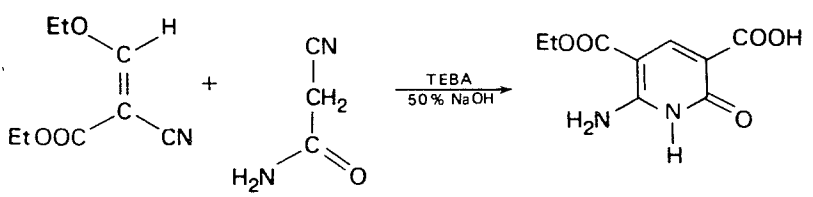
(Ref. 1224) (720)

(g) Syntheses of heterocyclic compounds have recently been reviewed[1225]. Syntheses of some pyridine derivatives (equations 721–724) and of 5-membered ring heterocycles with two nitrogens (equations 725–728), one nitrogen and one oxygen (equations 729 and 730) and one nitrogen and one sulphur (equation 731) in the ring are shown.



(Ref. 1226) (721)

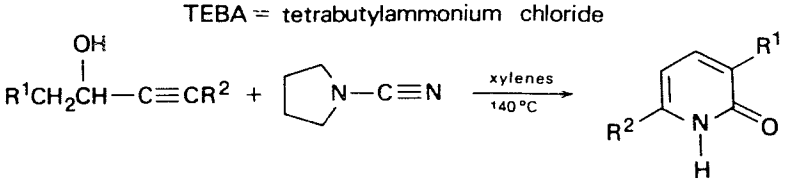
R	Ph	*t*-Bu	pyridyl
Yield (%)	85	30	6



85%

(Ref. 1227) (722)

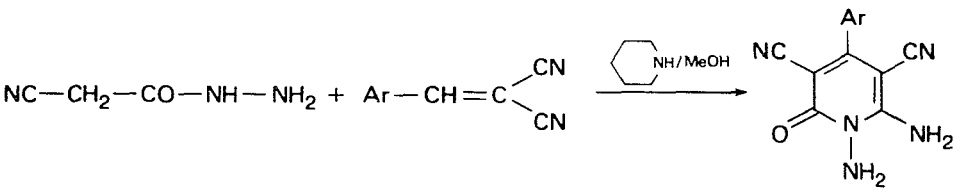
TEBA = tetrabutylammonium chloride



~60–80%

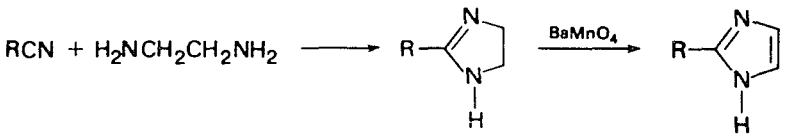
(Ref. 1228) (723)

R^1, R^2 = H, alkyl, Ph



95%

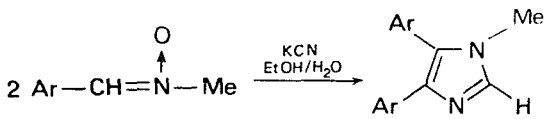
(Ref. 1229) (724)



76–96%

(Ref. 1230) (725)

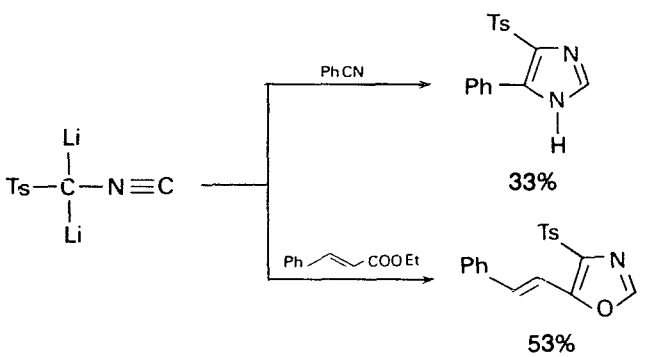
R = *n*-Bu, Ph, C_5H_5N



~70%

(Ref. 1231) (726)

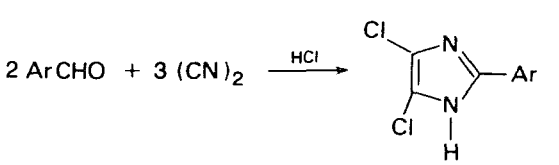
Ar = subst. Ph, pyridyl, thienyl



33%

53%

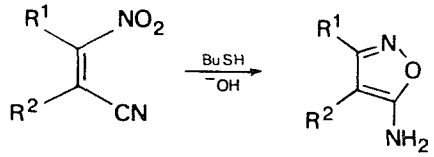
(Ref. 1232) (727)



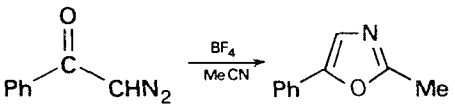
36–72%

(Ref. 1233) (728)

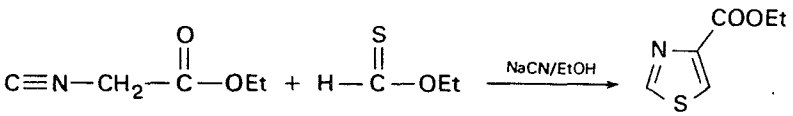
Ar = subst. Ph, furyl, thienyl



R^1, R^2 = Me, subst. 53–75% (Ref. 1234) (729)



94% (Ref. 1235) (730)



81–87% (Ref. 1236) (731)

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CHAPTER **27**

General and theoretical properties of triple-bonded molecules

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I. INTRODUCTION

The literature on triple-bonded molecules has grown almost explosively since the previous relevant volumes in this series appeared. There appears to be no way to do justice in a few pages to such a large body of knowledge. This writer has chosen instead to restrict discussion primarily to the cyano and isocyano bonds and apologizes to those scientists whose work may have been omitted from recognition.

II. THE SIMPLEST CYANIDES, CN^-, CN AND CN^+

The simplest CN species contain only one carbon and one nitrogen atom. Although from a gross structural point of view these CN^-, CN and CN^+ species are the simplest representatives, not all their properties are so easily dismissed. The cyanide anion CN^- is probably the best known to chemists. CN^- is isoelectronic with N_2 and CO and as a consequence its ground electronic configuration can be represented as: $(4\sigma)^2\ (1\pi)^4\ (5\sigma)^2$. N_2^+ and C_2 are isoelectronic with CN and CN^+, respectively, but the latter could have either of two configurations for its ground state:

$$(4\sigma)^2(1\pi)^4 \qquad {}^1\Sigma^+$$

or $$(4\sigma)^2(1\pi)^3(5\sigma) \qquad {}^3\pi,\ {}^1\pi$$

A. CN^-

A number of theoretical studies have been done on the cyanide anion. The total energies (electronic plus nuclear repulsion) calculated with *ab initio* techniques by the various workers are summarized in Table 1. An electron density map has been

TABLE 1. Total energies and equilibrium internuclear distances calculated for CN^-

Total energy[a]	Equilibrium ID[b]	Reference
−91.9273	1.153[c]	1
−86.8131		2
−91.3830		2
−92.1016		2
−91.9310	1.171[c]	3
−92.3106	1.171[c]	3
−92.2629	1.157[c]	4
−92.3182		5
−92.166	1.23[c]	6
−92.2465	1.171	7

[a] Hartrees.
[b] Internuclear distance (Å).
[c] Assumed.

TABLE 2. Orbital energies for CN^- (R = 2.214 Bohr)[a]

+0.5881	(6σ)
+0.4534	(2π)
−0.1668	(5σ)
−0.1733	(1π)
−0.3122	(4σ)
−0.9327	(3σ)
−10.9584	(2σ)
−15.2622	(1σ)

[a] Reproduced by permission of Elsevier Scientific Publishing Company, Amsterdam from J. B. Moffat, *J. Mol. Struct.*, **25**, 303 (1975).

reported[8] for CN^-. Molecular form factors resolve the electron density of solid-state structures in terms of molecules instead of atoms. Molecular form factors for CN^- calculated from *ab initio* wave functions have been used[9] to demonstrate the observability of the chemical bond by X-ray diffraction experiments. Orbital energies for CN^- are shown in Table 2. The expected electronic configuration is clearly evident.

The lowest energy ionization potential (LEIP) of CN^- has been calculated to be 4.54 eV, by application of Koopmans' theorem, to be compared with 3.82 eV found experimentally from the photoionization of hydrogen cyanide[10].

B. CN^+ and CN

Results of the first study of the spectrum of the CN^+ ion were reported in 1954[11]. Subsequent studies by Lutz in 1971 provided some indirect evidence for the ground state being $^1\Sigma^+$ rather than $^3\Pi$.[12]

The first calculations on CN^+ appeared in 1975[13]. These employed a basis set of nine s- and p-type Gaussian functions and were made for 15 internuclear separations from 1.9 to 3.0 Bohr (Table 3). The highest occupied orbital was of π type. A crossing of the 4σ and 1π one-electron energies was observed for an internuclear separation between 2.0 and 2.1 Bohr. If, at the calculated equilibrium internuclear separation of 2.25 Bohr, the addition of an electron to CN^+ is assumed to be to the 5σ orbital, an energy change of 14.10 eV occurs (Koopmans' theorem). The ionization potential of the CN radical has been determined experimentally as 14.03 eV, from the photoionization of HCN[14].

Potential energy curves for the four lowest $^3\Sigma^-$ states of NCO^+, namely $O + CN^+$ ($^1\Sigma^+$), $O + CN^+$ ($^1\Pi$), $O + CN^+$ ($^3\Pi$) and $O^+ + CN$ ($^2\Sigma^+$), have been calculated as functions of the distance between the C and N atoms and with the CO distance fixed at 20.0 Bohr[15]. If the first three are considered as the potential energy curves of CN^+, the ground state of CN^+ is found as $^3\Pi$. On the other hand, valence full-configuration interaction calculations for some low-lying electronic states of CN^+, carried out at five internuclear distances between 2.2 and 2.95 Bohr, suggest that the ground state is $^1\Sigma^+$[16]. However, these authors note that the root-mean-square of the differences between calculated and observed values of the electronic term quantities, *Te*, is approximately twice as large as the difference in the energies of the $^3\Pi$ I and $a^1\Sigma^+$ states. Further SCF calculations with double-zeta quality Gaussian lobe functions plus a diffuse 3s function predicts the $^3\Pi$ state to be the ground state for CN^+ with the $a^1\Sigma^+$ state lying 0.33 eV above the ground level[17]. *Ab initio* configuration interaction calculations, using a 9s5p/3s2p Gaussian basis with polarization functions, find the $^3\Pi$ to be 0.15 eV below the $^1\Sigma^+$ state[18], a result which was taken to be inconclusive. Another *ab initio* CI calculation also found the $^3\Pi$ to be lower than the $^1\Sigma^+$ state, but by 0.41 eV[19]. A most recent CI study employing an AO basis including f polarization functions performed on the $^1\Sigma^+$ and $^3\Pi$ states of the CN^+ ion at their equilibrium internuclear separations, 1.20 and 1.25 A, respectively[20], finds a $^1\Sigma^+$ ground state for CN^+.

III. HYDROGEN CYANIDE, HCN

The simplest neutral cyanide is hydrogen cyanide (hydrocyanic acid). A substantial amount of theoretical work has been done on this molecule. Any attempt to deal with the totality of such work would be beyond the scope of the present work. Consequently, discussions will be restricted to the quantum chemistry of the molecule, its structure, its oligomerization, and its isomerization to HNC.

TABLE 3. Total electronic energy (E) and orbital energies (ε_1) of CN^+ at various internuclear separations (R)[a-c]

R	E	$\varepsilon_{1\sigma}$	$\varepsilon_{2\sigma}$	$\varepsilon_{3\sigma}$	$\varepsilon_{1\pi}$	$\varepsilon_{4\sigma}$	$\varepsilon_{5\sigma}$	$\varepsilon_{2\pi}$
1.9	−91.4855	−16.0590	−11.8564	−1.7920	−0.9894	−0.9430	−0.5299	−0.1406
2.0	−91.5340	−16.0758	−11.8690	−1.7596	−0.9617	−0.9597	−0.5315	−0.1640
2.1	−91.5558	−16.0563	−11.8560	−1.7141	−0.9322	−0.9556	−0.5160	−0.1828
2.15	−91.5631	−16.1487	−11.8503	−1.7207	−0.9369	−0.9831	−0.5224	−0.2040
2.17	−91.5663	−16.1111	−11.8636	−1.7055	−0.9267	−0.9768	−0.5207	−0.2049
2.2	−91.5645	−16.1271	−11.8072	−1.6856	−0.9115	−0.9782	−0.5060	−0.2022
2.21	−91.5660	−16.1121	−11.8405	−1.6803	−0.9189	−0.9717	−0.5198	−0.2120
2.23	−91.5676	−16.1243	−11.8671	−1.6870	−0.9144	−0.9867	−0.5195	−0.2184
2.25	−91.5678	−16.1200	−11.8746	−1.6811	−0.9144	−0.9848	−0.5182	−0.2242
2.3	−91.5656	−16.1401	−11.8824	−1.6686	−0.9057	−0.9923	−0.5218	−0.2363
2.34	−91.5127	−16.1428	−11.8766	−1.6560	−0.8987	−0.9978	−0.5161	−0.2433
2.39	−91.5574	−16.1552	−11.8758	−1.6417	−0.8912	−1.0045	−0.5136	−0.2530
2.5	−91.5439	−16.1317	−11.8974	−1.6021	−0.8684	−1.0130	−0.5074	−0.2715
2.65	−91.5209	−16.1319	−11.9107	−1.5599	−0.8474	−1.0316	−0.4958	−0.2960
3.0	−91.4526	−16.1497	−11.8450	−1.4757	−0.8075	−1.0549	−0.4592	−0.3193

[a]Energies and distances in a.u.

[b]The iterations were performed to an overall energy convergence of 0.001 hartree. The error introduced in the orbital energies, which are not separately optimized, is somewhat higher.

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The first calculation done on the structure of the ground state of HCN employed the LCAO MO SCF approximation and a minimal basis set of Slater orbitals[21]. The internuclear distances were taken as the experimental equilibrium values, 1.058 and 1.157 Å for C—H and C≡N, respectively[22]. It is of interest to note that, according to a Mulliken population analysis[23] of the results, the nitrogen atom loses π electrons but gains sufficient σ charge to produce a net negative charge on the nitrogen.

Calculations on hydrogen cyanide have also been done with basis sets of Gaussian orbitals[24]. Sets ranging from 11 to 42 functions were examined. The 39 function set produced values for the H—C and C≡N bond lengths in good agreement with the experimental results at the energy minimum.

IV. THE NONREACTIVE DIMERIZATION OF HCN

The nonreactive dimerization, or self-association, of HCN has been of interest for a number of years. Gas-phase infrared studies[25,26] have shown only one band, at 2095 cm^{-1}, which was assigned to the C≡N stretching mode of the head-to-tail dimeric species, **1**. The heat of formation of the dimer, -5.7 ± 0.5 kcal mol^{-1}, was calculated

HCN···HCN

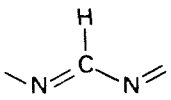
(1)

from the variation of the optical density of the 2095 cm^{-1} band with total pressure[26]. The temperature dependence of fundamental infrared absorbance intensities in monomeric and dimeric forms of HCN vapour has been used to calculate an energy difference of -3.80 ± 0.16 kcal mol^{-1} [27]. Over forty years ago a value of -2.6 kcal mol^{-1} was obtained from vapour density data[28]. Microwave spectroscopy[29] has produced supporting evidence for the linear structure deduced from infrared data.

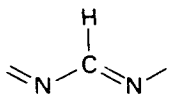
The results of a study of the infrared spectra of hydrogen cyanide and deuterium cyanide trapped in argon, nitrogen and carbon monoxide matrices[30] have also been interpreted as evidence for a linear dimer. A detailed study of the monomer bonds of various isotopic species of hydrogen cyanide in argon matrices has also been reported[31,32]. The spectrum of hydrogen cyanide was obtained by generating the dimer in an argon matrix by photolysis of *s*-tetrazine[33]. Walsh, Barnes, Suzuki and Orville-Thomas[34] have measured the infrared spectra of hydrogen and deuterium cyanide in neon, krypton, xenon, argon, nitrogen and carbon monoxide matrices at 4 K and 20 K. The bands observed have been assigned to monomer, dimer, trimer, tetramer and higher multimer species. The linear dimer is again observed, although there is some evidence for the existence of the cyclic dimer in argon matrices.

The first calculations (1969) on the dimer of HCN employed the CNDO/2 method[35]. The lowest energy was found with the cyclic dimer, where the nitrogen of one HCN molecule was situated directly below the hydrogen of the other HCN molecule. A heat of dimerization of -50 kcal mol^{-1} was calculated. In the same year, Rae[36] employed an SCF wave function for the HCN monomer and separately calculated the electrostatic, polarization, exchange repulsion and dispersion contribution to the intermolecular energy. A dimerization energy of 4.7 kcal mol^{-1} was found. *Ab initio* calculations with an STO-3G basis have been carried out on both the linear and cyclic dimer[37]. The linear dimer was shown to be the most stable of the two forms with an energy relative to the HCN monomers of 3.7 kcal mol^{-1}. The inability of the CNDO/2 method to predict the correct form of the dimer has been ascribed to the neglect of three- and four-centre repulsions.

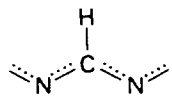
Ab initio crystal orbital approaches[38] to polymethineimine $[(HCN)_x]$ have shown that the alternating structures (**A** and **B**) are more stable than the nonalternating form (**C**). However, unrestricted Hartree–Fock calculations with an STO-3G basis have



(A)



(B)



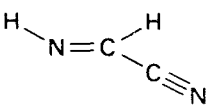
(C)

found the nonalternating structure to be lower in energy[39]. The dimers of HCN have also been studied with the CNDO/2, PRDDO and MNDO techniques[40]. The PRDDO and *ab initio* (STO-3G) both predict the linear dimeric form to be more stable than the cyclic dimer.

V. OLIGOMERIZATION OF HCN

There has been and continues to be considerable interest in the reactive dimerization of HCN, for a variety of reasons. The mechanisms by which HCN reacts with itself, the structure of the resulting molecules, and the relative stability of each has been examined both experimentally and theoretically. The results of such studies find application in discussions of the role of HCN in chemical evolution.

The existence of a variety of oligomers in hydrogen cyanide gas was demonstrated many years ago[41,42]. Völker[43] and others before him assumed that the HCN dimer was iminoacetonitrile (**2**). Subsequently[44] an alternative structure, a tautomer of **2**, aminocyanocarbene (**3**) was suggested to form spontaneously from **2**. It was such a



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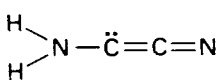
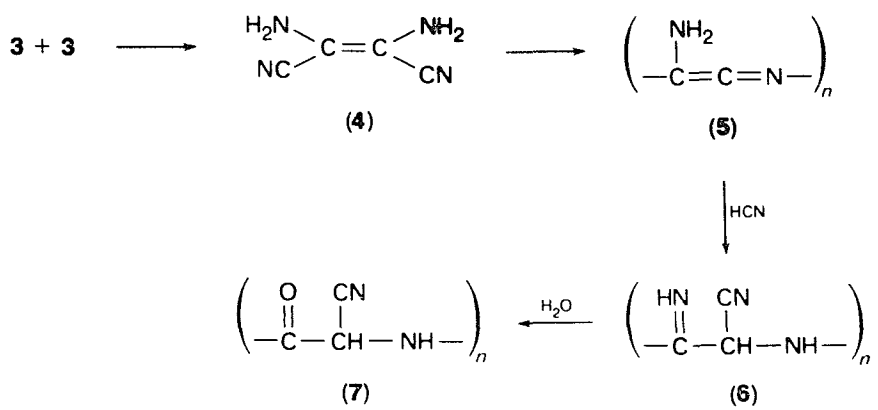
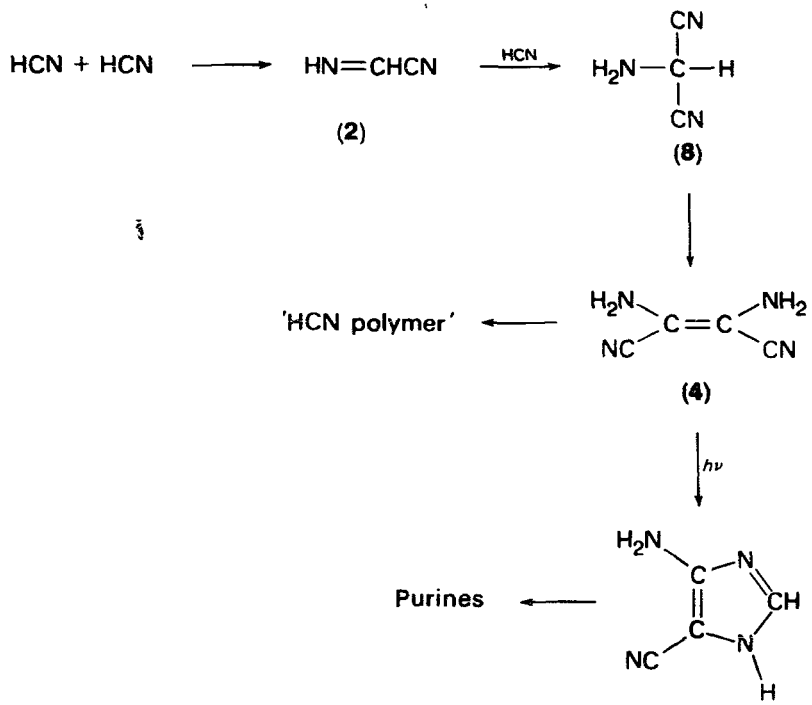


(3)

dimer of HCN that was postulated to be a key intermediate in the prebiotic synthesis of purines and proteins under simulated primitive earth conditions[44–49]. Matthews and Moser[45,46] suggested that the dimer species **2** was a direct precursor to HCN polymers, the process (Scheme 1) being one in which the species **3** dimerized to form **4** and polymerized to form **5**, which could further react with HCN to form **6**. It was suggested that mild hydrolysis of this polymer would produce peptides **7** and vigorous hydrolysis would produce amino acids.



SCHEME 1



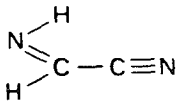
SCHEME 2

Ferris and coworkers[50] proposed an alternative scheme (Scheme 2). π-Electron LCAO–MO calculations[51] predicted that aminocyanocarbene (**3**) would have a total electronic energy lower than that of **2** as a result of electron delocalization in a triplet ground state. However, experimental work[52] on the synthesis and properties of **3** led to the suggestion that a considerably dipolar singlet electronic ground state was more probable. Iterative, all-valence-electron extended Hückel calculations were performed[53] for the spin-paired and biradical configurations of eight different geometric conformations of the two tautomeric forms **2** and **3**. The *cis* and *trans* isomers (**2a** and **2b**) of the imine dimer were calculated to be more stable than any of the six isomer conformations of **3**.

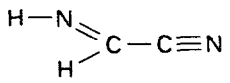
Jameson and Yang[54] applied the semiempirical INDO method to a number of postulated dimers of HCN (**2a**, **2b**, **3**, **9a–c**) and concluded that the dimers of lowest energy are iminoacetonitrile (*cis* and *trans*) and aminocyanocarbene. The *cis* conformer of the former is very slightly lower in energy than the *trans*. Aminocyanocarbene possesses a triplet ground state which is approximately 56 kcal mol^{-1} higher in energy than *cis*-iminoacetonitrile.

To differentiate between the oligomerization schemes above (Schemes 1 and 2)[44], Ferris and coworkers[55,56] investigated the proposal that iminoacetonitrile **2** has the properties of the carbene **3**. For this purpose a series of *N*-alkyliminoacetonitriles was prepared and the reactions of these with hydrogen cyanide and potassium hydroxide were investigated.

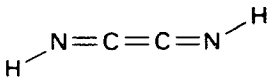
The addition of HCN to RN=CHCN, where *R* is *t*-Bu, *i*-Pr, *c*-Hex or Et, yields both **10** and **11**. The formation of **11** and not of **12** was taken to indicate that the oligomerization of HCN proceeds by stepwise addition of hydrogen cyanide to hydrogen cyanide oligomers, according to Scheme 3, and not by the dimerization of **2**



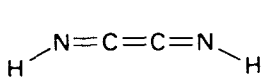
(2a)
trans-Iminoacetonitrile



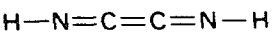
(2b)
cis-Iminoacetonitrile



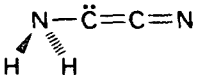
(9a)
trans-Vinylidenediimine



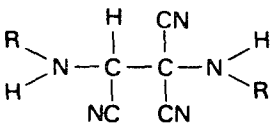
(9b)
cis-Vinylidenediimine



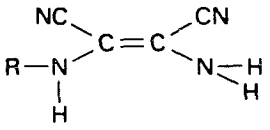
(9c)
Linear vinylidenediimine



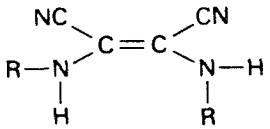
(3)
Aminocyanocarbene



(10)



(11)



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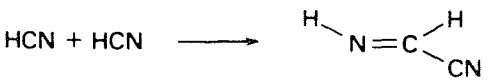
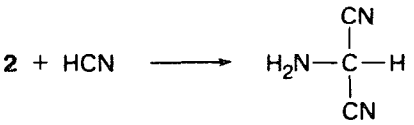
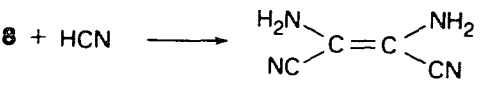


(2)



(8)

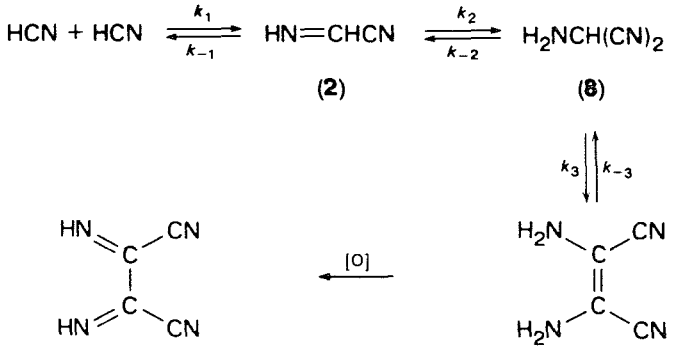


(4)

SCHEME 3

to produce **4**. It is concluded that the product of the reaction of two HCN molecules does not exhibit the properties of a carbene. In addition, these authors suggested that the mechanism of the oligomerization process showed that the 'HCN polymer' must be a mixture of low-molecular-weight compounds. No evidence for the presence of peptides or polymers was found[56,57]. Both urea and oxalic acid were found in the cyanide condensation system, the former in large quantity, the latter in smaller amounts, and amino acids were shown to result from the hydrolysis of the oligomerization mixture.

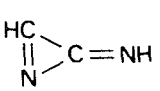
Scheme 4 has been proposed[58] in which an oligomeric equilibrium mixture of HCN, its dimer, trimer and tetramer is formed in cyanide condensation reactions. All of



SCHEME 4

these oligomers may form urea, oxalic acid and other products through hydrolytic and/or oxidation–reduction reactions. It was further suggested that the reaction of cyanide ions with aminomalononitrile could produce cyanogen. Evidence has also been presented[58,59] which demonstrates that oxidation and reduction leading to urea and the amino acid precursors can occur in the absence of oxygen, which was interpreted as demonstrating the feasibility of such reactions on the primitive earth.

The results of INDO calculations on a number of possible structures for the HCN dimer were reported in 1973 by Matthews and coworkers[60]. These calculations predicted that azacyclopropenylideneimine (**13**) should be considerably more stable than either aminocyanocarbene (**3**) or iminoacetonitrile (**2**), thus leading Matthews and coworkers to postulate that the dimerization of HCN should proceed through structure **13**. However, as they have pointed out, ring compounds are favoured by



(**13**)

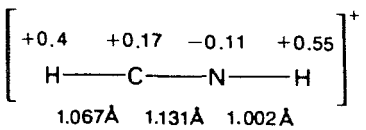
INDO calculations. Two years later, in 1975, the results of *ab initio* calculations with an STO-3G basis and geometry optimization showed that iminoacetonitrile (**2**) should be significantly more stable than either **13** or **3**[61]. Single calculations on the STO-3G optimized structures with an extended 6-31G basis did not change the stability hierarchy of the three structures. CNDO/2 calculations with energy partitioning also predict that iminoacetonitrile should be the most stable $(HCN)_2$ structure[62]. Further, the energetically most favourable mechanism for the reaction of two molecules of HCN involves the dissociation of HCN followed by the reaction of CN with HCN[62]. However, the calculations yielding such a mechanism are based on separated

molecules and as a consequence are applicable only to gas-phase reactions. Matthews and coworkers[63,64] proposed that azacyclopropenylideneimine condenses to produce the oligomers of HCN.

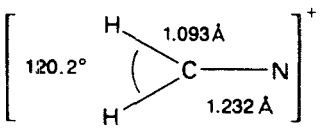
Ferris and Edelson[65] argue that the amino acids, not including glycine, arise from the hydrolysis of reduced oligomers of HCN, while glycine may form from the hydrolytic cleavage of diaminomaleonitrile or by hydrolysis of the HCN oligomers. They believe that it is unlikely that azacyclopropenylideneimine is the monomer unit which condenses to give the HCN oligomers. These authors also rule out the mechanism involving the dissociation of diaminomaleonitrile to a dimer species which then polymerizes, and instead claim that diaminomaleonitrile, and not the HCN dimer, must be the direct precursor to the HCN oligomers[65–67].

VI. H_2CN^- AND H_2CN^+

The first theoretical studies of protonated and of hydrided HCN were made 25 years ago. At that time Brown and Penfold[68] obtained values for the parameters in simple molecular orbital calculations by applying SCF MO techniques to H_2CN^- and related molecules. Some years later [69] *ab initio* calculations with Gaussian orbitals and a variety of sizes of basis sets predicted an energy decrease of 82 kcal mol^{-1} in forming H_2CN^+ by protonation of HCN and an increase of 55 kcal mol^{-1} on addition of H^- to HCN. In the last six or so years the interest in H_2CN^+ has increased, in part because of its importance as an interstellar species. The linear structure (**14**) of H_2CN^+ has been predicted[70] to lie 3.0 eV lower in energy than the formaldehyde-like (C_{2v}) isomer (**15**). The structures and energies of the lowest singlet states of three isomers of H_2CN^+ have been calculated[71,72].



(14)



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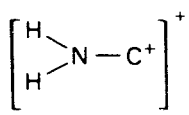


(16)

Although the H_2CN^+ molecular ion appears to play an important part in the formation of interstellar HCN and HNC, no agreement on the mechanism has been reached. Brown[73] has recently suggested that the important processes may be those shown in equations (1)–(3). Brown[73] notes that three isomers of H_2CN^+ (**14–16**) are

$$N^+ + CH_3 \longrightarrow H_2CN^+ + H \quad (1)$$

$$N + CH_3^+ \longrightarrow H_2CN^+ + H \quad (2)$$

$$H_2CN^+ + e \longrightarrow HCN + H \quad (3)$$

possible. The formation of the more stable linear isomer (**14**) would require the migration of a hydrogen atom from carbon to nitrogen, a highly energetic process. Thus, the H_2CN^+ on the right-hand side of reactions (1) and (2) is presumably the isomer **15**. Brown[73] further argues that the reactions producing HNC (equations (4) and (5)) should involve the isomer **16**.

$$C^+ + NH_3 \longrightarrow H_2CN^+ + H \quad (4)$$

$$H_2CN^+ + e \longrightarrow HNC + H \quad (5)$$

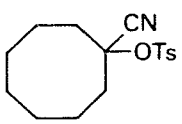
Conrad and Schaefer[74] have found that **16** lies below **15** in energy and that reactions (1), (2) and (4) are exothermic by 209, 110, and 143 kcal mol^{-1} assuming the linear isomer for H_2CN^+. If the product of reaction (4) is taken as isomer **16**, the exothermicity is reduced to 97 kcal mol^{-1}, which is sufficient to permit the surmounting of the activation barrier to **15** according to the calculations of Conrad and Schaefer. These authors thus conclude that, since reaction (4) is so exothermic, the linear isomer will be rapidly produced, and such an isomer can form either HCN or HNC by reaction (3). Thus reactions (1) and (2) are not required to rationalize the interstellar formation of HCN.

The structures and energies of the lowest triplet states of four isomers of H_2CN^+ have recently been determined by self-consistent field and configuration interaction calculations[75]. The structures considered were H_2CN^+, H_2NC^+, and *cis*- and *trans*-$HC{=}NH^+$. The lowest triplet state energy, possessed by H_2NC^+, is 97.2 kcal mol^{-1} above the energy of the linear ground state. It is suggested that reaction (4) may produce the triplet H_2NC^+ isomer which converts to the singlet H_2NC^+ isomer by phosphorescent emission, thereby reducing the energy of the H_2NC^+ to such an extent that it is unable to isomerize to the linear singlet ground state.

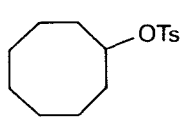
VII. CYANO AND ISOCYANO GROUPS AS SUBSTITUENTS IN CARBONIUM IONS, CARBANIONS AND RADICALS

The influence of substituent groups on carbonium ions has been of interest for a number of years. In particular, the cyano group, as an example of an electron-withdrawing group, has recently received special attention. Gassman and Talley[76] have pointed out that the rate of a solvolysis reaction would be expected to be reduced more by an α-cyano group than by either the α-trifluoromethyl or the α-keto group. Such a conclusion could be reached by noting that the values of the Taft polar substituent constant for $NCCH_2$, CF_3CH_2 and $CH_3C(=O)CH_2$ are 1.30, 0.92 and 0.60, respectively. It has been shown[77] in the solvolysis of sulphonate esters that the replacement of hydrogen by an α-trifluoromethyl group decreases the rate by a factor of 10^6, while with an α-keto group the factor is 10^7 [78]. However, Gassman and Talley[76] have measured the rates of solvolysis of 2-propyl tosylate and 2-cyano-2-propyl tosylate and found the former to be faster than the latter by a factor of approximately 3.5×10^3, considerably smaller than anticipated.

Nucleophilic solvent participation has been eliminated as the source of the relatively small H/CN rate ratio by examining the solvolysis of 1-cyano-1-cyclooctyl tosylate (**17**) in 2,2,2-trifluoroethanol, a relatively nonnucleophilic solvent. The solvolysis rate of cyclooctyl tosylate (**18**) in the same solvent has been found to be 1.87×10^3 times

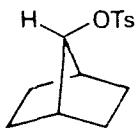


(**17**)



(**18**)

faster than that of the corresponding cyano substituted compound **17**. Gassman and Talley[76,79] have also investigated systems where delocalization of the positive charge occurs through neighbouring-group participation. For such purposes the effect of the addition of an α-cyano substituent on the rates of solvolysis of 7-bicyclo[2.2.1]heptyl



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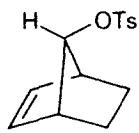

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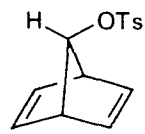


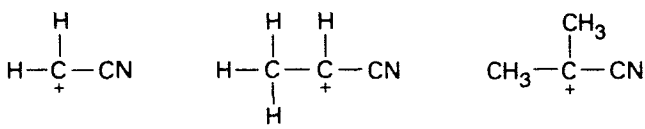
(21)

(19), 7-*anti*-bicyclo[2.2.1]hepten-2-yl (20), and 7-bicyclo[2.2.1]heptadienyl (21) tosylates were measured. H/α-cyano rate ratios of 10^2, 10^5 and 10^6, respectively, were found. It was concluded that an α-cyano group can be simultaneously inductively destabilizing and mesomerically stabilizing on an incipient carbonium-ion centre, with the largest rate retardation occurring with the most stable ions. Thus, α-cyano cations of type 22 may be stabilized by charge delocalization through resonance structures 23.

(22) (23)

Dixon, Charlier and Gassman[80] have performed partially geometrically optimized PRDDO calculations which show the nuclear configurations which would be expected as the result of charge delocalization.

Ab initio (STO-3G) calculations with complete geometry optimization have been reported[81] on three α-cyano-substituted carbonium ions, one primary (24), one secondary (25) and one tertiary (26). Similarly, geometry-optimized calculations on



(24) (25) (26)

the parent neutral nitriles and the parent carbonium ions have been performed. The energy required to form the α-cyano-substituted carbonium ion from its neutral parent was compared with that required in the corresponding unsubstituting case by employing the isodesmic reactions of equations (6)–(8). The results are summarized in

$$CH_2CN^+ + CH_4 \longrightarrow CH_3CN + CH_3^+ \quad (6)$$

$$CH_3CHCN^+ + C_2H_6 \longrightarrow CH_3CH_2CN + C_2H_5^+ \quad (7)$$

$$(CH_3)_2CCN^+ + C_3H_8 \longrightarrow (CH_3)_2CHCN + C_3H_7^+ \quad (8)$$

Table 4. According to these calculations, the methyl carbonium ion is positively stabilized by substitution of the hydrogen by the α-cyano group, but the ethyl and *i*-propyl carbonium ions are apparently destabilized. Thus the primary carbonium ion is stabilized by α-cyano substitution.

The values obtained for the various geometrical parameters of both the α-cyanocarbonium ions and the neutral parent molecules are given in Table 5. The CN and H—CCN bond lengths in the carbonium ions are larger than those in the parent neutral molecules, while the C—CN distances are shorter in the former compared to the latter. This is indicative of an increased delocalization of electrons in the carbonium ions as compared to the neutral cyanides and thus of a contribution from

TABLE 4. Stabilization energies of α-cyano-carbonium ions[a]

α-Cyanocarbonium ion	Stabilization energy (kcal mol^{-1})
CH_2CN^+	+0.14
CH_3CHCN^+	−5.4
$(CH_3)_2CCN^+$	−8.4

[a]Reproduced by permission of North-Holland Publishing Company, Amsterdam from J. B. Moffat, *Chem. Phys. Letters*, **76**, 304 (1980).

TABLE 5. Nuclear configurations[a] of α-cyanocarbonium ions and neutral parent molecules[c]

	H—CCN	C*—CCN[b]	C—CN	C≡N	HĈ(CN)	C*Ĉ(CN)[b]
CH_3CN	1.088		1.486	1.154	110.1	
CH_3CH_2CN	1.091	1.544	1.492	1.154	108.3	112.0
$(CH_3)_2CHCN$	1.092	1.549	1.499	1.154	106.4	109.7
CH_2CN^+	1.117		1.389	1.193	120.5	
CH_3CHCN^+	1.115	1.506	1.411	1.181	116.7	123.4
$(CH_3)_2CCN^+$		1.519	1.430	1.174		119.0

[a]Bond lengths (Å) and bond angles (deg.) optimized to ±0.001 Å and 0.1°, respectively.
[b]C* is the carbon of the methyl group.
[c]Reproduced by permission of North-Holland Publishing Company, Amsterdam from J. B. Moffat, *Chem. Phys. Letters*, **76**, 304 (1980).

the resonance structure **23**. A semiquantitative indication of the extent of delocalization may be obtained by comparing the changes in the C≡N bond lengths in passing from the neutral to the corresponding charged species. Such increases are 0.039, 0.027 and 0.020 Å for the methyl, ethyl and *i*-propyl species, respectively. The stabilization energy can be seen to decrease as the degree of delocalization decreases, as expected.

The substitution of CN for H on the parent carbonium ion reduces the positive charge on the CH_2 in the methylcarbonium ion, but increases the charge on the corresponding groups in the ethyl- and *i*-propyl-carbonium ions. This change is presumably due to both the decreased delocalization and an increased inductive effect (Table 6).

In addition to the changes in bond lengths there are significant differences in the bond angles between those found in the charged and neutral cyanides. For example the HĈC angle is 110.1° in acetonitrile, while it is 120.5° in the α-cyanomethyl-

TABLE 6. Charges on the α-cyanocarbonium ions and the parent ions

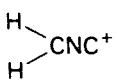
Ion	Group	Charge	Ion	Group	Charge
CH_2CN^+	CH_2	+0.714	CH_2H^+	CH_2	+0.741
CH_3CHCN^+	CH_3CH	+0.796	CH_3CHH^+	CH_3CH	+0.778
$(CH_3)_2CCN^+$	$(CH_3)_2C$	+0.857	$(CH_3)_2CH^+$	$(CH_3)_2C$	+0.807

carbonium ion. Similar differences can be observed between the other charged and neutral species. Such increases in bond angles will result in positive contributions to the nuclear repulsion energy, thereby contributing positively to the total electronic energy. It thus appears that any assessment of the stabilization of carbonium ions by the α substitution of cyano groups must consider not only the shift in electron densities so produced, but also the readjustment of nuclear configuration which ultimately results from the necessity to minimize the total electronic energy.

Gassman and coworkers[82] have employed the solvolysis of adamantanone cyanohydrin sulphonates for the purpose of evaluating the relative effects of H, α-CN and β-CN substitution. The H/α-CN rate ratio was found to be 2.1×10^3, similar to that observed for cyclooctyl tosylate (**18**) vs the tosylate of cyclooctanone cyanohydrin (**17**)[76,79]. Farcasiu[83,84] has measured the H/β-CN rate ratio as 1.3×10^5 for the solvolysis. Thus, a β-cyano group is approximately 100 times more effective in reducing the rate than is one which is at the α position. These authors conclude that the α-cyano-substituted cation is more stable than the β-cyano-substituted cation.

Olah and coworkers[85] have recently reported on the cyanodiphenylmethyl cation, which they believe is the first long-lived cyanocarbonium ion. The ^{15}N-enriched ion has shown a ^{15}N-NMR spectrum in which the cyano nitrogen appears as a singlet at δ 283.0, which is 30 ppm deshielded over that in the neutral precursor. Olah concludes, from the observed 30 ppm deshielding, that the bond between carbon and nitrogen is double, and notes that the ^{15}N chemical shift is close to that found with imines (δ 318).

The consequences of substitution of isocyano groups have been examined through a series of *ab initio* geometry-optimized calculations with STO-3G basis sets[86]. While there appears to be no unambiguous evidence in the literature even for the existence of isocyanocarbonium ions, such calculations can provide some insight into the nature and stability of these ions. The ions considered were **27–29**. The changes in energy



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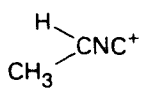

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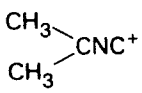

(29)

calculated for the isodesmic reactions (equations 9–11) were interpreted as stabilization energies of the α-isocyanocarbonium ions as compared to the corresponding unsubstituted carbonium ions. The three carbonium ions are all

$$CH_2NC^+ + CH_4 \longrightarrow CH_3NC + CH_3^+ \quad (9)$$

$$CH_3CHNC^+ + C_2H_6 \longrightarrow CH_3CH_2NC + C_2H_5^+ \quad (10)$$

$$(CH_3)_2CNC^+ + C_3H_6 \longrightarrow (CH_3)_2CHNC + C_3H_7^+ \quad (11)$$

positively stabilized by addition of the α-isocyano group (Table 7), the extent of the stabilization being largest for the primary carbonium ion and smallest for the tertiary ion.

With all three of the α-isocyanocarbonium ions the positive charges are centred on the two carbon atoms. In addition the C—NC bond in the charged species is shorter than that in the corresponding neutral molecule, while the N≡C bond length is larger in the carbonium ion than in the neutral species. These observations are consistent with a resonance hybridization expressed as **30** ⇌ **31**.

Hoz and Aurbach[87] have noted that carbanions are relatively unstable species,

(30) **(31)**

TABLE 7. Stabilization energies of α-isocyano-carbonium ions[a]

α-Isocyanocarbonium ion	Stabilization energy (kcal mol^{-1})
CH_2NC^+	25.6
CH_3CHNC^+	15.9
$(CH_3)_2CNC^+$	10.6

[a]Reprinted with permission from J. B. Moffat, *Tetrahedron Letters*, **22**, 1001 (1981). Copyright (1981), Pergamon Press, Ltd.

unless they contain electron-withdrawing substituents. As a consequence, information on a carbanion is usually obtained from the rate, type and stereochemistry of its reactions. These authors have prepared 3-alkoxycyclobutanecarbonitrile anion by reacting an alkoxide ion with bicyclobutanecarbonitrile, and by deprotonation of the *cis* and *trans* isomers of 3-alkoxycyclobutanecarbonitrile under ion pairing and under dissociating conditions. It is found that each of these three reactions produces a different type of carbanion. In the deprotonation reaction the intermediate carbanion is hydrogen bonded to the conjugate acid of the base, while the addition reaction produces a 'free' carbanion whose inversion rate is faster than the reorganization of the surrounding solvent molecules to give the hydrogen-bonded complex.

Theoretical studies[88] with a 4-31G basis carried out on the carbanions CH_2X^- where X includes CN, among other substituents, have shown that all the carbanions containing unsaturated substituents are planar, whereas those containing saturated substituents are pyramidal.

Viehe and coworkers[89] have developed and tested the concept of 'captodative' radical stabilization (sometimes referred to as merostabilization), in which the synergetic effect of donor and acceptor substituents on the same radical centre lead to an enhanced stabilization over that expected from the sum of the stabilization energies of the individual substituents. A theoretical study of radical substituent effects reported early in 1980 that no extra stabilization in captodative radicals could be observed[90]. Later in 1980, Schleyer and coworkers[91] further examined the synergetic captodative stabilization of radicals using unrestricted Hartree–Fock *ab initio* molecular orbital theory using the split valence 4-31G basis and geometry optimization. Among others, the H_2NCHCN radical was studied. The stabilizations of NH_2CH_2 and $NCCH_2$ relative to CH_3 are 10.2 and 12.5 kcal mol^{-1}, respectively, whereas that for H_2NCHCN is 26.1 kcal mol^{-1}, more than the sum of the previous two stabilizations. Schleyer concludes that the captodative effect can lead to extra stabilization of disubstituted radicals, and ascribes the difference with the earlier work[90] to the absence of geometry optimization.

Schleyer[91] employs perturbation molecular orbital theory to rationalize the effect (Figure 1). Figure 1(a) and (c) shows the interaction between a singly occupied molecular orbital (SOMO) with a vacant acceptor orbital, A, and with a filled donor orbital, D, respectively. As can be observed, the former results in stabilization through a one-electron interaction, while the latter, through a three-electron interaction, produces a doubly occupied orbital of lower energy and a singly occupied orbital of higher energy than the unperturbed SOMO. In Figure 1(b) the interaction of the donor-substituted radical orbital ψ_2 with the acceptor orbital, A, produces a more effective stabilization than in the monosubstituted radical, since the energy separation between ψ_2 and A in Figure 1(b) is smaller than that between the SOMO and A in Figure 1(a).

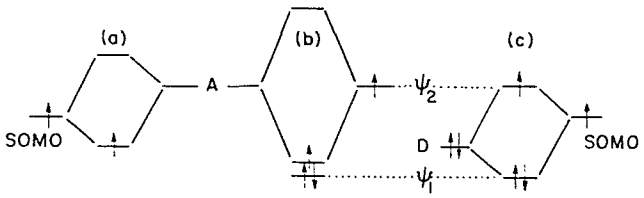

FIGURE 1. Interaction of an unperturbed radical orbital (SOMO), (a) with a vacant acceptor orbital, A, and (c) with a filled donor orbital, D. The latter results in a new singly occupied orbital, ψ_2. Captodative stabilization by interaction of ψ_2 with A is shown in (b). Reprinted with permission from D. Crans, T. Clark and P. von R. Schleyer, *Tetrahedron Letters*, **21**, 3681 (1980). Copyright (1980) Pergamon Press, Ltd.

VIII. THE CYANIDE–ISOCYANIDE ISOMERIZATION

The thermal isomerization of isocyanides to nitriles, while known for nearly 75 years[92], has found increased interest from both experimental and theoretical chemists in the last 25 years. The isomerization of *p*-tolyl isocyanide in solution and in the vapour phase[93] and of methyl[94] and methyl-d_3 isocyanides [95] in the gas phase has been shown to be unimolecular and first order. The large activation energies (33.8–38.4 kcal mol^{-1}) found experimentally for these reactions could be interpreted as suggesting bond scission. On the other hand the isomerization of *p*-tolyl isocyanide produced only *p*-toluonitrile, thus implying a continuity in the bond-breaking and bond-making processes. An increase in bond organization in the transition state was also suggested from the slightly negative entropy of activation.

Casanova, Werner and Schuster[96] have studied the isomerization in a series of aryl and alkyl isocyanides. Their results suggested that bond breaking and bond making are essentially synchronous, and that little charge separation develops in the transition state.

A. The HCN–HNC Isomerization

Van Dine and Hoffmann[97] appear to have been the first to examine the cyanide–isocyanide isomerization theoretically, in their case by employing the extended Hückel method. Since much of their work has concentrated on the methyl and phenyl cyanide–isocyanide isomerization, further discussion of their contributions will be reserved for a later section. Booth and Murrell[98], employing an *ab initio* SCF method, calculated an isomerization barrier of 2.97 eV (77.4 kcal mol^{-1}) from the cyanide, corresponding to an optimized saddle-point CN distance of 1.23 Å. SCF calculations with a double-zeta plus polarization basis set, that is with two basis functions for each orbital in an occupied shell and one additional set of polarization functions on each nucleus, have also been applied to a study of the HCN–HNC isomerization[99]. The saddle point was found at 70.2°, significantly closer to HCN than HNC, where the angle refers to that between the CN bond and the line joining the hydrogen atom and the centre of mass of the CN bond. The barrier height from HNC is calculated as 40.2 kcal mol^{-1}. Configuration interaction calculations[99] yield 73.7° for the angle and 34.9 kcal mol^{-1} for the barrier height. In addition to their interest in connection with the HCN–HNC process, these results are also valuable in demonstrating the relative accuracy of SCF calculations in comparison with configuration interaction results.

Triple-zeta quality basis sets have also recently been employed in calculations on HCN–HNC[100]. In the transition state the hydrogen is positively charged by 0.2, while the nitrogen is negatively charged by the same amount, and the carbon is neutral. These calculations find a barrier of 64 kcal mol^{-1} from the cyanide. An alternative intermolecular mechanism has also been considered[100], involving the interaction of a HCN molecule with the nitrogen atom of a cyanide ion. An activation barrier of 60 kcal mol^{-1} is calculated.

Vazquez and Gouyet[101] have examined the possibility that, in addition to thermal isomerization of HNC–HCN on the ground-state surface, an alternative isomerization mechanism involving the excited $2^1A'$ state may also produce HNC. Configuration interaction calculations produced a barrier of 3.1 eV from the cyanide and a separation of 0.8 eV between the cyanide and isocyanide. Thus it appears that there is negligible isomerization probability at room temperature. The isomerization becomes significant at 1000 K, a temperature at which HNC has been found in the laboratory. At room temperature the mole ratio of HNC/HCN is only approximately 10^{-4}, thus suggesting that thermal isomerization of HCN in the ground state may be important only at high temperatures. The height of the barrier to isomerization from the isocyanide makes the isocyanide to cyanide process at room temperature improbable. The frequency for hydrogen atoms surmounting this barrier is approximately 10^{-13} s^{-1}. Consequently, at room temperature at least, HNC should be relatively stable.

No barrier to isomerization was found for the $2^1A'$ surface, and the hydrogen can shift from the carbon to the nitrogen atom by an exothermic process, forming HNC[101]. The $2^1A'$ and the ground state $\tilde{X}^1A'$ surfaces approach most closely for an HNC angle of approximately 125°, where a transition from the electronically excited HNC to the HNC ground state would be favoured.

B. The MeCN–MeNC Isomerization

The isomerization of methyl isocyanide is one of the most studied unimolecular reactions from both experimental and theoretical points of view. It has been noted that Rabinovitch[94,95] provided the earliest data on this reaction. More recently Rabinovitch and coworkers[102] have studied the inert gas effect on the methyl isocyanide isomerization. Pritchard and coworkers have analysed thermal explosion data for methyl isocyanide[103] and unimolecular fall-off data for the isomerization[104].

Van Dine and Hoffmann[97] have employed the extended Hückel method to study the isomerization which was interpreted as taking place through a rotation of the methyl group about the centre of the CN bond. The peak of the activation barrier occurs at 88°, that is when the methyl group is approximately equidistant from the C and N of the CN group. Minima appear in the energy expressed as a function of the distance of the methyl group from the centre of the CN bond, irrespective of the value of θ. The positive charge on the methyl carbon atom is increased in the transition state and the methyl group is converted to trigonal symmetry. The bonding in the transition state between the methyl carbon and the C and N of the CN group is primarily of σ type.

It is of interest to note that the phenyl cyanide–isocyanide isomerization appears to take place by what Van Dine and Hoffmann[97] label as a π route, in which the plane of the phenyl ring remains perpendicular to the plane defined by CN and the bonded phenyl carbon.

Semiempirical calculations employing the MINDO/2 method produced an activation energy of 34.3 kcal mol^{-1} [105], while CNDO/2 calculations predicted a value of 32.9 kcal mol^{-1} [106] for the same quantity, compared to the experimental values of 38.4 kcal mol^{-1} [94] or the more recent value of 38.2 ± 0.2 kcal mol^{-1} [107]. From the

CNDO calculations a charge separation equivalent to $[CH_3^{+0.22}][NC^{-0.22}]$ was found for the intermediate as compared with $[CH_3^{+0.08}][CN^{-0.08}]$ and $[CH_3^{+0.12}][CN^{-0.12}]$ for the cyanide and isocyanide, respectively.

Partitioning of the energies into various component terms is often quite instructive[106]. The quantity which may be taken as characteristic of the chemical bond AB is $E_{AB}{}^R$ (equation 12), where the summation extends over all orbitals μ and ν

$$E_{AB}{}^R = 2 \sum_{\substack{\mu \epsilon A \\ \nu \epsilon B}} S_{\mu\nu} \beta_{\mu\nu} P_{\mu\nu} \tag{12}$$

associated with atoms A and B, respectively, $P_{\mu\nu}$ and $S_{\mu\nu}$ are the $\mu\nu$th elements of the bond order and overlap matrices, respectively, and $\beta_{\mu\nu}$ is a parameter occurring in the CNDO method. The CNDO energies calculated for the cyanide, isocyanide and

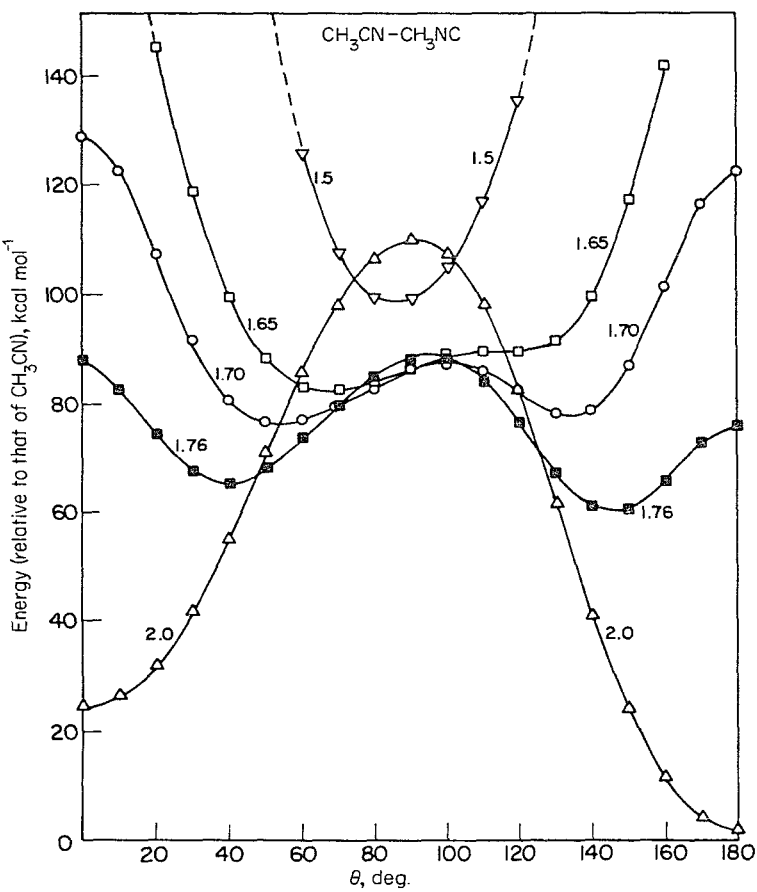

FIGURE 2. Energy relative to that of methyl cyanide for various orientations and distances of the methyl group with respect to the CN bond. The abscissa represents the angle (θ) made by the CN bond and the line R joining its centre and the carbon atom of the methyl group. The various values of R are shown on the figure. Reproduced by permission of North-Holland Publishing Company, Amsterdam from J. B. Moffat, *Chem. Phys. Letters*, **55**, 125 (1978).

intermediate were partitioned to yield $E_{AB}{}^{R}$ values[106]. For the transition state, the decrease in magnitude of the $E_{AB}{}^{R}$ value for the CN bond reflects a decrease in the triple-bond character of the nitrile. The values for the bond between the methyl carbon and the nitrile carbon, and the former and the nitrile nitrogen are both of substantial magnitude, suggesting that the intermediate can be viewed as a three-membered ring structure. In fact the magnitudes of these values are similar to those expected for the corresponding single bonds. Further decomposition of the $E_{AB}{}^{R}$ values shows a substantial portion of such single bonds to result from π-electron contributions.

Ab initio calculations with a set of four s and two p functions on C and N and two s functions on H produced a heat of isomerization of 17.4 kcal mol^{-1} and a transition energy of 58.8 kcal mol^{-1} [107]. The transition state was shown to involve a pyramidal group (HĈX angle 106°) with a methyl carbon more positively charged than that in either the cyanide or isocyanide.

Ab initio (STO-3G) geometry-optimized calculations[108] predict an energy of isomerization of 24.1 kcal mol^{-1} and a transition barrier of 87.8 kcal mol^{-1}. Pritchard and coworkers[109] have reported an enthalpy of isomerization of 23.7 ± 0.14 kcal mol^{-1}. The changes in energy (relative to that for methyl cyanide) for various orientations and distances of the methyl group with respect to the CN bond are shown in Figure 2.

Many-body perturbation theory has been applied to a study of the methyl cyanide–isocyanide isomerization[110]. Single, double and quadruple excitations are included in the calculations with double-zeta plus polarization contracted Gaussian basis sets. The enthalpy of isomerization and the activation barrier were predicted to be 22.7 and 41 kcal mol^{-1}, respectively.

C. Other Cyanide–Isocyanide Isomerizations

The isomerization energy of vinyl cyanide is predicted to be 17.7 kcal mol^{-1} with a 6-31G basis set[111] and geometry optimization. The barrier from the cyanide is 87.5 kcal mol^{-1}. In the transition state the carbon of the vinyl group nearest to the centre of the CN bond is approximately 1.7–1.8 Å from that centre. The ionic character of the transition state is considerably less than that in either the cyanide or isocyanide.

The isomerization of trifluoromethyl cyanide has been studied and the results compared with those found for methyl cyanide[108]. With an STO-3G basis set and geometry optimization, the energy of isomerization is calculated to be 11.5 kcal mol^{-1}, approximately one half the value found for methyl cyanide with the same quality of calculation. The transition energy is 80.0 kcal mol^{-1}, not appreciably different from the 87.8 kcal mol^{-1} found in the case of methyl cyanide. The changes in energy (relative to that of trifluoromethyl cyanide) for various orientations and distances of the trifluoromethyl group with respect to the CN bond are shown in Figure 3. As with vinyl cyanide, the distance of the trifluoromethyl carbon atom from the centre of the CN bond in the transition state is approximately 1.7–1.8 Å.

Figure 4 shows the LUMO and HOMO energies for the cyanides, isocyanides and transition-state species for both methyl and trifluoromethyl cyanide. As expected, the highest occupied molecular orbitals and lowest unoccupied molecular orbitals of both methyl and trifluoromethyl cyanide are of π symmetry. In the cyanides the orbitals immediately below the HOMO are of σ symmetry. In the isocyanides the HOMO are again of π symmetry, but now the LUMO are of σ symmetry and the orbitals immediately below the HOMO are of σ symmetry. From Figure 4 it can be seen that a small increase of LUMO (π^*) energy occurs on isomerization of either cyanide and an even smaller decrease occurs in the energy of the occupied π orbital. However, the

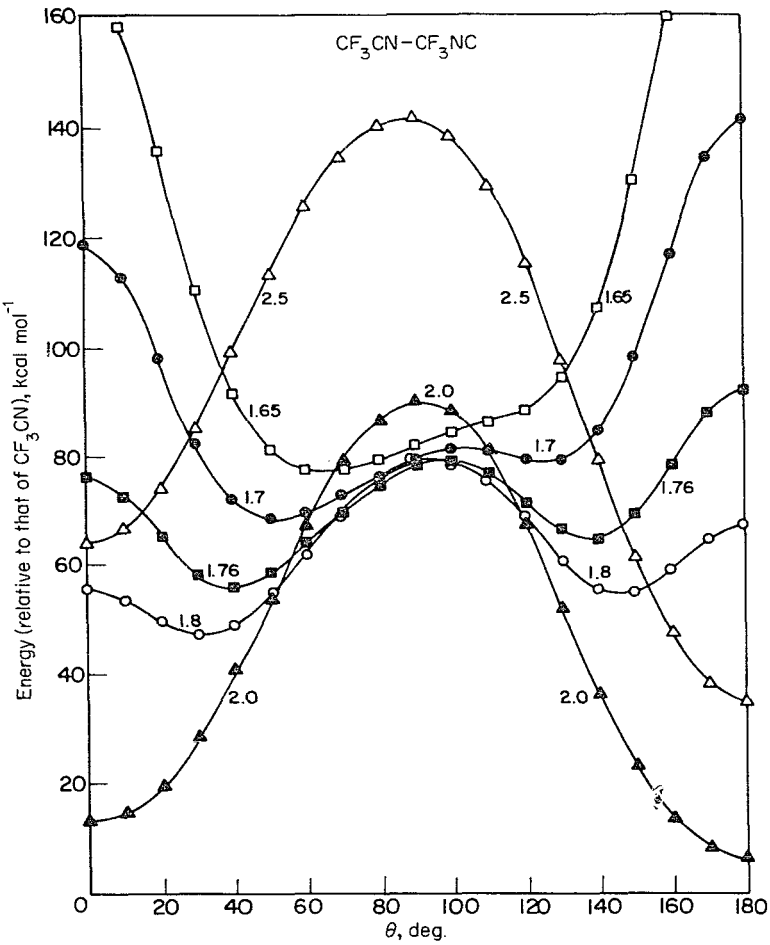

FIGURE 3. Energy relative to that of trifluoromethyl cyanide for various orientations and distances of the trifluoromethyl group with respect to the CN bond. The abscissa represents the angle (θ) made by the CN bond and the line R joining its centre and the carbon atom of the trifluoromethyl group. The various values of R are shown on the figure. Reproduced by permission of North-Holland Publishing Company, Amsterdam from J. B. Moffat, *Chem. Phys. Letters*, **55**, 125 (1978).

energy of the occupied σ orbital increases substantially and crosses that of the occupied π orbital so that the occupied σ orbital becomes the HOMO in both the transition states and the isocyanides. The LUMO in the transition states is also a σ orbital. Substitution of fluorine for hydrogen produces a stabilization of the highest occupied π orbital (HOMO) in the cyanide and a stabilization of both the highest occupied σ and π orbitals in both the transition state and isocyanide. In contrast the highest occupied σ orbital in the cyanide remains essentially unchanged in energy. This appears to be the reverse of the so-called perfluoro effect which has been observed in planar ethylenic molecules[112].

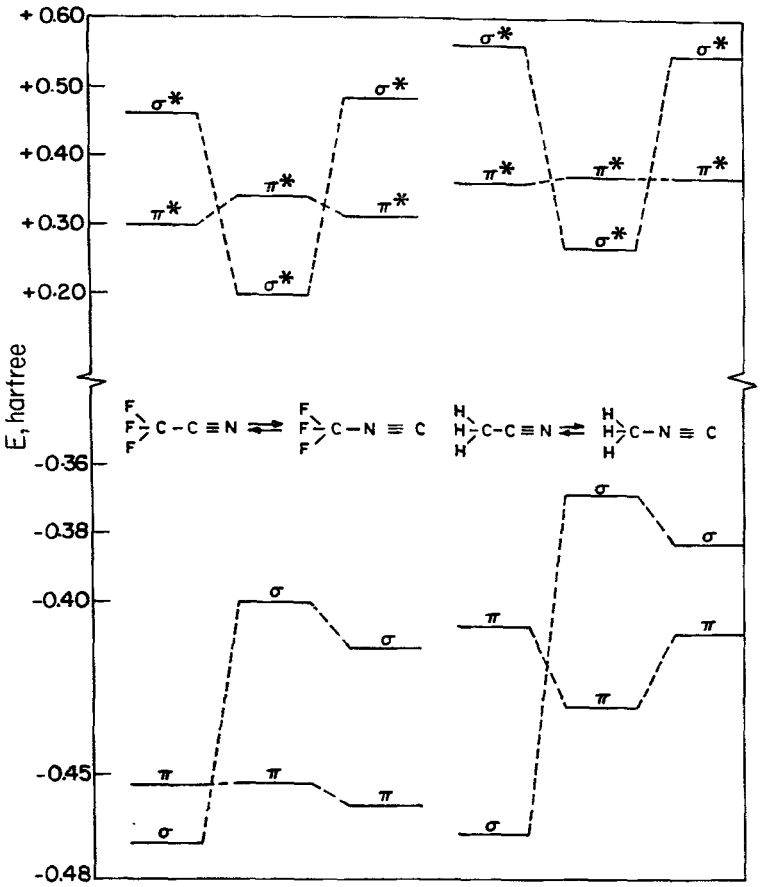

FIGURE 4. LUMO and HOMO energies for methyl and trifluoromethyl cyanides, isocyanides and transition-state species. Reproduced by permission of North-Holland Publishing Company, Amsterdam from J. B. Moffat, *Chem. Phys. Letters*, **55**, 125 (1978).

Table 8 summarizes the fraction of ionic character as obtained from a Mulliken population analysis for methyl and trifluoromethyl cyanides and isocyanides. As can be seen the ionic character in the isocyanides and transition states is quite similar but approximately twice that for the cyanides. The overlap populations of the nitrile bond are approximately identical in the methyl and trifluoromethyl molecules. In contrast the σ overlap population for the isocyanide bond is considerably larger in methyl isocyanide than in trifluoromethyl isocyanide, while the π overlap populations are similar in both isocyanides. The π overlap populations for the transition states suggest the existence of some π bonding between the carbon of the methyl or trifluoromethyl group and the carbon and nitrogen atoms of the nitrile group.

Propyl cyanide and isocyanide are found to differ in energy by 21.1 kcal mol^{-1}, no matter what conformation is assumed for the cyanide and isocyanide[113]. The fractional charge for the cyanide is 0.14 while that for the isocyanide is 0.24, only slightly higher than observed for methyl cyanide.

TABLE 8. Ionic character of cyanides, isocyanides and transition state[108]

Molecule	Ionic character
Methyl cyanide	+0.12
Methyl isocyanide	+0.23
Transition state	+0.21
Trifluoromethyl cyanide	+0.10
Trifluoromethyl isocyanide	+0.20
Transition state	+0.21

It is apparent, not surpisingly, that the energies of cyanide–isocyanide isomerization are dependent on the substituent group to which the cyanide is attached[114]. To examine the influence of such substituent groups it appears advantageous to study a number of isoelectronic substituents. It is well known that a partial cancellation of errors resulting from the use of minimal basis sets occurs in calculation of changes in

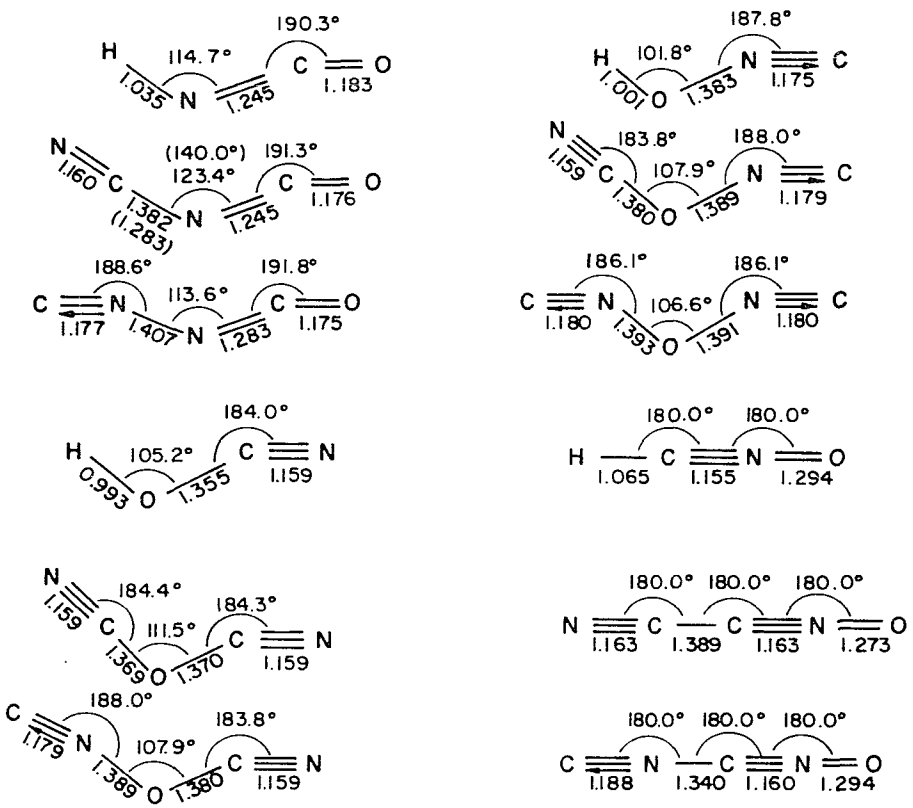

FIGURE 5. Optimized structures of the isomers of HNCO and its cyanides and isocyanides (STO-3G basis). Reproduced with permission from J. B. Moffat, *Intern. J. Quantum Chem.*, **15**, 547 (1979).

energy during a process such as isomerization. However, comparisons between substituent groups would be rendered less reliable in changing substituent groups to preserve their isoelectronic nature. However, if a substituent group is selected which is itself capable of isomerization, the comparison of results will be rendered more meaningful. Cyanogen isocyanate (NCNCO) was chosen as an example[114]. Since the isocyanate group has four structurally isomeric forms, the cyanide–isocyanide isomerization is examined for four isoelectronic cyanide–isocyanide pairs, where the substituent groups are altered only by structural rearrangement (equations 13–16).

$$NC{-}NCO \rightleftharpoons CN{-}NCO \quad (13)$$

$$NC{-}OCN \rightleftharpoons CN{-}OCN \quad (14)$$

$$NC{-}CNO \rightleftharpoons CN{-}CNO \quad (15)$$

$$NC{-}ONC \rightleftharpoons CN{-}ONC \quad (16)$$

The optimized structures of the cyanides and isocyanides of HNCO are shown in Figure 5. It is of some interest to note the predicted bending in many of the XCN and XNC bonds, in particular those where X is either O or N. The optimized configurations for the transition states are shown in Figure 6. These were obtained by assuming a

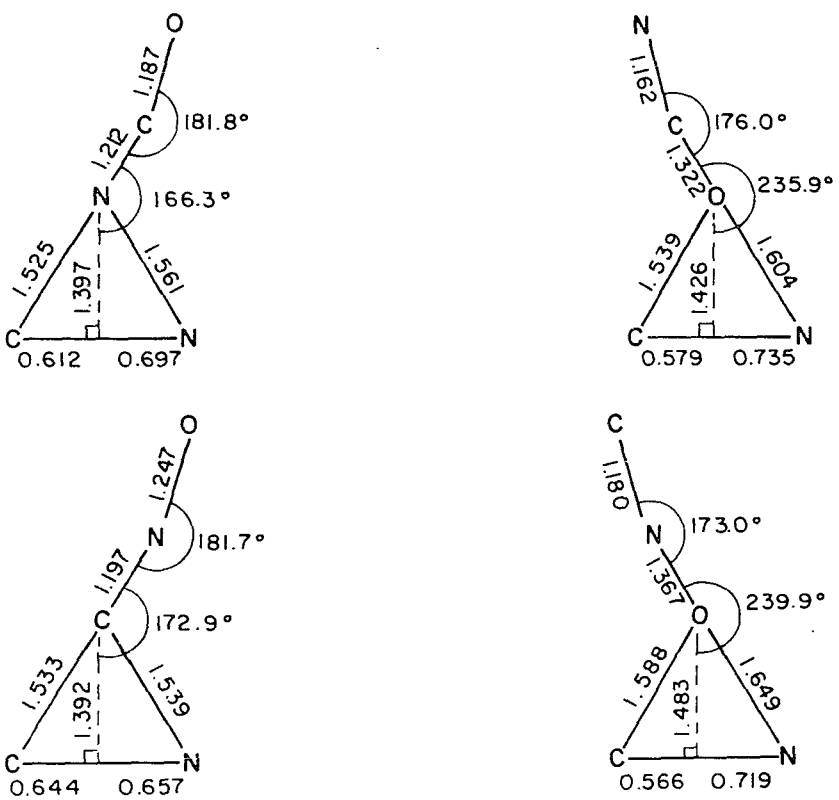

FIGURE 6. Optimized configurations for the transition states in the isomerization of the isomers of cyanogen isocyanate. Reproduced with permission from J. B. Moffat, *Intern. J. Quantum. Chem.*, **15**, 547 (1979).

simple triangular configuration of the CN bond and the substituent group atom nearest the CN bond.

The calculated energies of the hypothetical transition states differ from each other by as much as 60 kcal mol^{-1}. The transition state barriers also differ by as much as 40 kcal mol^{-1} (Figure 7 and Table 9).

Since the atomic composition of each of the substituent groups is identical, the changes in the energies of isomerization and in the transition state barriers must reflect, at least in part, the variations in the distribution of electron density within the molecule. As a first approximation, although these perturbations are produced by changes within the substituent groups, they will be reflected in the cyanide or isocyanide groups themselves. It can then be postulated that the activation barrier can be considered as generated by the alteration in charge in passing from the cyanide to

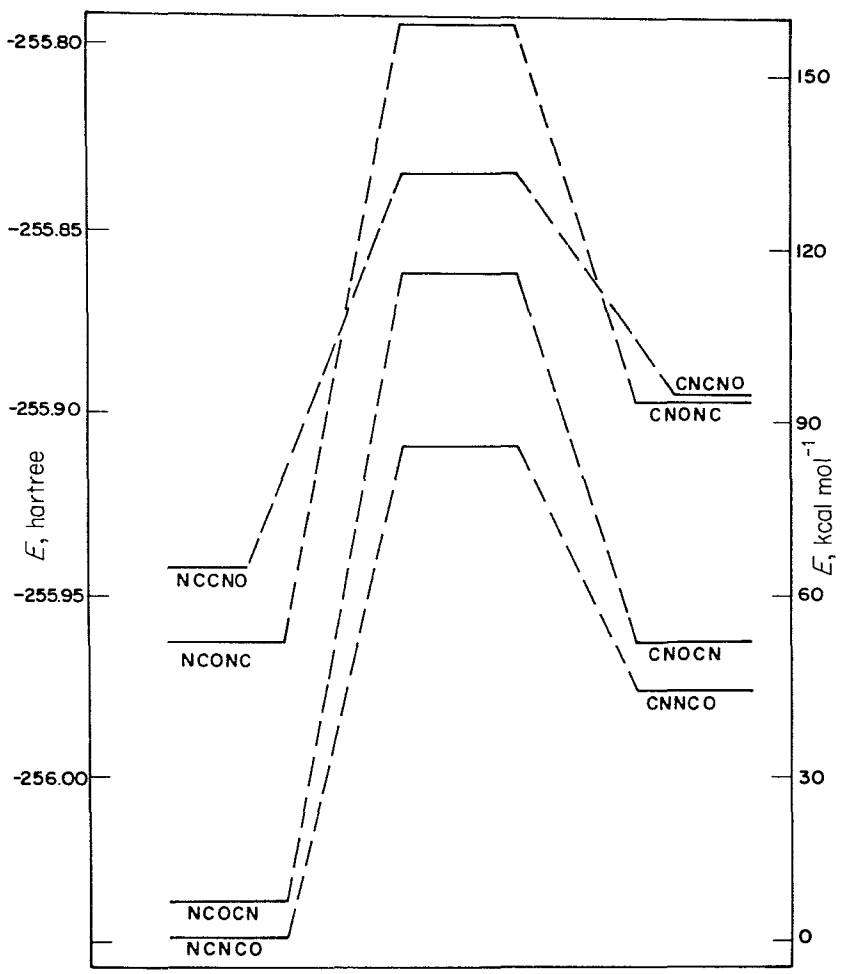

FIGURE 7. Cyanogen isocyanate and its isomers. Electronic energies of the optimized structures of the cyanides, isocyanides and transition states. Reproduced with permission from J. B. Moffat, *Intern. J. Quantum Chem.* **15**, 547 (1979).

TABLE 9. Energies of isomerization and energy barriers for the cyanide–isocyanide reaction[a]

Isomerization reaction	Energy of isomerization (kcal mol^{-1})	Energy barrier for isomerization (kcal mol^{-1})
NCCNO ⟶ CNCNO	29.8	67.5
NCNCO ⟶ CNNCO	42.2	84.3
NCONC ⟶ CNONC	41.4	106.8
NCOCN ⟶ CNOCN	44.6	107.9

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the transition state, plus the subsequent change in passing to the isocyanide. The activation barriers can be seen to correlate approximately with the sums of the absolute values of these two charge differences (Figure 8). For purposes of comparison the points for methyl and trifluoromethyl cyanide have also been added to the figure.

The height of the transition-state barrier in the cyanide–isocyanide isomerization is dependent upon the bonding capabilities of the associated pairs of molecules in the transition state relative to those in the cyanide molecule itself. Consequently, a transition state in which the three atoms of the CNX triangle are relatively strongly bound to each other should possess a greater stability, a lower energy for that state, and consequently, a smaller transition-state barrier. The strength of the binding in the transition state may be related to the overlap populations. The overlap populations of

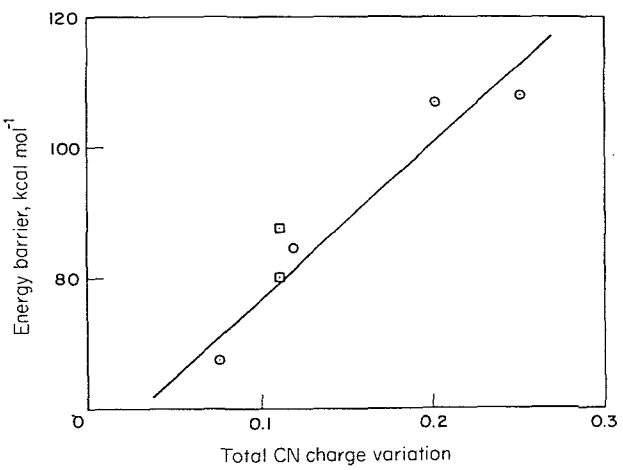

FIGURE 8. Cyanogen isocyanate and its isomers. Energy barriers in the cyanide–isocyanide isomerization versus total CN charge variation (sum of the absolute values of the differences in net charges on CN in the transition state and the cyanide and between the transition state and the isocyanide). The circles correspond to the values found for NCCNO and its isomers. The squares correspond to the values for CH_3CN and CF_3CN. Reproduced with permission from J. B. Moffat, *Intern. J. Quantum Chem.*, **15**, 547 (1979).

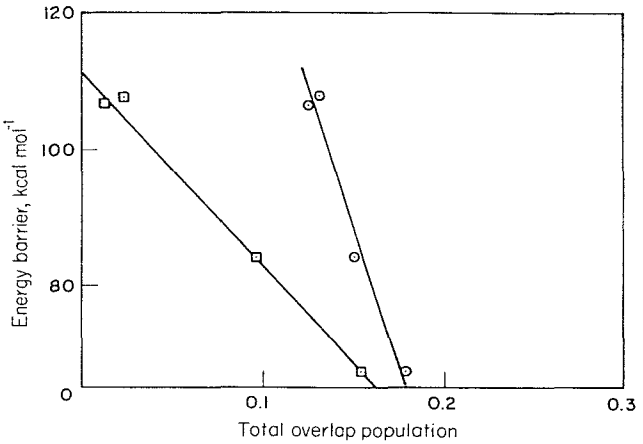

FIGURE 9. Cyanogen isocyanate and its isomers. Energy barrier versus total overlap population for CX (⊙) and NX (⊡), where X is the atom of the substituent group nearest to the CN bond. Reproduced with permission from J. B. Moffat, *Intern. J. Quantum Chem.*, **15**, 547 (1979).

the CN pairs are approximately the same for each of the four transition states, while those of both CX and NX decrease as the size of the barrier increases, the latter reflecting a decreasing binding between the CN pair and the substituent CNO isomeric group. Figure 9 shows that the transition-state barrier decreases in an approximately linear manner as the total overlap population increases.

Correlation effects have been studied in HCN, LiCN, BCN and the corresponding isocyanides[115]. The isomerization energy and activation barrier for HCN are calculated as 15 ± 2 kcal mol^{-1} and 30 kcal mol^{-1}, respectively. LiNC and BNC are found to be more stable than the corresponding cyanides by 3.9 and 12.4 kcal mol^{-1}, respectively.

Ab initio calculations on the isomers of diazomethane[116] have included cyanamide and isocyanamide. Geometry-optimized energies with STO-3G and 6-31G basis sets show that isocyanamide is 46.9 and 37.9 kcal mol^{-1}, respectively, higher in energy than cyanamide, with diazomethane lying still higher in energy (Figure 10).

Ab initio calculations and the self-consistent electron pairs (SCEP) method have been employed[117] to show that isocyanamide is 53 kcal mol^{-1} less stable than cyanamide, with 11 kcal mol^{-1} of this being due to correlation energy. The activation barrier from isocyanamide is 46 kcal mol^{-1}, corresponding to 98 kcal mol^{-1} from cyanamide, a value which is of approximately the same size as that found for the barriers with NCONC and NCOCN[114].

The energies of isomerization of methyl, ethyl and isopropyl cyanides and isocyanides, and the corresponding cations formed on abstraction of an α-hydride ion are summarized in Table 10[118]. Values shown have been obtained by *ab initio* calculations with an STO-3G basis set. The energy changes for the neutral molecules are very similar, while those for the carbonium ions reflect the stabilization by substitution with isocyano groups and the destabilization by cyano groups. In the neutral molecules the charge on the cyano and isocyano groups is always negative, while in the carbonium ions these groups are positively charged. The differences in the charges on the cyano and isocyano groups for a given substituent group is always negative, that is, the charge on the isocyanide group is in all cases less than that on the cyanide group in the corresponding molecule. However, these charge differences are

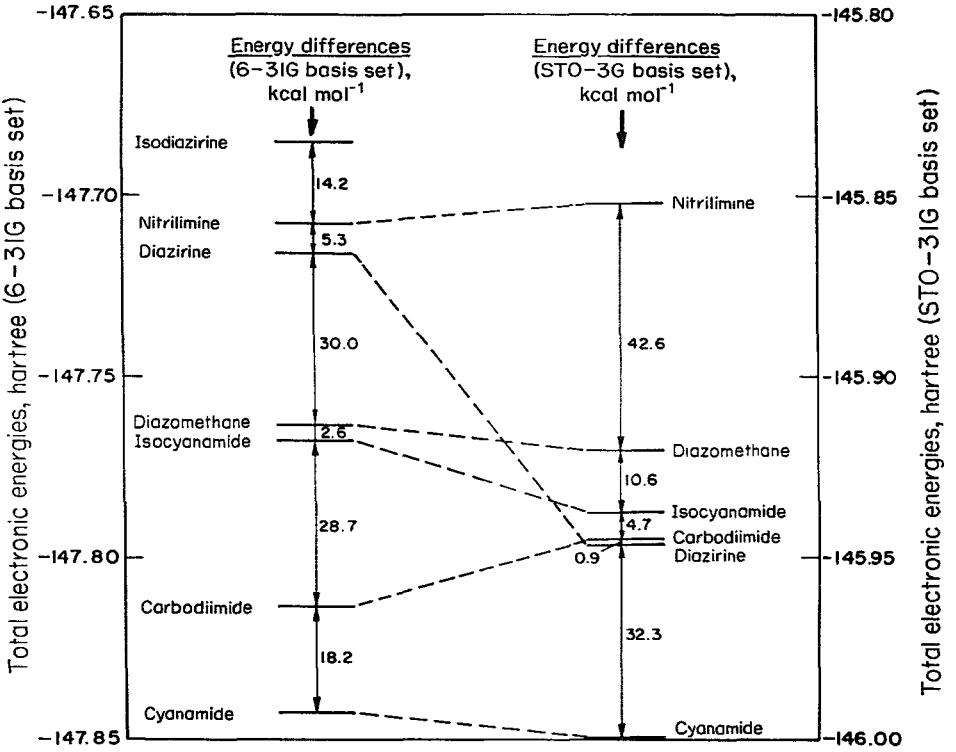

FIGURE 10. Total electronic energies and energy differences calculated with STO-3G and 6-31G basis sets for the isomers of diazomethane. Reproduced by permission of Elsevier Scientific Publishing Company, Amsterdam from J. B. Moffat, *J. Mol. Struct.*, **52**, 275 (1979).

approximately the same for the neutral molecules and for the charged molecules, but approximately half the magnitude for the latter species. It may be concluded that the energy of isomerization is at least in part related to the shift in electron density which occurs in the isomerization process.

TABLE 10. Energies for cyanide–isocyanide isomerization[a]

Cyanide		isocyanide	ΔE (kcal mol^{-1})	Charge on CN or NC		
				Cyanide	Isocyanide	Δ Charge
CH_3CN	⟶	CH_3NC	24.1	−0.123	−0.234	−0.111
C_2H_5CN	⟶	C_2H_5NC	22.3	−0.135	−0.247	−0.112
C_3H_7CN	⟶	C_3H_7NC	22.0	−0.145	−0.254	−0.109
CH_2CN^+	⟶	CH_2NC^+	−1.4	+0.286	+0.230	−0.056
$C_2H_4CN^+$	⟶	$C_2H_4NC^+$	0.7	+0.204	+0.157	−0.047
$C_3H_6CN^+$	⟶	$C_3H_6NC^+$	2.4	+0.143	+0.095	−0.048

[a]Reproduced with permission from J. B. Moffat, *Intern. J. Quantum Chem.*, **19**, 771 (1981).

IX. THE CHEMICAL BOND IN CYANO MOLECULES

While the calculation of accurate wave functions for systems of chemical interest is of obvious importance in any theoretical treatment of molecules, the interpretation of such data in terms of classical chemical concepts presents an even greater challenge.

The method most frequently employed to extract chemical information from molecular wave functions is that due to Mulliken[119], and often referred to as a population analysis. This technique provides information on the charge densities and overlap populations in a molecule. The method is not without its difficulties, however, but these will not be discussed here.

There have been a number of more recent attempts to describe the nature of the bonds in a molecule by the use of the calculated wave functions. In one of these a procedure has been proposed for partitioning the molecular density ρ, pair density π and molecular energy E[120]. The atoms involved in the formation of a molecule are

TABLE 11

(a) Energy-partitioning noninterference bond components (eV)[a,b]

Bond	System	QCN	QCT	SPN	SPT	QC	SP	VS
Li—H	LiH	1.0	−0.4	−11.3	7.1	−1.4	−4.3	−5.7
B—H	BH	−1.9	−0.5	−6.6	0.9	−2.4	−5.8	−8.2
N—H	NH	−1.2	−1.4	−16.5	11.3	−2.6	−5.2	−7.8
F—H	HF	−1.7	0.3	−6.1	−0.6	−1.4	−6.8	−8.2
—O—H	H_2O	−2.2	−0.5	−8.8	2.0	−2.6	−6.8	−9.4
≡C—H	HCN	−3.4	0.3	−6.0	−1.0	−3.1	−7.1	−10.2
Li—Li	Li_2	−1.1	0.0	−2.8	0.0	−1.1	−2.8	−3.9
Be—Be	Be_2	−1.9	0.0	−2.5	0.0	−1.9	−2.5	−4.4
F—F	F_2	0.0	0.0	−6.0	0.0	0.0	−6.0	−6.0
F—C≡	FCN	−3.7	0.5	−7.8	−0.2	−3.2	−8.0	−11.2
≡C—C≡	C_2N_2	−6.5	0.2	−7.8	0.1	−6.3	−7.7	−14.1
C=C	C_2	−1.9	0.0	−15.8	0.0	−1.9	−15.8	−17.6
C≡N	CN^-	−9.2	2.2	−34.4	16.0	−7.0	−18.4	−25.4
—C≡N	HCN	−6.6	−1.3	−18.7	−0.6	−7.9	−19.3	−27.1
	FCN	−6.7	−0.1	−19.0	1.8	−6.9	−17.3	−24.2
	C_2N_2	−8.2	−0.0	−18.7	0.3	−8.2	−18.4	−26.6
N≡N	N_2	−5.6	0.0	−20.2	0.0	−5.6	−20.2	−25.9

[a] QCN refers to the 'quasi-classical neutral' contribution to the pair density, i.e.:

$$\pi^{QCN}(AB) = \rho^{PR}(A)\rho^{PR}(B)$$

which is the density of electron pairs where one electron is from promoted atom A and the other from promoted atom B. $\rho^{PR}(A)$ is the density of atom A in the promoted state.

QCT refers to the change in ${\pi_C}^{QCN}(AB)$, the coulombic part of $\pi^{QCN}(AB)$, due to modification of $\rho^{PR}(A)$ by $\rho^{T}(A)$:

$${\pi_C}^{QCT}(AB) = [\rho^{PR}(A) + \rho^{T}(A)][\rho^{PR}(B) + \rho^{T}(B)] - \rho^{PR}(A)\rho^{PR}(B).$$

SPN refers to ${\pi_X}^{SPN}(AB)$, the change in the electron pair density between atoms A and B due to sharing penetration.

SPT refers to ${\pi_X}^{SPT}(AB)$, the change in sharing penetration after charge transfer.

QC is the sum of the neutral and charge-transfer components of the quasi-classical pair density.

SP is the sum of the neutral and charge-transfer components of the sharing penetration.

VS is the sum of the previous two terms, QC and SP, and refers to the valence state of the particular bond.

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(b) Energy-partitioning interference components (eV)[a,b]

Bond	System	Intrabond SIN	Intrabond SIT	Interbond SIN	Interbond SIT	SI	SI + VS
Li—H	LiH	−1.7	0.0			−1.7	−7.4
B—H	BH	−2.2	0.1			−2.0	−10.2
N—H	NH	−8.1	0.1			−8.0	−15.8
F—H	HF	−6.3	−0.3			−6.6	−14.8
—O—H	H_2O	−10.8	−0.5	1.3	0.1	−9.9	−19.3
≡C—H	HCN	−4.5	−0.1	0.6	−0.0	−4.1	−14.2
Li—Li	Li_2	0.4	0.0			0.4	−3.5
Be—Be	Be_2	−1.0	0.0			−1.0	−5.4
F—F	F_2	−11.1	0.0			−11.1	−17.1
F—C≡	FCN	−11.0	−0.1	0.9	−0.1	−10.3	−21.5
≡C—C≡	C_2N_2	−6.0	−0.1	2.5	−0.1	−3.5	−17.5
C=C	C_2	−19.4	0.0			−19.4	−37.0
C≡N	CN^-	−15.3	−0.1			−15.3	−40.7
—C≡N	HCN	−17.4	0.1	0.4	0.1	−16.8	−43.9
	FCN	−17.5	−0.1	0.7	−0.0	−16.9	−41.1
	C_2N_2	−17.7	−0.0	0.9	0.0	−16.8	−43.4
N≡N	N_2	−19.8	0.0			−19.8	−45.6

[a]Intrabond SIN refers to

$$E^{SIN}(AB, A) + E^{SIN}(AB, B)$$

which is the energy derived from the change in π_C due to electron pairs where one electron is associated with the promotion density $\rho^{PR}(C)$, the other with the interference density $\rho^{I}(AB)$:

$$\pi_C{}^{SIN}(AB, C) = 2\rho^{PR}(C)\rho^{I}(AB)$$

Intrabond SIT refers to

$$E^{SIT}(AB, A) + E^{SIT}(AB, B)$$

which is the energy associated with the change in π_C due to electron pairs where one electron is associated with the charge-transfer density $\rho^{T}(C)$, the other with $\rho^{I}(AB)$:

$$\pi_C{}^{SIT}(AB, C) = 2\rho^{T}(C)\rho^{I}(AB)$$

The interbond terms SIN and SIT refer to

$$\sum_{C(\neq A,B)} E^{SIN}(AB, C)$$

and

$$\sum_{C(\neq A,B)} E^{SIT}(AB, C), \text{ respectively.}$$

The term SI represents the sum of the previous four columns, i.e. the total sharing interference energy.

The column labelled SI + VS is the sum of the previous column and the last column of Table 11(a).

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taken initially in their ground states at infinite separation. Since the electrons of one atom are independent of those on another, the pair densities can be labelled as 'quasi-classical'. The next step in the conceptual formation of the molecule requires the atoms to be promoted to certain 'promotion states' with the atoms remaining at infinite separation. The promoted atoms are then moved together to their equilibrium

TABLE 12. Partitioned two-centre energies of C≡C bonds in nitriles[a,b]

Molecule	R^c	$E_{CC}{}^V$	$E_{CC}{}^J$	$E_{CC}{}^K$	$E_{CC}{}^N$	$E_\sigma{}^R$	$E_\pi{}^R$	$E_{CC}{}^R$	E_{CC}	$E_{CC}{}^R/E_{CC}$
HC_2CN	2.278[d]	−12.766	6.419	−0.562	7.024	−1.361	−0.9904	−2.351	−2.236	1.051
	2.273[f]	−12.783	6.428	−0.564	7.038	−1.362	−0.9950	−2.357	−2.238	1.053
CH_3C_2CN	2.273[d]	−12.764	6.408	−0.541	7.038	−1.361	−0.9644	−2.326	−2.185	1.065
NCC_2CN	2.251[f]	−12.751	6.356	−0.535	7.109	−1.367	−0.9698	−2.337	−2.158	1.083
	2.249[d]	−12.758	6.359	−0.536	7.115	−1.369	−0.9700	−2.339	−2.159	1.083
NCC_2C_2CN	2.249[f]	−12.766	6.408	−0.541	7.038	−1.369	−0.9640	−2.333	−2.185	1.068
									mean	1.067 ± 0.016

[a] Reprinted with permission from J. B. Moffat and K. F. Tang, *J. Phys. Chem.*, **79**, 654 (1975).
[b] R is the bond length, and the total molecular electronic energy is partitioned as

$$E = \sum_{A} E_A + \sum_{A<B} E_{AB} \qquad \text{(A and B refer to atoms)}$$

and

$$E_{AB} = E_{AB}{}^R + E_{AB}{}^V + E_{AB}{}^J + E_{AB}{}^K + E_{AB}{}^N$$

where the two-centre terms are

$$E_{AB}{}^R = 2 \sum_{\substack{\mu \in A \\ \nu \in B}} P_{\mu\nu} \beta^0_{\mu\nu} S_{\mu\nu}$$

$$E_{AB}{}^V = -P_A V_{AB} - P_B V_{BA}$$

$$E_{AB}{}^J = P_A P_B \tau_{AB}$$

$$E_{AB}{}^K = -\tfrac{1}{2} \tau_{AB} \sum_{\substack{\mu \in A \\ \nu \in B}} P^2_{\mu\nu}$$

$$E_{AB}{}^N = Z_A Z_B / R_{AB}$$

These two-centre terms represent the contribution of the resonance integrals to the energy of the A—B bond, the potential energy of the electrons on atom A in the field of nucleus B and vice versa, the repulsion of the electrons on atoms A and B, the electronic exchange interactions of the electrons on atoms A and B, and the nuclear repulsion energy of the nuclei A and B, respectively.

In these two-centre terms, $P_{\mu\nu}$ represents elements of the bond-order matrix:

$$P_{\mu\nu} = \sum_i n_i C_{i\mu} C_{i\nu}$$

and

$$\psi_i = \sum_\mu C_{i\mu} \phi_\mu$$

where ψ_i is the ith molecular orbital and n_i is the occupation number thereof. Also,

$$P_A = \sum_{\mu \epsilon A} P_{\mu\mu}$$

$S_{\mu\nu}$ is the overlap and $\beta^0_{\mu\nu}$ and τ_{AB} are parameters within the CNDO method.

[c]Bond distances and energies in a.u. except where otherwise specified.

[d]Ref. 134.

[e]Ref. 136.

[f]Ref. 137.

internuclear separations in the molecules without changing the promotion atomic densities or the pair densities. The electron density and pair density for the system are now brought to their values in the molecule by the sharing of electrons between atoms and by the transfer of charge from one atom to another. Two types of sharing effects are postulated, namely sharing penetration and sharing interference, the former arising from the change in the electron–electron repulsion due to the change in the average distance between electrons, the latter from the overlap of the atomic wave functions.

For the method to have chemical significance it would be anticipated that one or more of the terms partitioned out for a given bond should have values for that bond which are similar in all molecules containing that bond. In other words there should exist a partitioned quantity which is characteristic of a given bond. The theory has been applied to the *ab initio* wave functions of a series of nitriles (CN^-, HCN, FCN, C_2N_2)[121]. Values obtained for the bonds in these nitriles and in those of a variety of diatomic molecules are shown in Table 11. It can be readily observed that the sharing interference values for the C≡N bond are quite similar and therefore can be taken as characteristic of the bond. It has also been shown[122] that a correlation exists between the experimentally measured bond energy (or bond dissociation energy) and the intrabond interference energy (Figure 11).

A technique for partitioning of the energies obtained from the semiempirical CNDO method has been devised[123] and applied to a variety of molecules containing CN single, double and triple bonds[124]. The one-electron two-centre energy term within this theory is directly related to the interference energy and should therefore be characteristic of the bond. To illustrate, the values obtained for the C≡C and C≡N bonds are collected in Tables 12 and 13. The similarities of the various values of E_{CC}^R and E_{CN}^R provide evidence in support of the nature of these quantities. This partitioning method has also been applied, as mentioned earlier, to the isomerization

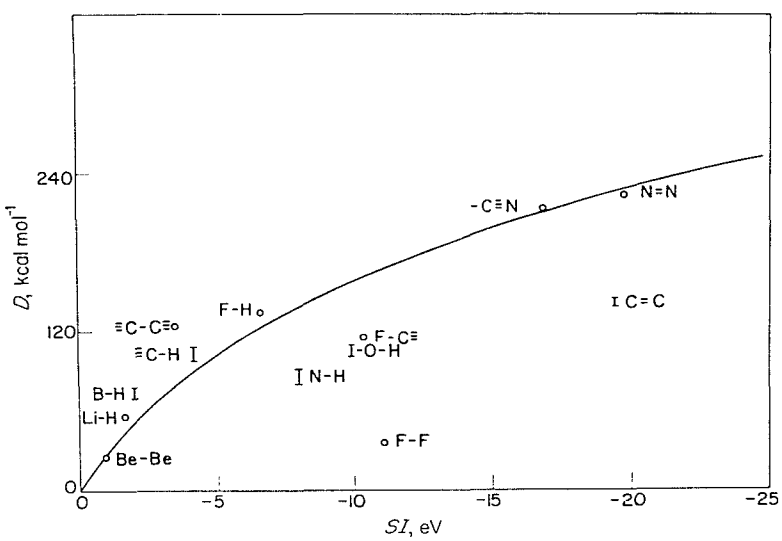

FIGURE 11. Experimental bond dissociation energy (D) versus sharing interference energy (SI). Reproduced by permission of North-Holland Publishing Company, Amsterdam from J. B. Moffat and H. E. Popkie, *Chem. Phys. Letters*, **5**, 331 (1970).

TABLE 13. Partitioned two-centre energies of C≡N bonds in nitriles[a,b]

Molecule	R^c	$E_{CN}{}^V$	$E_{CN}{}^J$	$E_{CN}{}^K$	$E_{CN}{}^N$	$E_\sigma{}^R$	$E_\pi{}^R$	$E_{CN}{}^R$	E_{CN}	$E_{CN}{}^R/E_{CN}$
CH_2CHCN	2.204[e]	−16.961	8.399	−0.594	9.074	−1.362	−0.9483	−2.309	−2.171	1.064
CH_2CHCN	2.198[d]	−16.774	8.415	−0.595	9.100	−1.365	−0.9537	−2.319	−2.173	1.067
HC_2CN	2.189[d]	−16.774	8.363	−0.592	9.135	−1.365	−0.9620	−2.327	−2.165	1.075
$NC(CH_2)CN$	2.188[d]	−16.794	8.408	−0.603	9.139			−2.345	−2.195	1.068
HCN	2.187[h]	−16.865	8.483	−0.627	9.145	−1.367	−1.0076	−2.373	−2.237	1.061
CH_3CN	2.1866[d]	−16.839	8.451	−0.603	9.146	−1.367	−0.9655	−2.342	−2.187	1.071
HC_2CN	2.1864[f]	−16.759	8.371	−0.593	9.147			−2.332	−2.166	1.077
CH_3C_2CN	2.1864[d]	−16.784	8.398	−0.591	9.147	−1.369	−0.9634	−2.332	−2.162	1.079
NCCN	2.1864[d]	−16.715	8.328	−0.594	9.147	−1.370	−0.9676	−2.337	−2.171	1.076
	2.186[g]	−16.718	8.330	−0.594	9.149	−1.370	−0.9679	−2.338	−2.171	1.077
C_2H_5CN	2.1858[d]	−16.861	8.469	−0.605	9.150			−2.349	−2.195	1.071
HCN	2.183[d]	−16.885	8.494	−0.628	9.160	−1.369	−1.0100	−2.379	−2.238	1.063
HCN	2.179[f]	−16.908	8.506	−0.629	9.178	−1.374	−1.0153	−2.389	−2.242	1.066
NCC_2C_2CN	2.154[g]	−16.914	8.442	−0.596	9.284	−1.383	−0.9893	−2.372	−2.156	1.100
NCC_2CN	2.154[d]	−16.903	8.433	−0.597	9.284	−1.383	−0.9907	−2.374	−2.156	1.101
	2.154[g]	−16.903	8.426	−0.597	9.284	−1.386	−0.9920	−2.378	−2.168	1.097
									mean	1.071 ± 0.030

[a] Reprinted with permission from J. B. Moffat and K. F. Tang, *J. Phys. Chem.*, **79**, 654 (1975).
[b] See footnote *b* of Table 12.
[c] Bond distances and energies in a.u. except where otherwise specified.
[d] Ref. 134.
[e] Ref. 135.
[f] Ref. 136.
[g] Ref. 137.
[h] Ref. 69.

of methyl isocyanide[106], the reactive dimerization of HCN[62] and the formation of acrylonitrile and propiolonitrile from acetylene and HCN[125].

A bond strength index has been defined[126] as the sum, over all orbitals between any pair of atoms, of the product of the individual bond order, $P_{\mu\nu}$, and the corresponding overlap integral, $S_{\mu\nu}$, where

$$P_{\mu\nu} = \sum_{i}^{\text{occ}} n_i C_{i\mu} C_{i\nu}$$

and

$$\psi_i = \sum_{\mu} C_{i\mu} \phi_\mu$$

where ψ_i and ϕ_μ are the ith molecular orbital and the μth atomic orbital, respectively. The heat of formation of a molecule can then be written as a linear combination of the bond-strength index for each of the bonds in the molecule. By using the bond additivity method devised by Benson and Buss[127] for the calculation of the values of thermodynamic functions, and extended to provide data for nitriles[128], the heat of formation of nitriles has been correlated to the bond-strength indices in these molecules[129].

A group contribution method for the calculation of electronic correlation energies of molecules has been derived[130]. The correlation energy of a molecule can be taken as the difference between the experimentally measured dissociation energy and that calculated from Hartree–Fock or near-Hartree–Fock calculations plus the atomic correlation energies. Consequently for those molecules where the necessary data is available, molecular correlation energies can be calculated. A linear equation as a function of the number and types of bonds can then be written for a given molecule and set equal to the molecular correlation energy. This can be repeated for a number of molecules containing similar bonds until a sufficient number of equations in the unknowns, the bond correlation energies, is available to permit solution. The bond

TABLE 14. Bond correlation energies[a]

Bond	Correlation energy (hartree)	Source
C—H	−0.0739	CH_4
C—C	−0.1245	C_2H_6
N—H	−0.1204	NH_3
N—N	−0.2213	N_2H_4
C=O	−0.4500	H_2CO
C≡N	−0.4310	HCN
F—C	−0.4354	FCN
C=C	−0.2486	C_2H_4
Cl—C	−0.8150	ClCN
C≡C	−0.3167	C_2H_2
O—H	−0.1790	H_2O
C—O	−0.3503	CH_3OH
O—O	−0.3805	H_2O_2
C—N	−0.2335	$HCONH_2$
C=N	−0.4046	C_2H_5N
B—F	−0.5614	BF_3
B—H	−0.0733	BH_3

[a] Reproduced by permission of Elsevier Scientific Publishing Company, Amsterdam from J. B. Moffat, *J. Mol. Struct.*, **15**, 325 (1973).

TABLE 15. Electronic, dissociation and molecular correlation energies[a] for 32 simple organic molecules[aa]

Molecule	Electronic energy (E_{elec})	ΔH_f^0 (kcal mol^{-1}) at 298 K	Dissociation energy (from ΔH_f^0)	Dissociation energy (from E_{elec})	Molecular correlation energy (calc.)	Molecular correlation energy (estimated, using group method)
FCN	−191.77984[b]	−3[c]	0.4774	0.2810	−0.8664	−0.8664[ab]
HCN	−92.91596[b]	31.2[c]	0.4853	0.3264	−0.5049	−0.5049[ab]
ClCN	−551.82472[b]	31.6[i]	0.4433	0.2533	−1.2460	−1.2460[ab]
N≡C—C≡N	−184.65680[b]	73.84[i]	0.4777	0.7878	−1.0021	−0.9865
H—C≡C—C≡N	−168.5784[b]	90.35[e]	0.9381	0.6116	−0.9885	−0.9461
NH_3	−56.1714[d]	−11.04[e]	0.4436	0.2705	−0.3611	−0.3611[ab]
N_2H_4	−111.1261[d]	+22.75[c]	0.6512	0.3243	−0.7029	−0.7029[ab]
CH_4	−40.1822[d]	−17.895[c]	0.6310	0.4936	−0.2954	−0.2954[ab]
C_2H_2	−76.85397[b]	+54.19[c]	0.6252	0.4767	−0.4645	−0.4645[ab]
C_2H_4	−78.0052[d]	+12.496[c]	0.8562	0.6280	−0.5442	−0.5442[ab]
C_2H_6	−79.1981[d]	−20.236[n]	1.0728	0.8209	−0.5679	−0.5679[ab]
Cyclopropene	−115.7655[d]	+66.6[s]	1.126	0.1996	−0.8179	−0.7932
Cyclopropane	−117.0099[t]	+12.74[i]	1.2938	0.9439	−0.8239	−0.8169
Benzene	−230.463[u]	−19.82[i]	2.1031	1.3313	−1.7198	−1.5627
Methylacetylene	−115.5830[v]	+44.32[i]	1.0790	0.5171	−1.0359	−0.7368
Propene	−116.92656[x]	+4.88[i]	1.3063	0.8607	−0.9196	−0.8165
Cyclobutene	−154.70085[y]	+31.00[i]	1.5382	0.9464	−1.2238	−1.0655
Butadiene	−154.70269[y]	26.33[i]	1.5457	0.9482	−1.2295	−1.0651
H_2O	−76.0594[f]	−57.80[c]	0.3499	0.2500	−0.3579	−0.3579[ab]
H_2O_2	−150.7992[l]	−32.53[c]	0.4030	0.1805	−0.7385	−0.7385[ab]
H_2CO	−113.8917[g]	−27.7[c]	0.5755	0.3229	−0.5978	−0.5978[ab]
HCOOH	−188.6877[h]	−90.49[i]	0.7689	0.3804	−1.0625	−1.0532
CH_3OH	−114.9355[m]	−48.08[i]	0.7725	0.4375	−0.7510	−0.7510[ab]
$HCONH_2$	−168.8684[d]	−44.5[i]	0.8637	0.4695	−0.9982	−0.9982[ab]
HCOF	−212.6841[d]	−90[c]	0.6218	0.2768	−1.0850	−0.9593
CH_3CN	−131.71850[q]	12.7[i]	0.9528	0.4403	−1.0165	−0.7772
C_2H_5N	−132.9726[d]	30.12[d]	1.0890	0.6944	−0.8986	−0.8986[ab]
H_2CCO	−151.4001[r]	−14.60[i]	0.8282	0.2135	−1.1887	−0.8464
Ethylene oxide	−152.8012[d]	−12.19[n]	0.9888	0.6146	−0.9482	−1.1207
BHF_2	−224.0573[w]	−176.59[z]	0.6338	0.2097	−1.1971	−1.1961
BF_3	−322.9018[w]	−271.6[z]	0.7322	0.1449	−1.6843	−1.6843[ab]
BH_3	−26.3546[w]	+23.80[z]	0.4204	0.3255	−0.2199	−0.2199[ab]

[a] Energies are in atomic units.
[b–z] Source of data may be found in original reference.
[aa] Reproduced by permission of Elsevier Scientific Publishing Company, Amsterdam from J. B. Moffat, *J. Mol. Struct.*, **15**, 325 (1973).
[ab] Molecule used in forming table.

correlation energies can then be employed to calculate molecular correlation energies for those molecules not previously involved in obtaining the bond contributions. The contributions to correlation energy for a number of bonds are summarized in Table 14. Some values for molecular correlation energies obtained from these bond contributions are shown in Table 15.

The concept of group contributions has also been employed[131] to obtain bond contributions to *ab initio* electronic energies. Examination of the geometry-optimized STO-3G energies from a variety of calculations has shown that the electronic energies change in a consistent manner as larger molecules are formed as a result of substituting atoms or groups for hydrogen on the parent molecule. For example, if methyl cyanide is formed from methane by substitution of a cyano group for a hydrogen atom, the energy is decreased by 90.54469 hartree. The energy of diketene is lowered by 90.54957 hartree for each cyano substituted to form dicyanoketene[132]. The addition of a cyano group to HCN to form cyanogen lowers the energy by 90.54426 hartree[133]. The similarity in these values is readily evident. Of course, the values for the contribution of a particular bond do depend on the molecule under consideration. Consequently, at this point in the development of the method, higher order corrections are being neglected. Nevertheless, for a first-order estimate of the total electronic energy of a molecule, the method appears to be quite satisfactory. Methods for the introduction of higher order contributions are now being considered.

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CHAPTER **28**

Recent advances in the synthesis of triple-bonded groups

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I. INTRODUCTION

The sections on nitriles are a supplement to Chapter 2 of the volume *The Chemistry of the Cyano Group*[1]. The arrangement follows rather closely that of the earlier one with a few exceptions . Thus, we have included several new subdivisions such as Beckmann fragmentations and ring-cleavage of heterocycles. The literature references have been chosen on the basis either of additional information concerning already existing methods or of new developments in preparative nitrile chemistry.

The sections on acetylenes cover the literature from the middle of 1976 until approximately the middle of 1980. As is to be expected for a range of only a few years, most citations refer to already known methods.

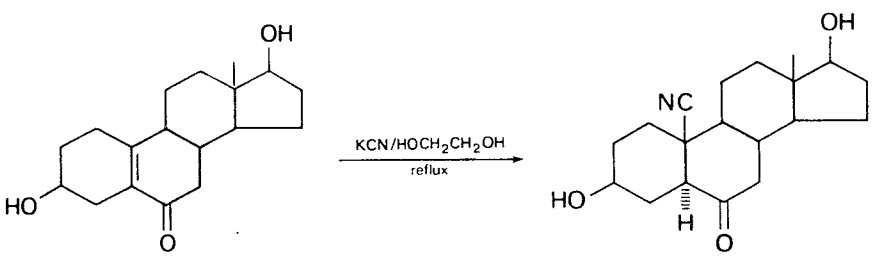
II. PREPARATION OF NITRILES BY ADDITION OF HYDROGEN CYANIDE OR ITS DERIVATIVES

A. Addition to Carbon–Carbon Multiple Bonds

Olefinic double bonds bearing no activating groups can be cyanated by the photochemical addition of sulphonyl cyanides[2] (equation 1).

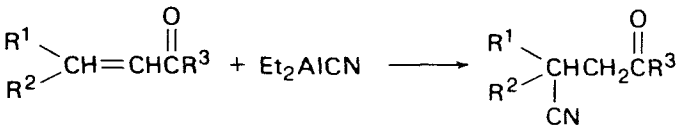
$$ArSO_2CN + CH_2{=}CHBu\text{-}n \xrightarrow[2537\ Å]{h\nu} ArSO_2CH_2CH(CN)Bu\text{-}n \qquad (1)$$

Activation by a carbonyl group or similar electronegative functions is frequently used for the addition of cyanide ions to carbon–carbon double bonds[3] (equation 2).



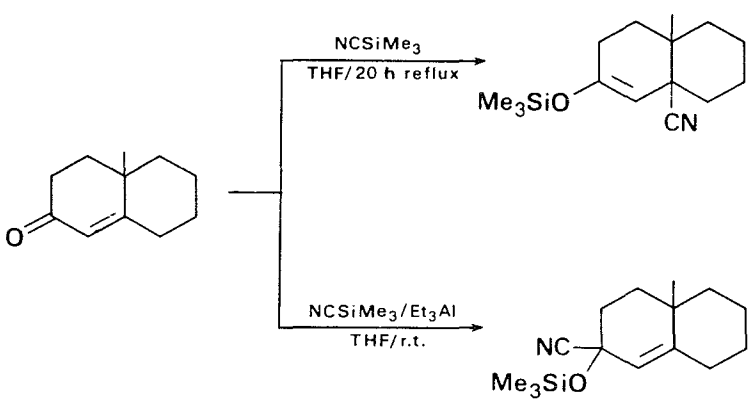
(2)

A review has been published about the hydrocyanation of conjugated carbonyl compounds[4]. Instead of hydrogen cyanide itself the reaction product with aluminium trialkyls may be used for such additions (equation 3). Two main methods are used for



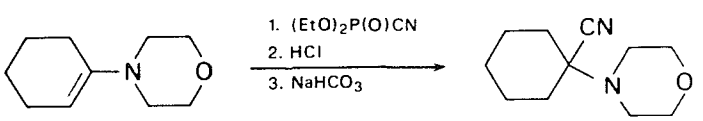
(3)

the addition of organoaluminium cyanides. One employs a combination of hydrogen cyanide and an aluminium trialkyl in tetrahydrofuran, the other uses an alkyl aluminium cyanide in an inert solvent such as benzene or toluene. The carbonyl function of the enone is activated through coordination with the Lewis-acidic organoaluminium species[5]. In addition there has been reported the use of trimethylsilyl cyanide which is a typical 1,2-addition reagent for carbonyl compounds[6], either alone or with triethylaluminium[7]. Depending on the reaction conditions either 1,4- or 1,2-addition with enones is observed (equation 4).



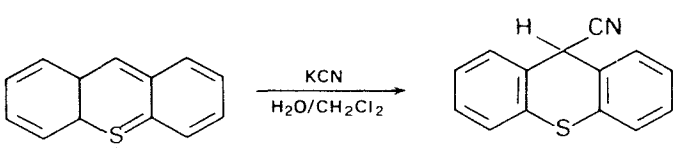
(4)

Carbon–carbon double bonds of enamines give the corresponding cyanoamines with diethyl phosphorocyanidate[8] (equation 5).

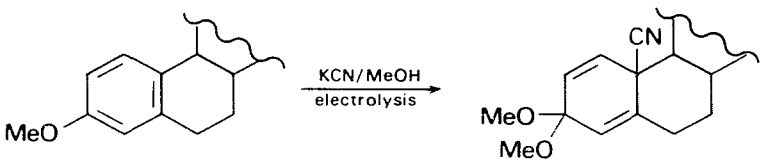


(5)

The thioxanthylium system possesses a sulphonium atom which sufficiently activates its π bonds for the addition of cyanide ions[9] (equation 6). Anodic oxidation of cyanide ions in the presence of aromatic rings yields addition products. In the example in equation (7) the cyano group enters the positions *ortho* or *para* to the methoxy function[10] (equation 7).



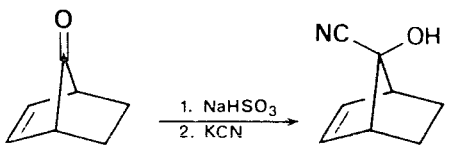
(6)



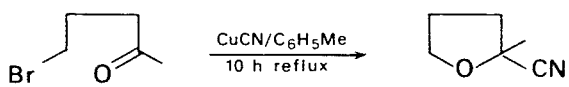
(7)

B. Addition to Carbon–Oxygen Double Bonds

Reviews have appeared concerning the application of cyanohydrins in organic syntheses[11] and reactions of trimethylsilyl cyanide[6]. Examples of the classical cyanohydrin synthesis are the addition of cyanide ion to the bisulphite adduct of norbornen-7-one, which produces the *syn* nitrile[12] (equation 8). Here the trimethylsilyl cyanide method furnishes a mixture of isomers. The cyanohydrin synthesis starting from benzaldehyde in the presence of D-hydroxynitrile lyase affords a product in 96% yield and 90% optical purity[13]. The addition of cyanide ion to a carbonyl group may be followed by an intramolecular alkylation of the resulting cyanohydrin anion if a suitable centre is available, as for instance in equation (9)[14].



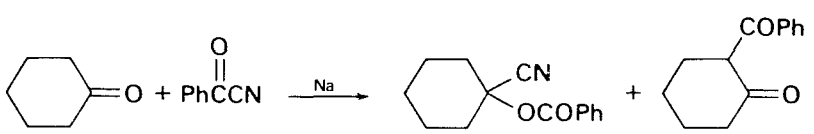
(8)



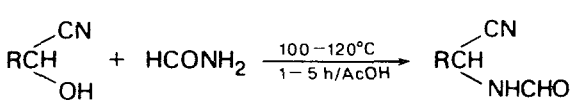
(9)

The production of a benzoic acid cyanohydrin ester in the reaction of cyclohexanone with benzoyl cyanide in the presence of sodium appears to be a normal cyanohydrin synthesis, the required cyanide anions being produced by the concurrent acylation of cyclohexanone with benzoyl cyanide[15] (equation 10).

Cyanohydrins are converted to formylated α-aminonitriles when heated with formamide in the presence of acetic acid[16] (equation 11).



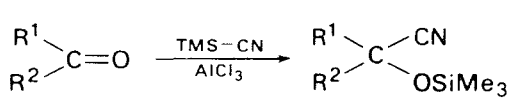
(10)



(11)

Syntheses of cyanohydrins using potassium cyanide/crown ethers have been published[17].

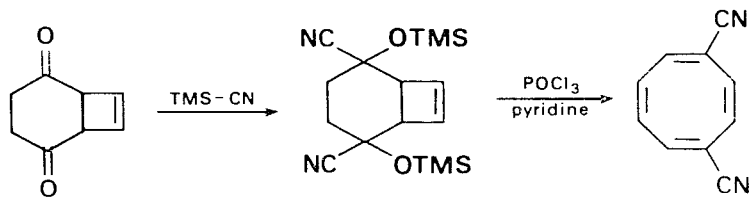
The considerable interest in the reactions of trimethylsilyl cyanide (TMS-CN) may be seen from the following reactions. Small amounts of a Lewis acid such as aluminium chloride catalyse the addition of TMS-CN to carbonyl groups[18,19] (equation 12). Zinc



(12)

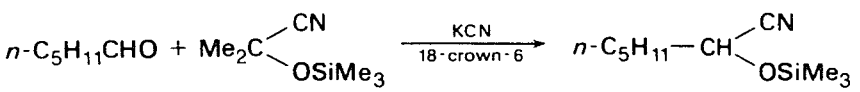
iodide is another suitable catalyst for the reaction[20]. Even in cases where the unfavourable equilibrium of the addition of hydrogen cyanide precludes the application of the classical method, such as with aromatic aldehydes or ketones, the TMS-CN method is successful. Another advantage is that the reaction will give exclusively the 1,2-adduct with numerous conjugated enones[19]. *p*-Quinones react regiospecifically at their carbonyl functions[21]. The cyanosilylation products are easily converted into the free cyanohydrins by dilute mineral acids[20].

It is possible to obtain the α,β-unsaturated nitriles from the TMS-CN adducts directly by treatment with phosphoryl chloride and pyridine[22] (equation 13).



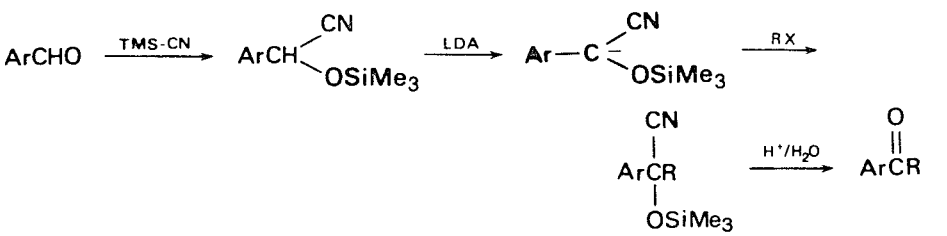
(13)

Catalysis by potassium cyanide/crown ether allows transcyanosilylation reactions[23] (equation 14).

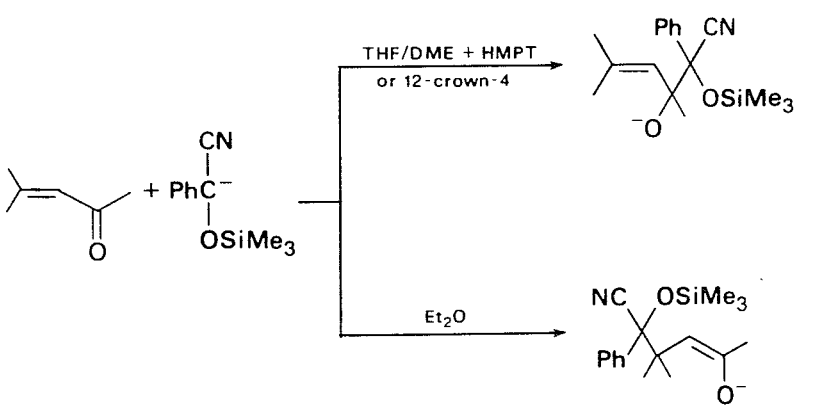


(14)

TMS-CN is also a reagent for the 'Umpolung' of carbonyl groups[24]. The cyanosilylation products of aromatic aldehydes on treatment with strong bases such as lithium diisopropylamide (LDA) furnish stabilized carbanions which can be alkylated. Subsequent hydrolytic cleavage then yields the ketones (equation 15). Reaction of the carbanion with conjugated enones will give the products of either 1,2- or 1,4-addition, depending on the conditions[25] (equation 16).

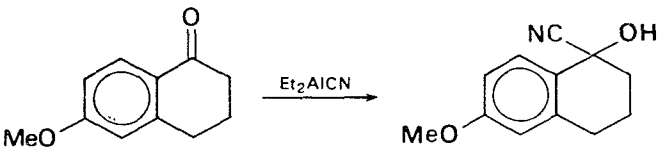


(15)



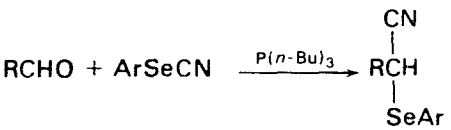
(16)

As in the case of activated carbon–carbon double bonds, the hydrocyanation reaction of carbonyl groups can also be accomplished by the use of dialkylaluminium cyanides[26] (equation 17).



(17)

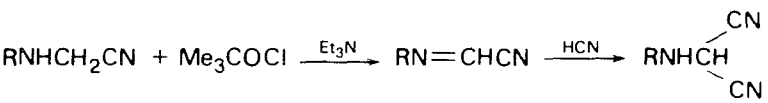
Aldehydes give direct cyanoselenenylation by reaction with selenocyanates in the presence of trialkylphosphines[27] (equation 18). The products may be converted to α,β-unsaturated nitriles by oxidation with hydrogen peroxide.



(18)

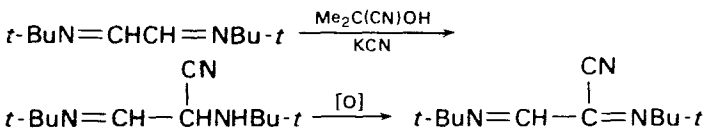
C. Addition to Carbon–Nitrogen Multiple Bonds

Cyanoimines, prepared by oxidation of aminoacetonitriles with *t*-butyl hypochlorite/triethylamine, add hydrogen cyanide to give the corresponding aminomalononitriles[28] (equation 19).



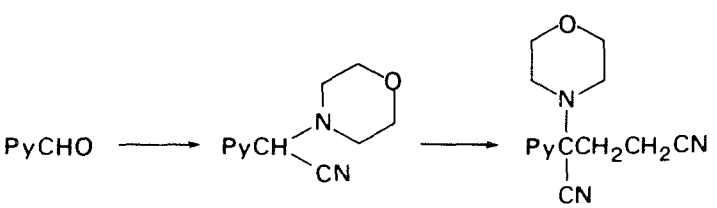
(19)

Acetone cyanohydrin has been used to convert the bis(*t*-butyl)imine of glyoxal to the monoadduct with hydrogen cyanide. The resulting compound upon oxidation with manganese dioxide or hypochlorite furnishes the cyanoimine[29] (equation 20).



(20)

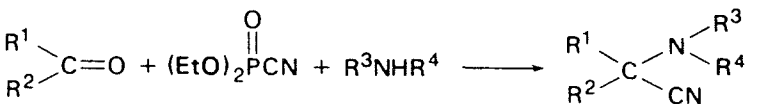
The α-morpholinoacetonitrile obtained from pyridine-3-aldehyde with morpholinium perchlorate/KCN can be used as an acyl carbanion equivalent. After treatment with KOH/acrylonitrile the Michael adduct is obtained[30] (equation 21).



(21)

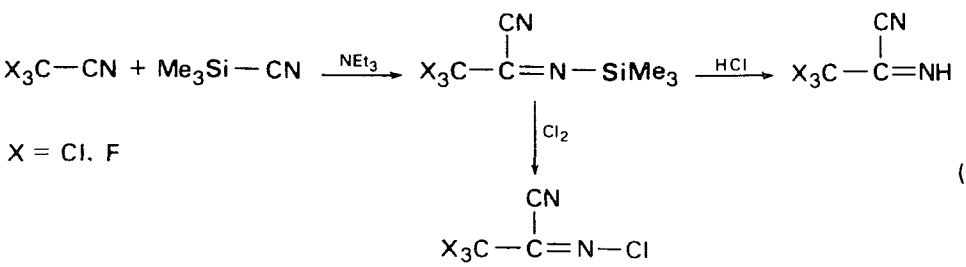
Diethyl phosphorocyanidate has been used as a cyanating agent in the Strecker synthesis with secondary amines[31] (equation 22).

Nitriles bearing electronegative substituents will add TMS-CN in the presence of



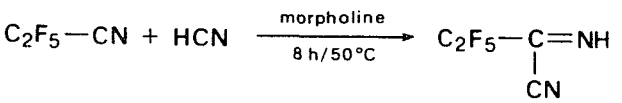
(22)

tertiary amines to give cyanoimines. The lability of the Si—N bond in the resulting products may be used for the synthesis of further cyanoimines[32] (equation 23).



(23)

Perfluoroalkyl nitriles add hydrogen cyanide under basic conditions to give the corresponding cyanoimines directly[33] (equation 24).



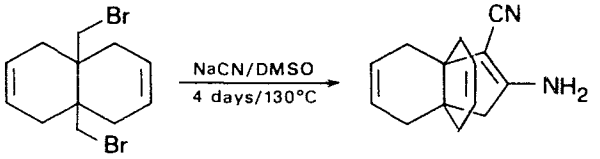
(24)

III. PREPARATION OF NITRILES BY SUBSTITUTION

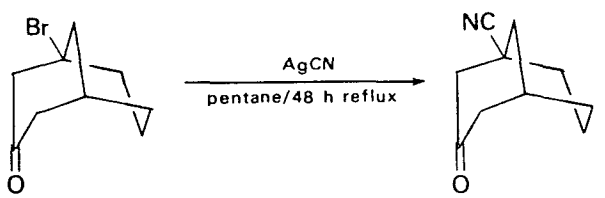
A. Reaction of Hydrogen Cyanide or its Salts with Organic Compounds

1. *Substitution of halogen*

Substitution of bromine by cyanide followed by ring-closure has been used in propellane chemistry[34] (equation 25). An entry to carbon-substituted bicyclo[3.3.1]nonan-3-ones is possible by the bridgehead substitution of bromine by cyanide[35] (equation 26).



(25)



(26)

Several publications deal with the synthesis of acyl cyanides. Alkyl chloroformates are converted to the corresponding cyanoformates with alkali cyanides by phase-transfer catalysis using 18-crown-6 ethers[36]. Aroyl chlorides are transformed into aroyl cyanides with sodium cyanide in methylene chloride–water and with tetrabutylammonium bromide as a catalyst[37].

Anhydrous thallium cyanide, prepared under nonaqueous conditions from thallium phenolate and hydrogen cyanide in ether, is another reagent for the conversion of acid chlorides into acyl cyanides[38]. The applicability of TMS-CN for the synthesis of acyl cyanides has been studied[39] (equation 27). The method is also suitable for the preparation of α-haloacyl cyanides.

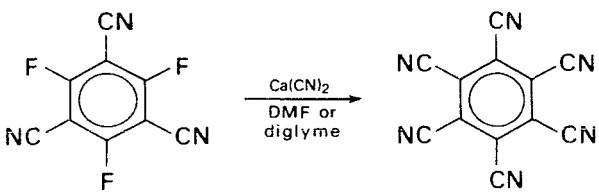
$$RCOX + Me_3SiCN \longrightarrow RCOCN + Me_3SiX \qquad (27)$$

X = Cl, Br

Aromatic, heterocyclic, olefinic and *t*-alkyl acyl chlorides are easily converted into the corresponding acyl cyanides by the action of tributyltin cyanide[40] (equation 28). With primary or secondary alkyl groups dimer formation occurs.

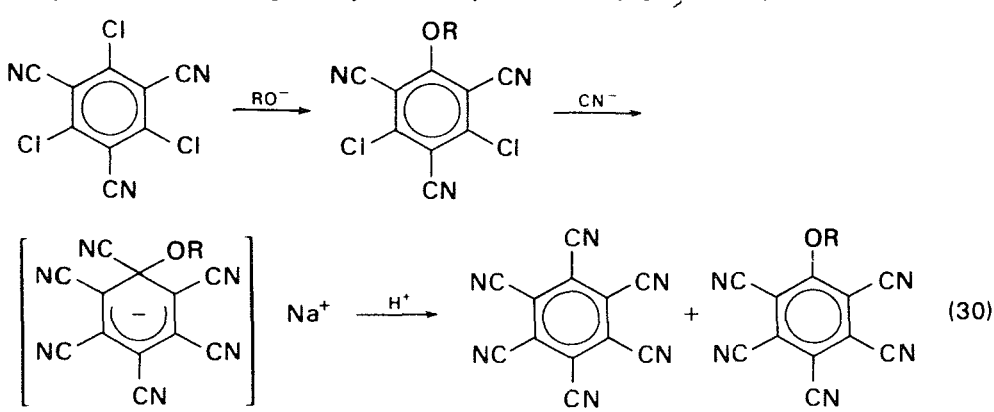
$$RCOCl + (n\text{-}Bu)_3SnCN \longrightarrow RCOCN + (n\text{-}Bu)_3SnCl \qquad (28)$$

Aromatic halogen, if sufficiently activated, can be displaced by cyanide anion, although difficulties may be encountered because of the enhanced reactivity of the products. In a heterogeneous reaction 1,3,5-tricyano-2,4,6-trifluorobenzene reacts with calcium cyanide to give hexacyanobenzene[41] (equation 29).



(29)

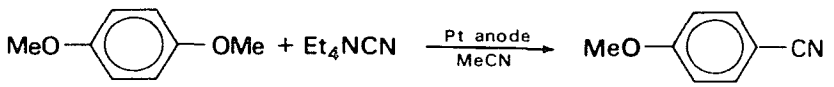
Another synthesis of hexacyanobenzene makes use of the stability of the 1,2,3,4,5,6-hexacyano-1-alkoxycyclohexadienide anion, which prevents the reaction between 1-alkoxy-2,4,6-tricyano-3,5-dichlorobenzene and sodium cyanide going any further under basic conditions. Protonation of the anion yields then a mixture of hexacyanobenzene and pentacyanoalkoxybenzene[42] (equation 30).



(30)

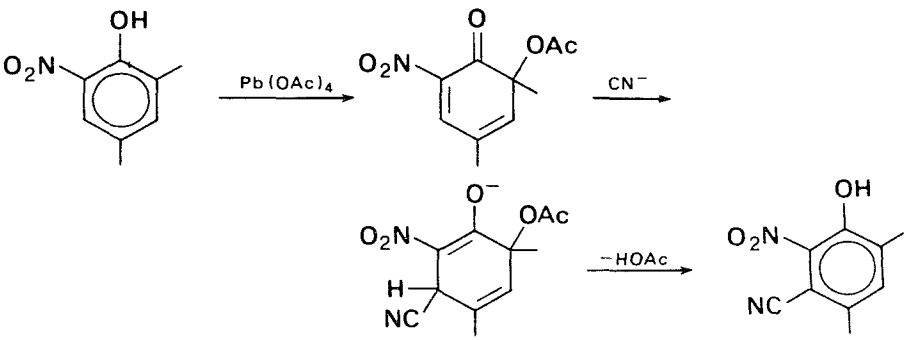
2. *Substitution of oxygen groups*

The anodic oxidation of cyanide-ion solutions containing aromatic substrates results in the replacement of aromatic hydrogen or also aromatic methoxy groups (equation 31), a third type of reaction being the introduction of the cyano function in an α position in a tertiary amino group[43].



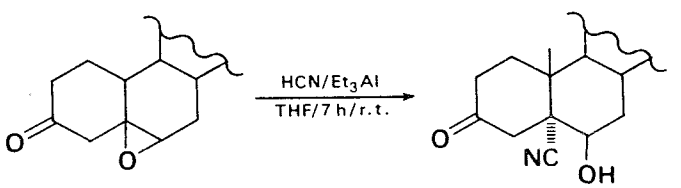
95% (47% conversion) (31)

Hemiquinol acetates, obtainable by lead tetraacetate oxidation of *o*-nitrophenols, undergo 1,4-addition reactions with cyanide anion followed by elimination of acetic acid. The overall reaction is the substitution of the hydrogen atom *ortho* to the nitro group by a cyano group[44] (equation 32).



(32)

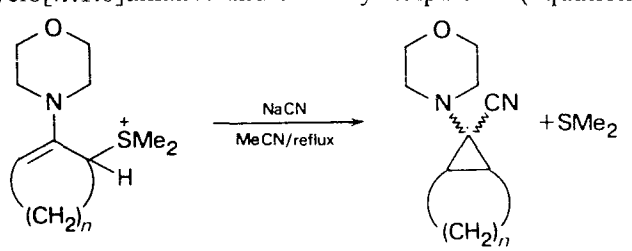
The avoidance of the drastic conditions often necessary for the ring-cleavage of oxirans by cyanide anions is possible by using organoaluminium cyanides, for example in the case of steroidal 5,6α-epoxides[45] (equation 33).



(33)

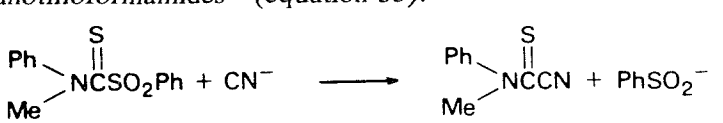
3. *Substitution of sulphur groups*

Cyclic enamines with a dimethylsulphonium group in the α′-position of the ring undergo rearrangement by attack of cyanide anions and yield cyano(amino)bicyclo[*n*.1.0]alkanes and dimethyl sulphide[46] (equation 34).



(34)

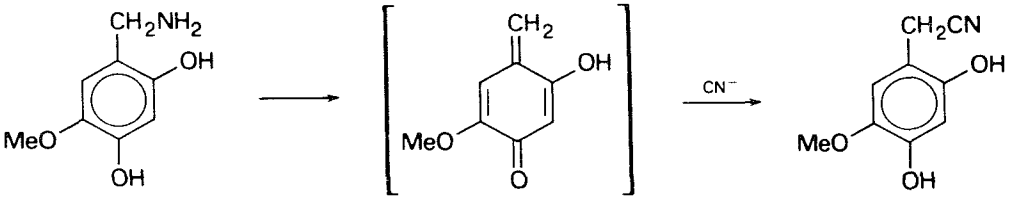
N,N-Disubstituted *C*-sulphonylthioformamides are cleaved by cyanide anions to give the cyanothioformamides[47] (equation 35).



(35)

4. Substitution of amino groups

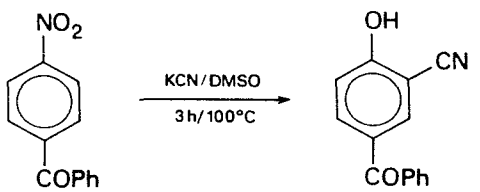
O- or *p*-hydroxybenzylamines, obtained by Mannich reaction of phenols or by reductive alkylation of aldehydes, may be used instead of the corresponding benzyl halides for the synthesis of benzyl cyanides. Presumably the reaction occurs via quinone methides[48] (equation 36).



(36)

5. Substitution of hydrogen

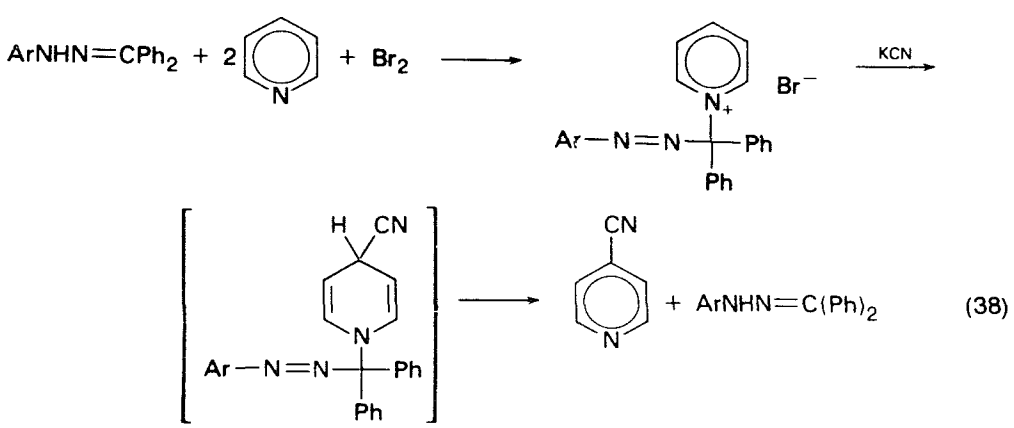
Nitroarenes having an additional activating group like acyl are starting materials for a synthesis of *o*-cyanophenols. For example, 4-nitrobenzophenone is converted to the 3-cyano-4-hydroxybenzophenone with potassium cyanide in DMSO (equation 37).



(37)

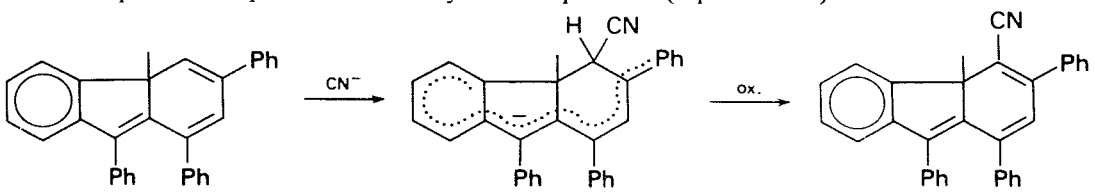
Apparently, after the substitution of one of the hydrogens *ortho* to the nitro group by cyanide, the nitro group itself is then replaced by hydroxide. The latter is thought to evolve from the reduction of nitro groups[49].

Numerous reactions for the conversion of 4-substituted pyridines are known, but only a few methods exist for the introduction of a cyano group in position 4 of the pyridine nucleus. By reacting benzophenone arylhydrazones with bromine and pyridine it is possible to synthesize pyridinium cations, which are easily converted into 4-cyanopyridines with potassium cyanide[50] (equation 38).



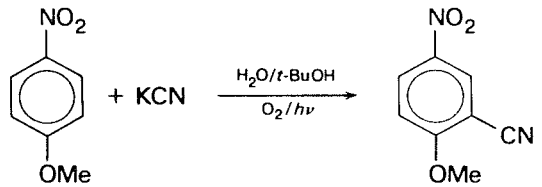
(38)

The addition of cyanide anions to phenyl-substituted fluorene derivatives results in the formation of a stabilized carbanion system, which can be oxidized by anthraquinone sulphonate to the cyano compound[51] (equation 39).



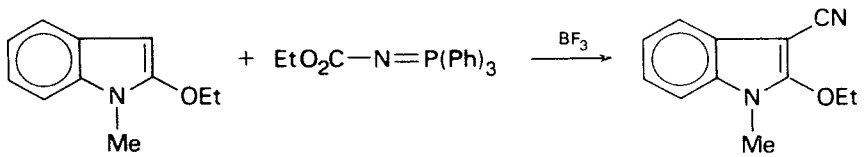
(39)

Substitution of aromatic hydrogens is also possible by photoinduced reaction with cyanide anions and oxygen[52] (equation 40).



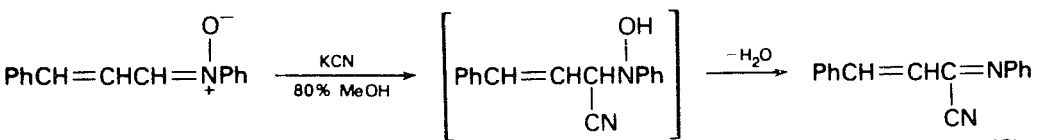
(40)

Up to four cyano groups can be introduced into the *meso* positions of porphyrins by anodic oxidation in the presence of cyanide anions[53]. An agent for the introduction of cyano groups into sufficiently nucleophilic heterocycles is *N*-carbethoxytriphenyliminophosphorane. Catalysed by Lewis acids, the reaction with 1-methyl-2-ethoxyindole gives the 3-cyano compound[54] (equation 41).



(41)

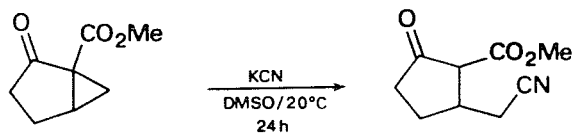
A reaction analogous to the behaviour of pyridine *N*-oxides is the synthesis of the cyanoimine from cinnamaldehyde phenylnitrone with potassium cyanide, presumably via the 1,3-addition product[55] (equation 42).



(42)

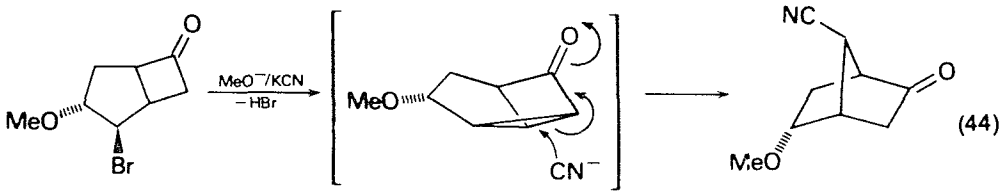
6. *Substitution by cleavage of carbon–carbon bonds*

Nucleophilic attack of cyanide anions on cyclopropanes results in ring-cleavage on condition that the resulting carbanion is sufficiently stabilized, as in equation (43)[56].



(43)

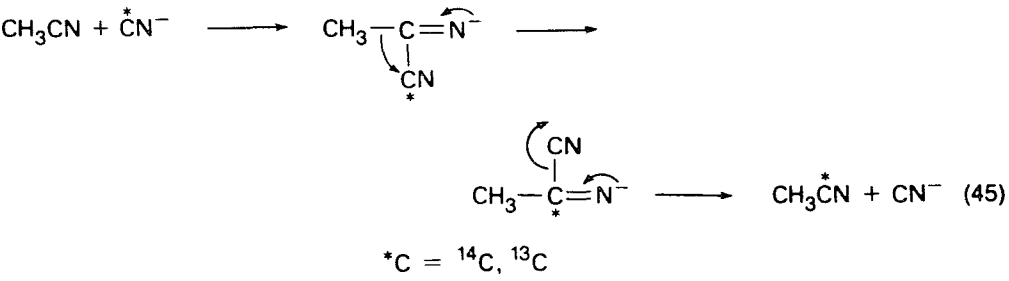
The reaction of 3-*endo*-alkoxy-2-*exo*-bromobicyclo[3.2.0]heptan-6-ones with potassium cyanide and catalytic amounts of methoxide yields the 5-*endo*-alkoxy-7-*anti*-cyanobicyclo[2.2.1]heptan-2-ones[57] (equation 44). The reaction



(44)

apparently proceeds through a tricyclic intermediate, whose cyclopropane ring is cleaved by cyanide anion.

The exchange reaction between labelled cyanide and the nitrile function of acetonitrile occurring in the presence of 18-crown-6 is formulated as a multistep sequence rather than the less likely S_N2 displacement[58] (equation 45).



(45)

$^*C = {}^{14}C, {}^{13}C$

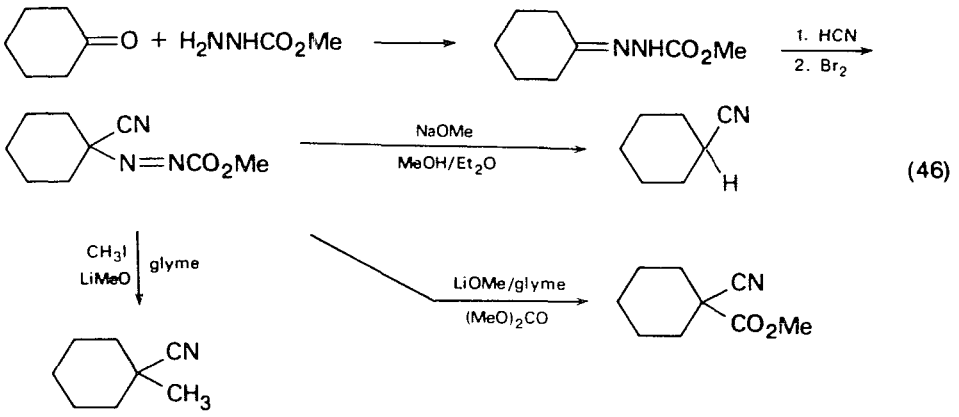
B. Transformation of Carbonyl Groups into Cyanoalkyl Groups

Since S_N2 displacements on secondary halides with inorganic cyanides are frequently associated with difficulties, some interesting methods have been developed for the transformation of a carbonyl function into a cyanoalkyl group. These reactions are included here as being substitutions at least in a formal sense.

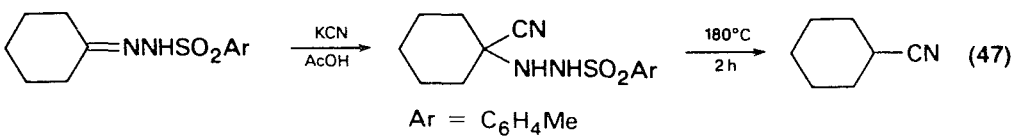
One method involves the base-induced decomposition of methyl dialkylcyanodiazenecarboxylates[59]. These compounds are prepared by condensation of methyl hydrazinecarboxylate with ketones, addition of hydrogen cyanide to the resulting hydrazones and final oxidation by bromine. Their decomposition with sodium methylate in methanol/ether leads to the dialkylacetonitriles, reaction with lithium methylate in the presence of an alkylating agent to the trialkylacetonitriles and finally treatment with alkoxide and dimethyl carbonate to dialkylcyanoacetic ester. The example with cyclohexanone shown in equation (46) may be illustrative.

Arylsulphonylhydrazones may serve as starting materials for a similar transformation[60]. Addition of hydrogen cyanide gives the corresponding α-cyanohydrazines, which by thermal decomposition yield the dialkylacetonitriles (equation 47). With Ar = 2,4,6-triisopropylphenyl the hydrazone is heated with excess potassium cyanide in methanol to give the final product directly[61].

A review has appeared containing information about the use of tosylmethylisocyanide (TosMIC) in the transformation of carbonyl compounds[62]. This reagent is metalated by treatment with alkoxide bases in aprotic solvents[63,64], the anion then being reacted with aldehydes or ketones to give the 1-formylamino-1-tosylalkene which with alkoxides in alcohols fragmentates to the

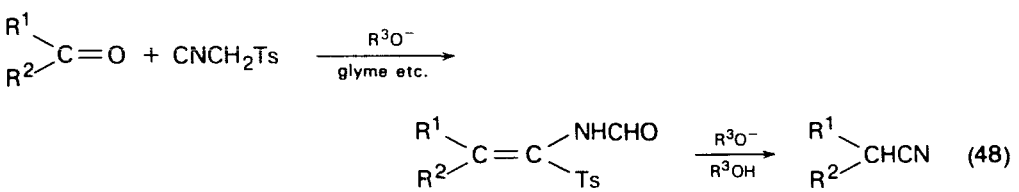


(46)



(47)

Ar = C_6H_4Me

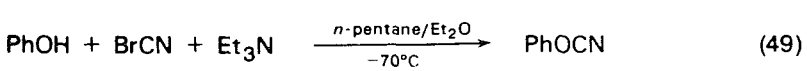


(48)

nitrile (equation 48). The transformation may be performed in one step by alkoxides in alcoholic solution[63].

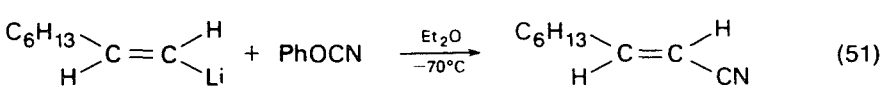
C. Reaction of Cyanogen Chloride or Cyanates with Nucleophiles

Sulphinate anions may be transformed to the corresponding sulphonyl cyanides by reacting their aqueous solutions with an excess of cyanogen chloride at room temperature[65]. The less volatile phenyl cyanate may be used instead of cyanogen chloride for many reactions. Prepared by the action of cyanogen bromide on phenol/triethylamine (equation 49) it cyanates lithium acetylides or metalated olefins (equations 50 and 51)[66]. Starting from the *E* or *Z* olefins the corresponding products are obtained in isomerically pure form.



(49)

(50)



(51)

IV. PREPARATION OF NITRILES BY ELIMINATION

A. Starting from Aldehydes, Ketones and their Derivatives

1. Dehydration of oximes

A variety of reagents are used to effect the dehydration of oximes (equation 52).

$$RCH{=}NOH \xrightarrow{-H_2O} RCN \qquad (52)$$

Inorganic reagents which have been used are sulphuryl fluoride[67], titanium tetrachloride–pyridine[68] or selenium dioxide[69]. Further examples are diphenyl phosphorochloridate, prepared from carbon tetrachloride[70], methanesulphonyl choride/triethylamine[71], hexafluoroacetic anhydride[72], *p*-chlorophenyl chlorosulphite/pyridine[73] or cyanuric chloride with pyridine[74] or triethylamine[75]. A one-pot method uses the reaction of an aldehyde with hydroxylamine hydrochloride followed by dicyclohexylcarbodiimide in the presence of triethylamine/$CuSO_4$[76]. At low temperature and neutral medium *N,N'*-carbonyldiimidazole is used[77].

Hydroxylamine hydrochloride in refluxing DMF converts aldehydes[78] or 3-chloropropeniminium salts, obtained as intermediates in the Vilsmeier–Haack synthesis, directly into nitriles (equation 53). Hydroxylamine derivatives such as hydroxylamino-*O*-sulphonic acid[79] or *O*-(2,4-dinitrophenyl)hydroxylamine[80] may be used for the direct conversion of aldehydes into nitriles.

$$ArC(Cl){=}CHCH{=}\overset{+}{N}(R)R\ ClO_4^- \xrightarrow[DMF\,/\,reflux]{H_2NOH\cdot HCl} ArC(Cl){=}CHCN \qquad (53)$$

Additional examples of dehydrating agents are phenyl chlorosulphite[81] and trifluoromethylsulphonic anhydride[82].

2,4,6-Trinitrotoluene is converted to the benzonitrile in one step by treatment with nitrosyl chloride–pyridine[83], the oxime nitrite being the intermediate (equation 54).

$$ArCH_3 \xrightarrow[pyridine]{NOCl} [ArCH{=}NOH \longrightarrow ArCH{=}NONO] \xrightarrow{-HNO_2} ArCN \qquad (54)$$

A variety of dehydrating agents, whose action can be formulated via different oxime esters or ethers has been published (equations 55–60).

$$RCHO \xrightarrow[reflux]{H_2NOH/HCO_2H} [RCH{=}N{-}O{-}CHO] \longrightarrow RCN \quad \text{(Ref. 84)} \qquad (55)$$

$$RCH{=}NOH \xrightarrow[220°C]{HMPT} [RCH{=}N{-}O{-}P(O)(NMe_2)_2] \longrightarrow RCN \quad \text{(Ref. 85)} \qquad (56)$$

$$RCH{=}NOH \xrightarrow{MeC{\equiv}\overset{+}{N}HEt\ BF_4^-} [RCH{=}N{-}O{-}C(Me){=}NEt] \longrightarrow RCN \quad \text{(Ref. 86)} \qquad (57)$$

$$ArCH{=}NOH \xrightarrow{Cl_3CCN} \left[ArCH{=}N{-}O{-}\overset{\displaystyle CCl_3}{\overset{|}{C}}{=}NH \right] \longrightarrow RCN \quad \text{(Ref. 87)} \quad (58)$$

$$RCH{=}NOH \xrightarrow{(Me)_2\overset{+}{N}{=}CCl_2} \left[RCH{=}N{-}O{-}\overset{\displaystyle Cl}{\overset{|}{C}}{=}\overset{+}{N}Me_2 \right] \longrightarrow RCN$$

(Ref. 88) (59)

$$RCH{=}NOH \xrightarrow[MeSO_3H]{HC(OEt)_3} [RCH{=}N{-}O{-}CH(OEt)_2] \longrightarrow RCN$$

(Ref. 89) (60)

Nitrosation of triphenylphosphoranes bearing electron-withdrawing groups on the carbanion centre yields oximes which decompose in analogy to the mechanism of the Wittig reaction (equation 61). Examples of this method have been reported with R = PhCH=CH—[90], PhCO[91,92] and Ts[93].

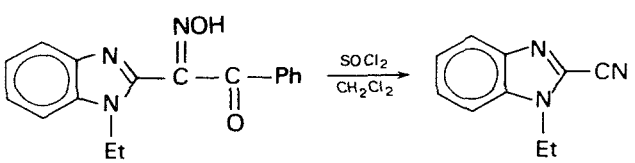
$$R\bar{C}H{-}\overset{+}{P}Ph_3 \xrightarrow{[NO^+]} \left[R{-}\overset{\displaystyle N{-}O^-}{\overset{\|}{C}}{-}\overset{+}{P}Ph_3 \right] \longrightarrow RCN + O{=}PPh_3 \qquad (61)$$

2. *Beckmann fragmentations*[94]

Ketoximes are susceptible to cleavage reactions under electrophilic conditions, mainly with acylating reagents, provided there is in the α position a group A which can leave the molecule as a cation, such as a carbonyl function or a heterosubstituted carbon atom (equation 62).

$$\begin{matrix} R^1 \\ A \end{matrix}\!\!>\!C{=}NOH \longrightarrow \begin{matrix} R \\ A \end{matrix}\!\!>\!C{=}N{-}X \longrightarrow RCN + A^+ + X^- \qquad (62)$$

Monoximes of α-diketones react with thionyl chloride in refluxing methylene chloride to give the nitrile, e.g. equation (63)[95].

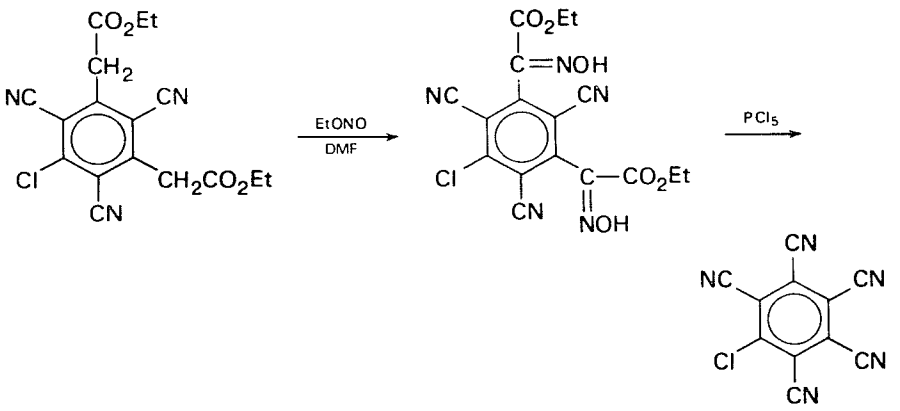


(63)

In a one-pot reaction, phenylacetic acid is nitrosated in the presence of trifluoroacetic acid and its anhydride at low temperature, then heated to reflux to yield benzonitrile[96] (equation 64).

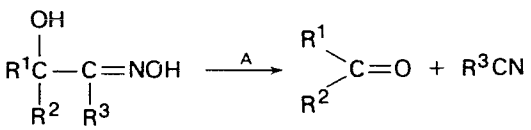
$$PhCH_2CO_2H \xrightarrow[2\ \text{reflux}]{1\ NaNO_2/CF_3CO_2H/(CF_3CO)_2O/0-20^\circ C} PhCN \qquad (64)$$

The final steps in a preparation of chloropentacyanobenzene are bisnitrosation of diethyl 5-chloro-2,4,6-tricyanobenzene-1,3-diacetate with ethyl nitrite in DMF followed by treatment with phosphorus pentachloride[97] (equation 65).



(65)

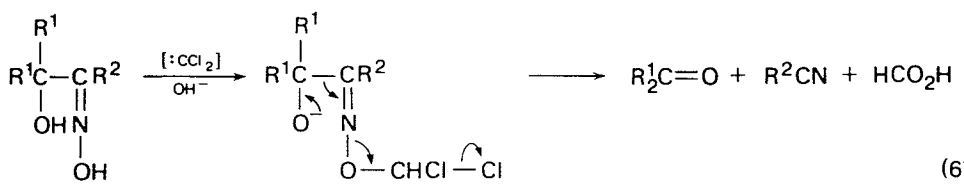
A mild fragmentation method involves the treatment of α-hydroxyketoximes with acid anhydrides or halides in the presence of triethylamine or pyridine[98,99] (equation 66).



(66)

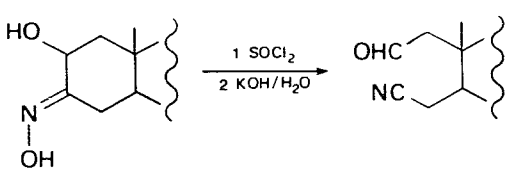
A = $(CF_3SO_2)_2O$, $(CF_3CO)_2O$ or CF_3SO_2Cl in Et_3N or pyridine

Dichlorocarbene, generated in a phase-transfer reaction from chloroform/alkali, converts oximate anions of α-hydroxyketoximes into the oxime dichloromethyl ethers, which decompose into nitriles and formic acid[100] (equation 67).

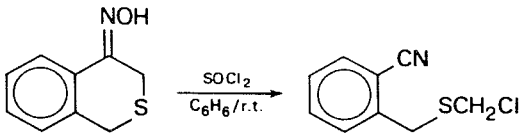


(67)

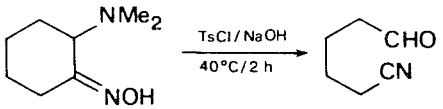
Cyclic ketoximes with suitable α substituents afford ring-cleavage products, e.g. equation (68)[101]. Ketoximes having one[102] or two[89] methoxyl groups in the α position react in an analogous manner. 3-Thiatetralone oxime is cleaved by thionyl chloride at room temperature to the corresponding chloromethyl thioether[103] (equation 69). Treatment of 2-dimethylaminocyclohexanone oxime with tosyl chloride/alkali gives ω-cyanovaleraldehyde[104] (equation 70).



(68)

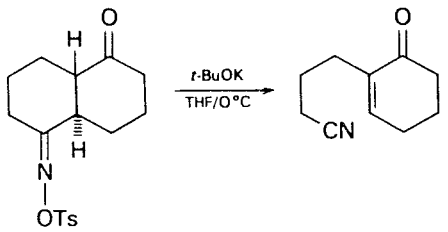


(69)



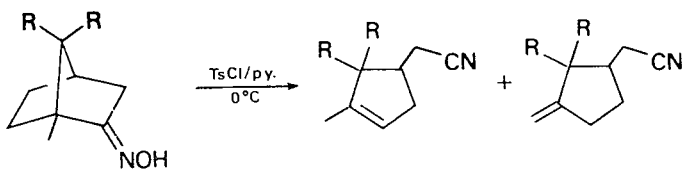
(70)

Generation of a carbanion centre in the β position to the ketoxime function may lead to an olefin-forming Beckmann fragmentation[105] (equation 71).



(71)

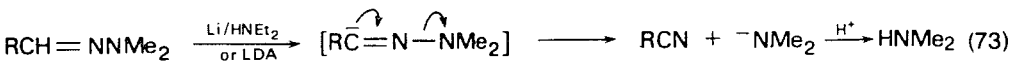
Another olefin-forming fragmentation starts from derivatives of camphor oxime[106]. A mixture of two unsaturated ring-cleavage products results upon treatment with tosyl chloride/pyridine (equation 72).



(72)

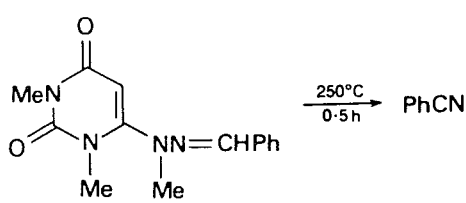
3. *Miscellaneous reactions*

Hydrazones of aldehydes offer the opportunity to synthesize nitriles by cleavage of the N—N bond, as in strongly basic media dimethylhydrazones of aromatic[107] or *t*-alkyl[108] aldehydes decompose into the nitriles and dimethylamine (equation 73).



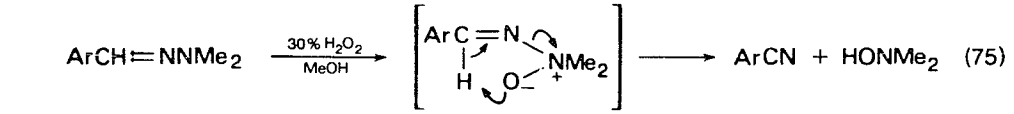
(73)

Aldehyde hydrazones derived from heterocyclic hydrazines can be thermally cleaved to yield nitriles. The azomethine from benzaldehyde and a 1-aminopyridone yields benzonitrile and the pyridone after 1 h at 220°C[109]. In another nitrile synthesis, a pyrimidinedione derivative is used[110] (equation 74).

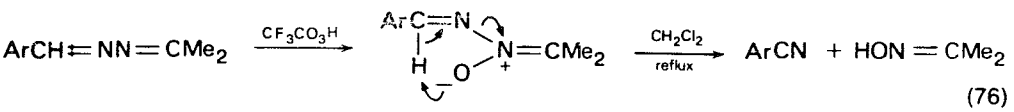


(74)

The dimethylhydrazone of *p*-methoxybenzaldehyde yields upon oxidation with hydrogen peroxide the corresponding nitrile together with *N,N*-dimethylhydroxylamine[111]. This is a reaction analogous to the Cope olefin synthesis; the hydrazone *N*-oxide being the intermediate (equation 75). A similar reaction is observed with the monoxides of aldazines or mixed aldehyde–ketone azines, giving nitriles and oximes[112] (equation 76).

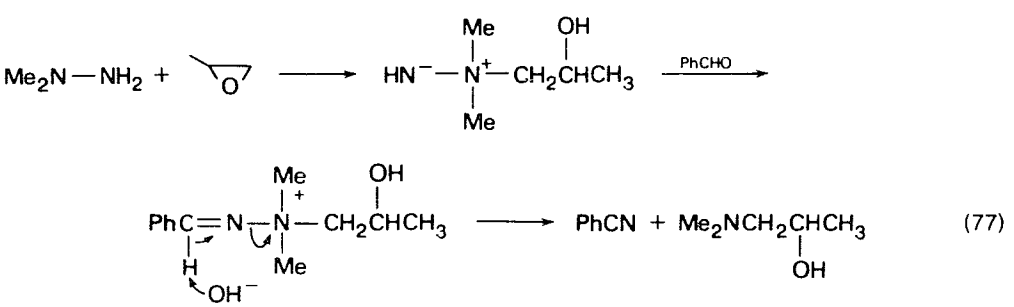


(75)



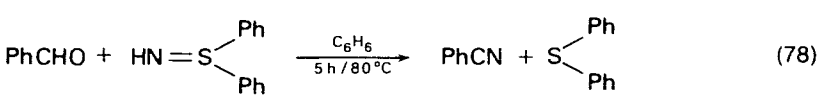
(76)

The diphenylhydrazone of benzaldehyde has been transformed to benzonitrile by photochemical oxidation[113]. 2,6-Dichlorobenzaldehyde hydrazone is converted to the nitrile by oxidation with mercuric oxide[114]. Two mechanisms are considered possible via the corresponding diazo compound. Apparently by a redox reaction, aldehydes are transformed to nitriles by treatment with hydrazine/potassium cyanide, ammonia being the other reaction product[115]. An ammonium imide, generated by reaction between dimethylhydrazine and propylene oxide, converts benzaldehyde into benzonitrile, obviously by a Hofmann elimination reaction[116] (equation 77).



(77)

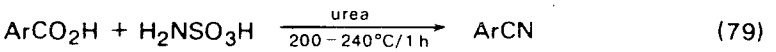
Diphenylsulphimide is another reagent for the conversion of benzaldehyde into benzonitrile, diphenyl sulphide being the other reaction product[117] (equation 78).



(78)

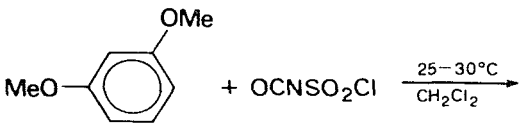
B. Starting from Carboxylic Acids and their Derivatives

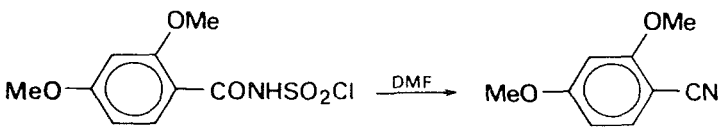
Carboxylic acids can be directly converted into nitriles by treatment with aminosulphonic acid/urea at elevated temperatures[118] (equation 79). An alternative method uses methanesulphonamide together with phosphorus pentachloride[119].



(79)

A most versatile reagent in carboxylic acid chemistry is chlorosulphonyl isocyanate, on which a review has been published[120]. It allows the introduction of a nitrile group into an arene sufficiently activated by electron-donating groups[121] via an amide function (equation 80). On reaction with carboxylic acids chlorosulphonyl isocyanate give *N*-chlorosulphonamides which are decomposed to nitriles in DMF[122,123] (equation 81).

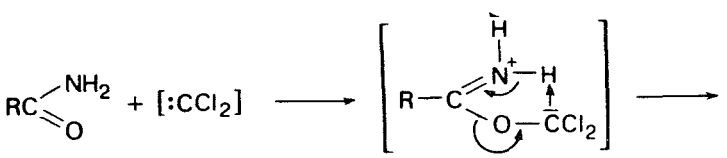




(80)

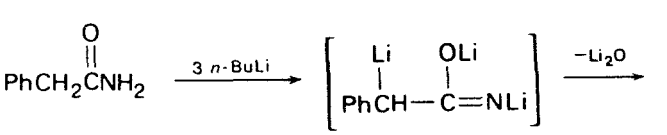
$$RCO_2H + ClSO_2NCO \xrightarrow{-CO_2} RCONHSO_2Cl \xrightarrow{DMF} RCN + SO_3 + HCl \qquad (81)$$

A variety of dehydrating agents have been reported for the conversion of amides into nitriles, such as HMPT[124], pyrophosphoryl chloride[125], the combination of triphenylphosphine and carbon tetrachloride[126], titanium tetrachloride/triethylamine[127], phosphonitrile chloride[128], phosphorous acid tris(diethylamide)[129], cyanuric chloride[130] or the classical method using phosphoryl chloride in the presence of either triethylamine[131] or NaCl[132]. As in the oxime series, dichlorocarbene, prepared in a phase-transfer system, will convert amides into nitriles[133] (equation 82).



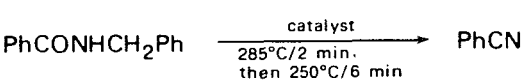
$$RCN + 2\,NaCl + NaO_2CH \qquad (82)$$

Phenyl- and diphenyl-acetamides react with three equivalents of *n*-butyllithium to give the corresponding nitriles[134] (equation 83).

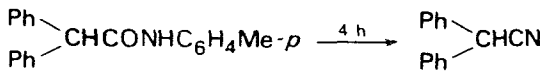


(83)

The transformation of secondary amides into nitriles is possible by a thermal reaction catalysed by chlorotris(triphenylphosphine)rhodium at temperatures from 250–285°C[135] (equation 84) or by reaction with hexamethylcyclotrisilazane at 240°C[136] (equation 85).



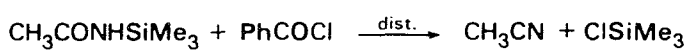
(84)



(85)

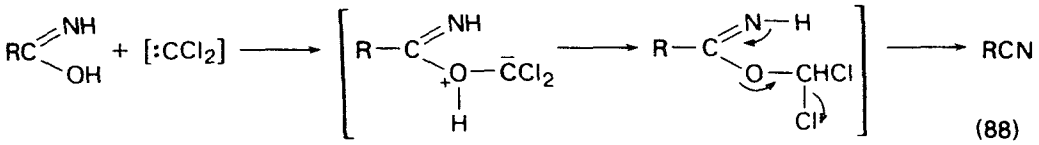
A one-pot transformation of esters uses dimethylaluminium amide in boiling xylene, when a carbonamide or its aluminium derivative is the intermediate[137] (equation 86). *N*-Trimethylsilylacetamide is converted by benzoyl chloride into acetonitrile[138] (equation 87).

(86)



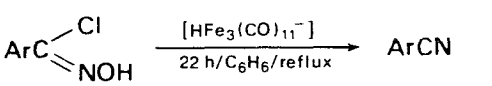
(87)

Carboxylic acid derivatives other than amides may also serve as starting materials for nitrile syntheses, e.g., hydroxamic acids yield nitriles with dichlorocarbene[139] (equation 88).



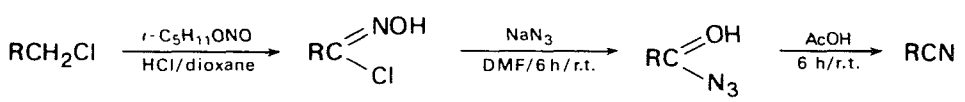
(88)

Triirondodecacarbonyl and methanol yield the hydridoundecacarbonyltriferrate anion, which is the active species in a reaction furnishing nitriles from aromatic hydroxamic acid chlorides[140] (equation 89).

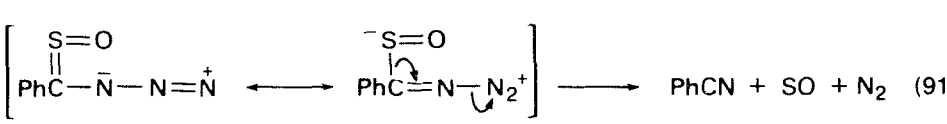


(89)

Chloromethyl groups are transformed to nitriles by a sequence of steps of which the last one represents a fragmentation of a hydroxamic acid azide[141] (equation 90). This fragmentation bears close resemblance to the conversion of thiobenzoyl azide *S*-oxide[142] (equation 91).

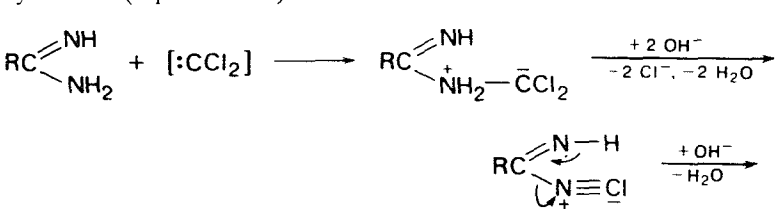


R = hetaryl (90)



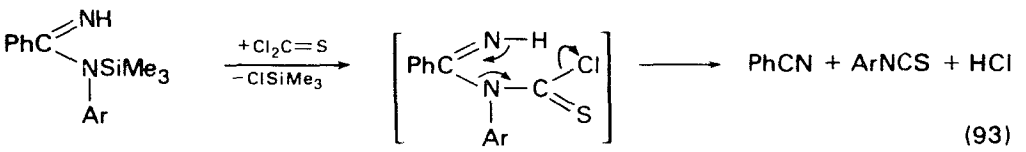
(91)

Amidines give nitriles on reaction with dichlorocarbene in a phase-transfer system[143] (equation 92).



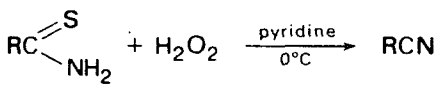
(92)

N-(Trimethylsilyl)tolylbenzamidine exchanges its silyl group against the chlorothiocarbonyl group, the intermediate then fragmenting to benzonitrile, *p*-tolyl isothiocyanate and hydrogen chloride[144] (equation 93).



(93)

Oxidation of thioamides with hydrogen peroxide in the presence of pyridine yields nitriles[145] (equation 94).

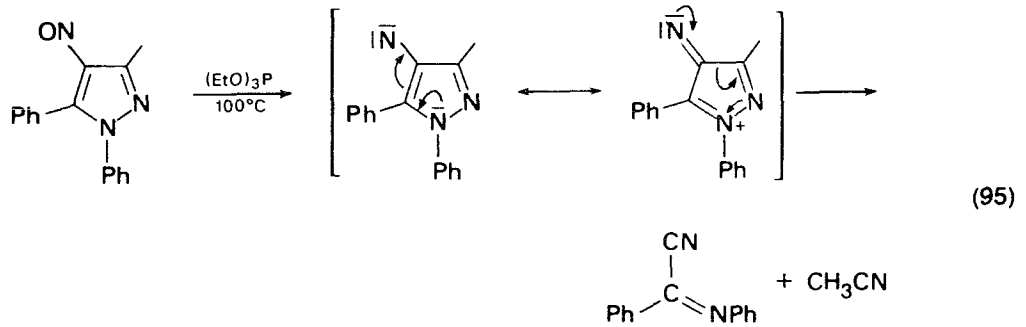


(94)

V. PREPARATION OF NITRILES BY RING-CLEAVAGE OF HETEROCYCLES

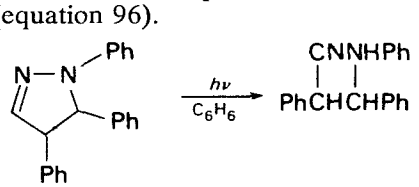
Heterocyclic compounds containing at least one nitrogen atom in their ring-system may be valuable starting materials for nitrile synthesis. Mainly five- and some six-membered rings have been reported to undergo suitable cleavage reactions.

Action of triethyl phosphite on 1,5-diphenyl-3-methyl-4-nitrosopyrazole results in a novel cleavage of the pyrazole ring, yielding the phenylimine of benzoyl cyanide and acetonitrile[146] (equation 95).



(95)

Δ^2-Pyrazolines unsubstituted at position 3 are rearranged photochemically to β-aminonitriles[147] (equation 96).

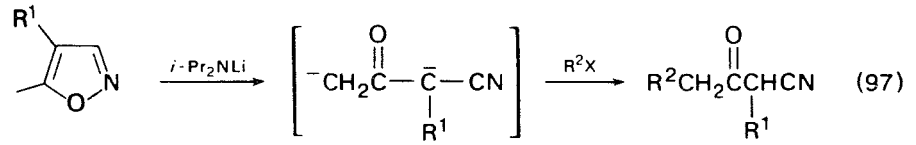


(96)

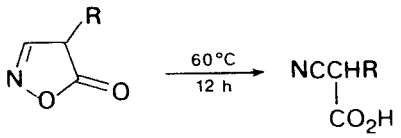
Isoxazoles containing hydrogen in position 3 are known to be converted by bases to α-cyanoketones[1]. Ring-opening with strong bases under aprotic conditions results in the formation of acetoacetonitrile dianions[148] (equation 97).

4-Alkylisoxazolin-5-ones are thermally converted to α-cyanocarboxylic acids[149] (equation 98).

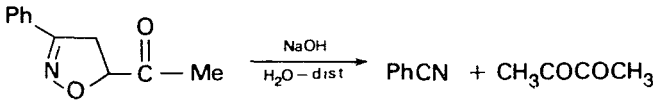
Benzonitrile and butanedione are the products of alkaline cleavage of 3-phenyl-5-acetyl-2-isoxazoline[150] (equation 99).



(97)

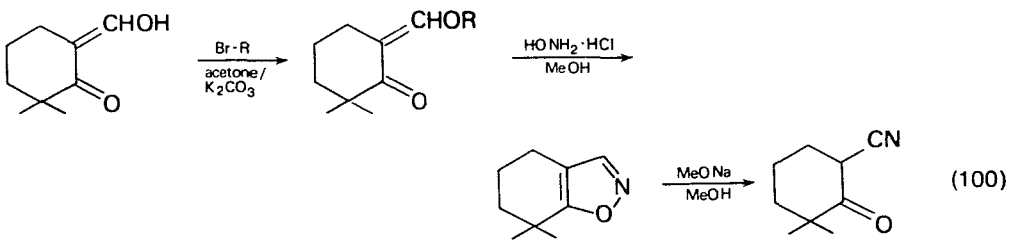


(98)



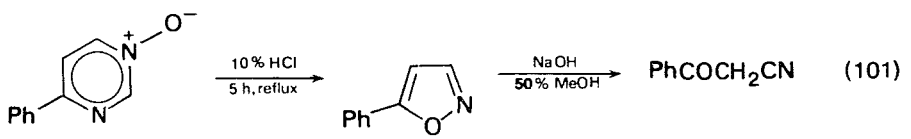
(99)

An α-formylketone can be converted via the corresponding isoxazole into an α-cyanoketone[151] (equation 100).



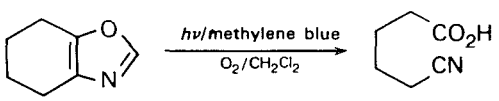
(100)

5-Phenylisoxazole, obtained by boiling 6-phenylpyrimidine-*N*-oxide with dilute hydrochloric acid, is cleaved to benzoylacetonitrile with sodium hydroxide[152] (equation 101).



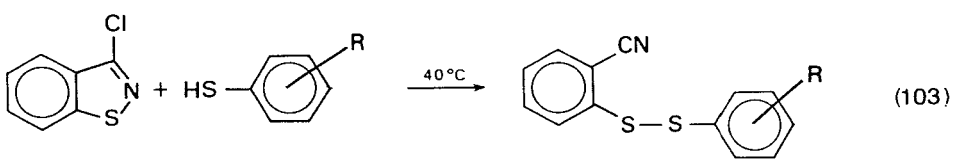
(101)

Fused-ring oxazoles react with singlet oxygen to give ω-cyanocarboxylic acids[153] (equation 102).



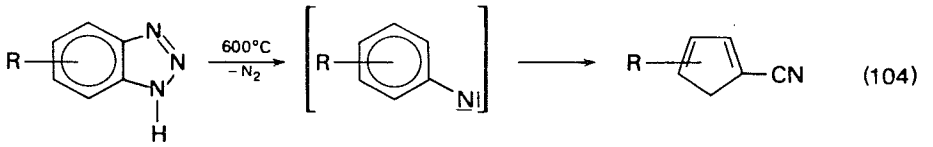
(102)

Thiophenols have been found to cleave the hetero ring of 3-chlorobenzo[*d*]isothiazole at 40°C with formation of *o*-cyanodiphenyldisulphides[154] (equation 103).



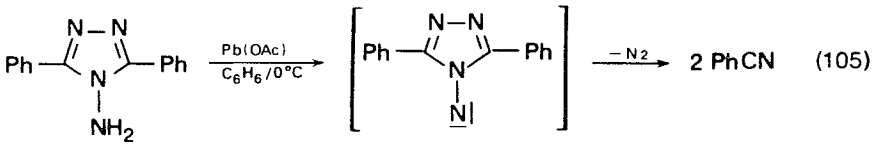
(103)

Triazoloarenes eliminate molecular nitrogen on gas-phase pyrolysis to give aryl nitrenes, which rearrange to cyano-substituted cyclopentadienes[155] (equation 104).



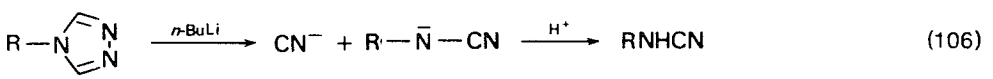
(104)

Lead tetraacetate oxidation of 4-amino-3,5-diphenyl-1,2,4-triazole gives the nitrene which splits into molecular nitrogen and two moles of benzonitrile[156] (equation 105).



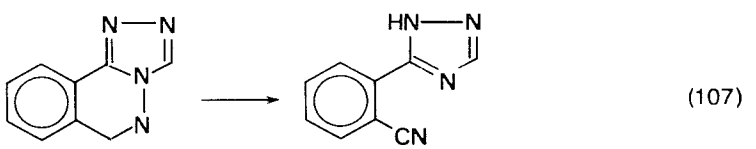
(105)

The scission of *N*-substituted 1,2,4-triazoles with *n*-BuLi allows a simple access to monosubstituted cyanamides[157] (equation 106).



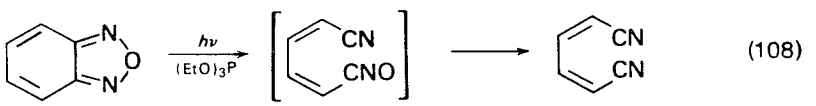
(106)

Refluxing the triazolophthalazine shown in equation (107) in ethanol with a catalytic amount of potassium hydroxide produces the *o*-triazolylbenzonitrile[158] (equation 107).



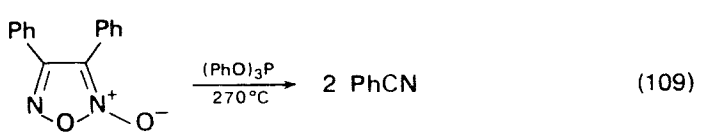
(107)

Benzo- and naphtho- furazanes can be photolytically deoxygenated with triethyl phosphite as oxygen acceptor to give *Z,Z*-butadienedinitriles. The reaction proceeds via the nitrile oxide[159] (equation 108).



(108)

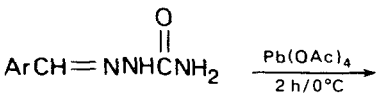
1,2,5-Oxadiazole-*N*-oxides are deoxygenated with triphenyl phosphite at elevated temperatures to give two moles of nitrile[160] (equation 109).

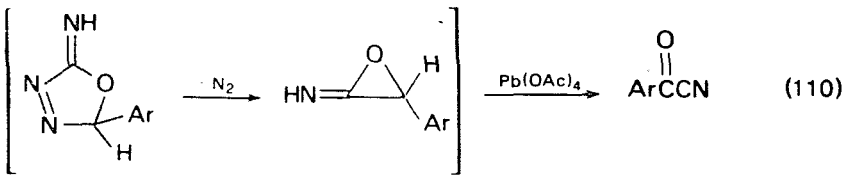


(109)

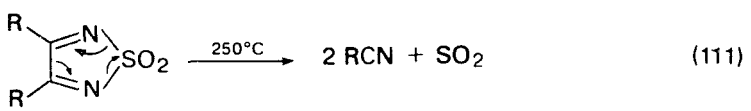
The semicarbazone of 4-dimethylaminobenzaldehyde is oxidized with lead tetraacetate to yield 4-dimethylaminobenzoyl cyanide. Intermediates of this reaction are an imino-1,3,4-oxadiazoline, followed by an iminooxirane[161] (equation 110).

At 250°C 1,2,5-thiadiazole-1,1-dioxides lose sulphur dioxide with the production of two moles of nitrile[162] (equation 111).



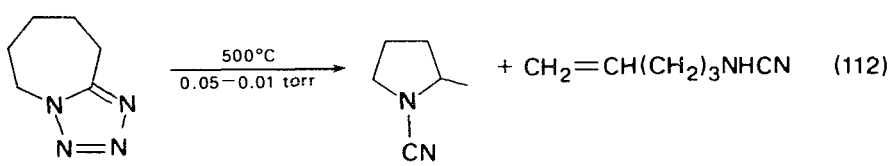


(110)



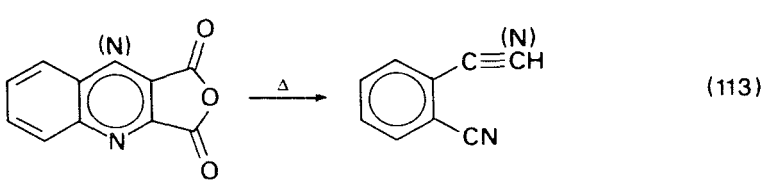
(111)

The thermal decomposition of polymethylenetetrazoles yields substituted cyanamides. Pentamethylenetetrazole is cleaved to nitrogen and a mixture of *N*-cyano-2-methylpyrrolidine and 4-pentenylcyanamide[163] (equation 112).



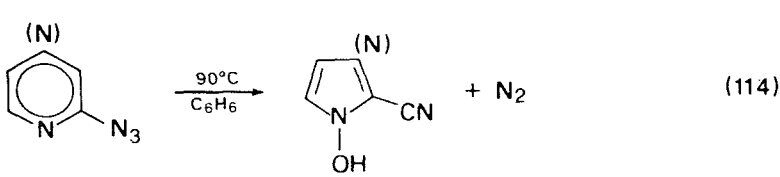
(112)

Thermolytic fragmentation of quinoxaline- and quinoline-2,3-dicarboxylic anhydrides in the gas phase gives phthalonitrile and 2-cyanophenylacetylene, respectively[164] (equation 113).



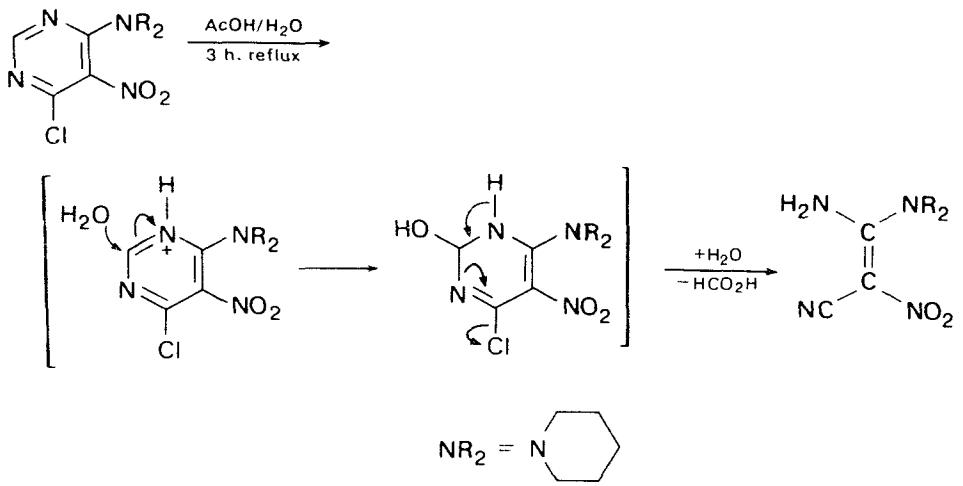
(113)

The thermal decomposition of 2-azidopyridine-1-oxides or 2-azidopyrazine-1-oxides is accompanied by ring-contraction. The products are 2-cyano-1-hydroxypyrroles or 2-cyano-1-hydroxyimidazoles respectively[165] (equation 114).



(114)

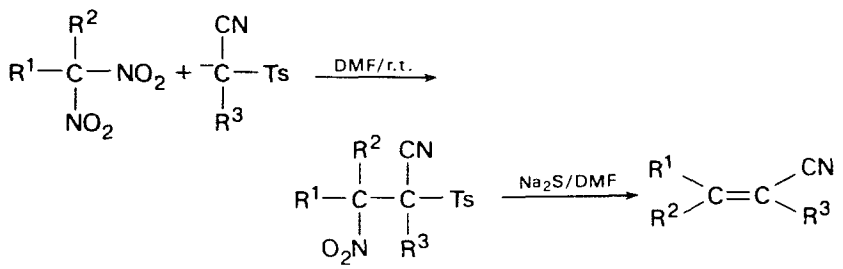
Under acidic conditions 4-chloro-5-nitro-6-piperidinopyrimidine is cleaved to 2-nitro-3-amino-3-piperidinoacrylonitrile[166] (equation 115).



(115)

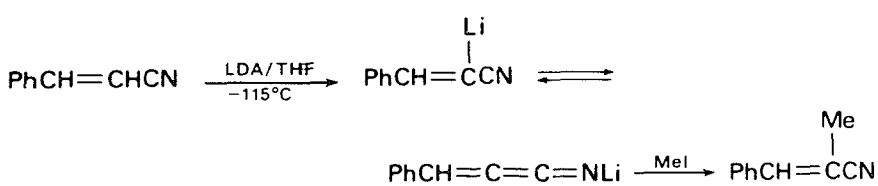
VI. PREPARATION OF NITRILES BY CONVERSION OF OTHER NITRILES

One important aspect of nitrile chemistry is the stabilizing effect which the cyano group exerts on adjacent carbanion or radical centres. Many of the methods in this chapter take advantage of this effect. Cyanomethylsulphone anions react with geminal dinitro compounds to give β-nitrocyanosulphones which can be converted by reductive elimination into cyanoalkenes[167] (equation 116).



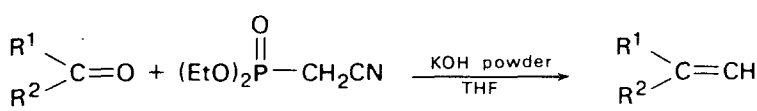
(116)

trans-Cinnamonitrile is metalated by LDA at low temperatures to give the α-lithio derivative, which furnishes alkenenitriles with alkylating agents[168] (equation 117).



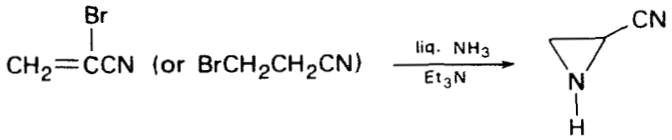
(117)

The Wittig–Horner olefin synthesis has been used in a solid–liquid two-phase system to prepare alkenenitriles[169] (equation 118).



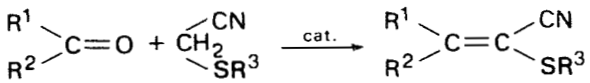
(118)

Unsubstituted 2-cyanoaziridine is prepared by a Michael addition–ring-closure sequence from α-bromoacrylonitrile and ammonia[170] (equation 119).



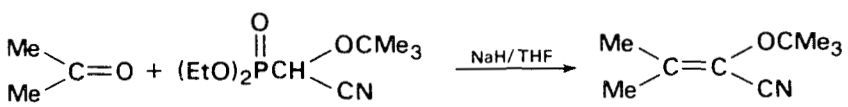
(119)

Thioalkylacetonitriles readily undergo Knoevenagel condensations with aldehydes or ketones in the presence of sodium ethylate[171], piperidine[172] or Triton B[173] (equation 120).



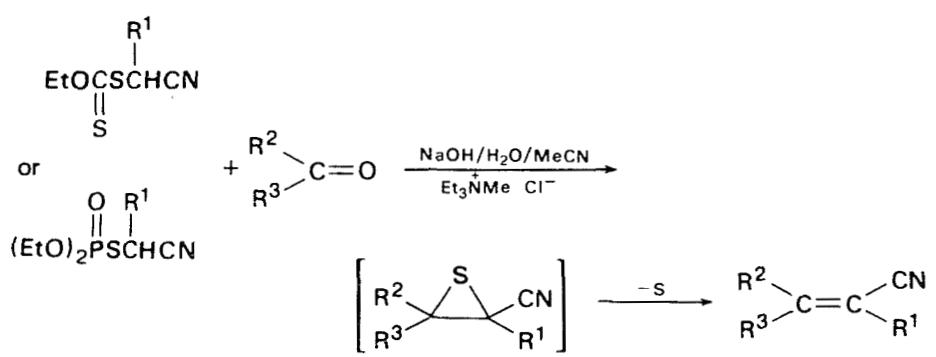
(120)

α-Alkoxyacrylonitriles have been prepared by the Horner–Emmons modification of the Wittig reaction[174] (equation 121).



(121)

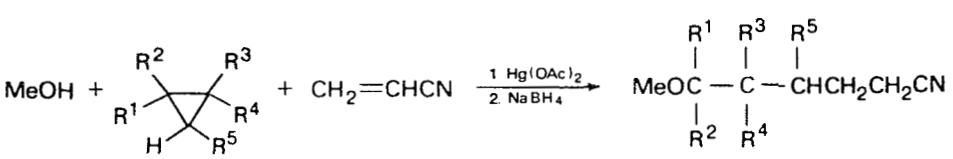
An olefin synthesis especially suitable for aliphatic ketones or aldehydes, giving 2-alkenenitriles, uses *O*-ethyl-*S*-cyanomethyl dithiocarbonate or *S*-cyanomethyl diethyl phosphorothioate in a two-phase system[175] (equation 122).



(122)

The use of the cyanosilylation products of aromatic aldehydes as carbonyl equivalents[24,25] has already been reported in Section II.B.

The radical chain reaction, started by the reduction of alkyl mercuric salts with sodium borohydride in the presence of electron-deficient alkenes has been used as a nitrile synthesis. For example cyclopropanes, which are precursors for 3-methoxyalkyl mercuric salts, can undergo C—C bond-formation reactions with acrylonitrile[176] (equation 123).



(123)

Heavy metal (Ag, Mn, Pb, Cu) oxides initiate the radical addition of nitriles to terminal alkenes[177] (equation 124).

$$RCH{=}CH_2 + \underset{|}{\overset{CH_3}{}}CH_2CN \xrightarrow[220\,^\circ C/10\ h]{PbO_2} RCH_2CH_2\underset{|}{\overset{CH_3}{}}CHCN \qquad (124)$$

Electrolysis of cyanoalkanes at high electrode potentials (8–10 V) in the presence of bromoalkanes gives the α-*C*-alkylation products[178]. Aromatic compounds undergo a photochemical cyanomethylation reaction with chloroacetonitrile[179]. Electrolysis of acetonitrile together with alkyl benzoates in acidic medium results in the formation of benzoylacetonitrile[180].

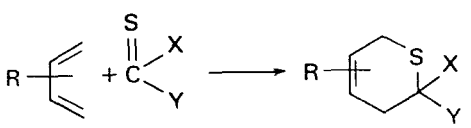
The reaction of aroyl cyanides with dichloromethylenetriphenylphosphoranes, prepared *in situ*, provides a convenient synthesis of 2-aryl-3,3-dichloroacrylonitriles[181] (equation 125).

$$ArC(=O)CN + [Ph_3P{=}CCl_2] \longrightarrow ArC(=CCl_2)CN \qquad (125)$$

Triphenyliminophosphoranes react with acyl cyanides to form iminonitriles[182] (equation 126).

$$RC(=O)CN + Ph_3P{=}NPh \xrightarrow[2\ h\ reflux]{CH_2Cl_2} RC(=NPh)CN \qquad (126)$$

A number of Diels–Alder reactions have been reported using cyano-activated thiocarbonyls as dienophiles. The corresponding thiacyclohexenes are formed by addition of thiophosgene[183], methyl cyanodithioformate[184], thiomesoxalic diamide[132] or *N*-substituted cyanothioformamides[185] (equation 127). Methyl



(127)

cyanodithioformate[186] and cyanodithioformamides[187] have also been used in ene-addition reactions. 1,3-Dipoles add readily to cyanothioformamides[188]. Cyanogen azide with olefins gives *N*-cyanoimines and/or 1-cyanoaziridines[189] (equations 128 and 129).

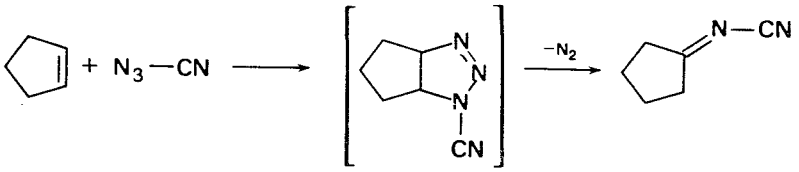
The reaction of cyanogen azide with enamines of cyclic ketones constitutes a new method for effecting ring-contractions[190] (equation 130).

Cyanogen azide reacts selectively with acylmethylenephosphoranes yielding *N*-cyano-α-diazoimines[191] (equation 131).

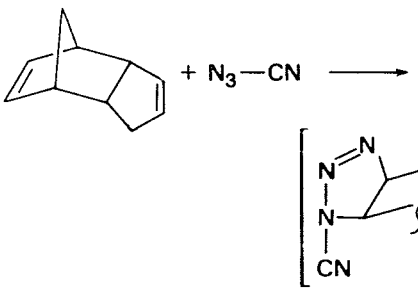
A modification of the 'hypoiodite reaction' has been used to transform the methyl group in position 13 in steroids into a cyanomethyl function. The photolysis of the 11-nitrite converts this methyl group into a radical centre, to which the cyano group of a cyanohydrin in position 17 is transferred[192] (equation 132).

By heating dicyanomethylenesulphuranes with triphenylphosphine at 130°C for several hours dialkylmalonitriles are produced[193,194] (equation 133).

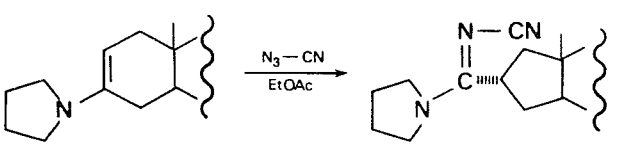
Chloromethylenemalononitrile and ethyl chloromethylenecyanoacetate react with aromatic compounds in the presence of aluminium chloride to give the arylmethylenemalonic acid derivatives[195] (equation 134).



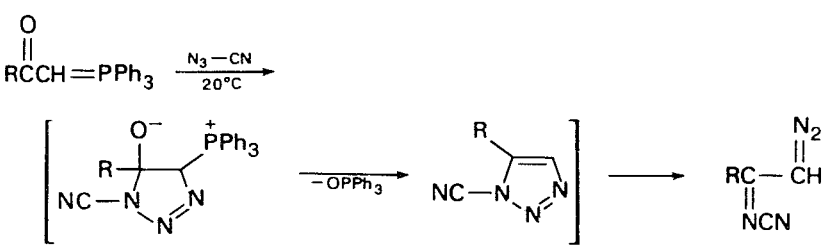
(128)



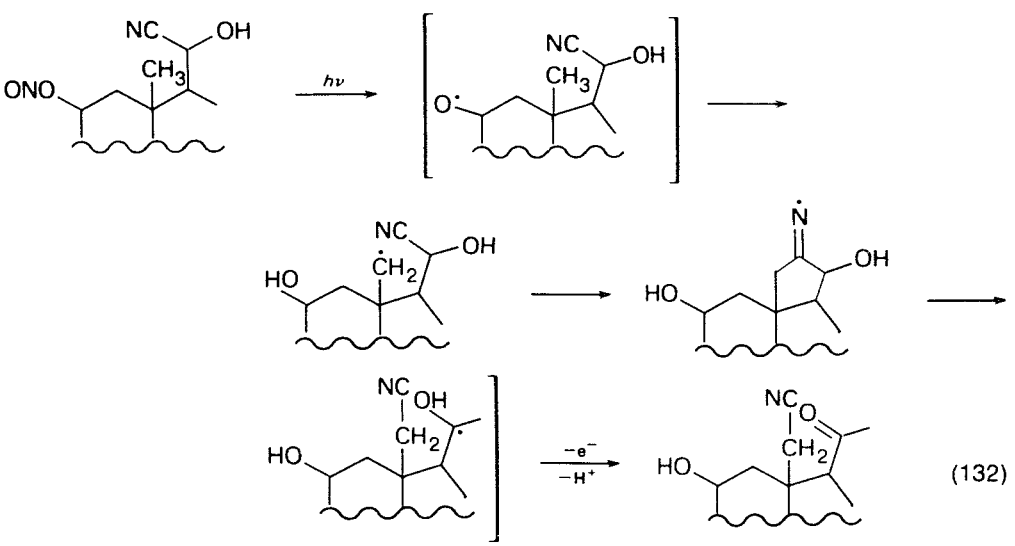
(129)



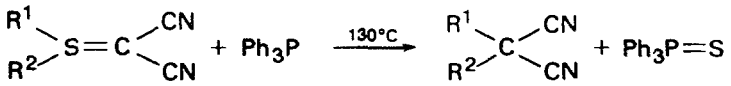
(130)



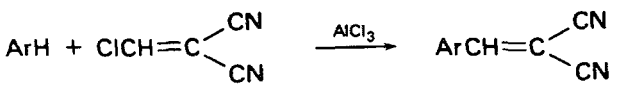
(131)



(132)



(133)

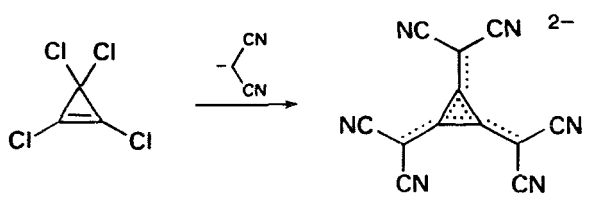


(134)

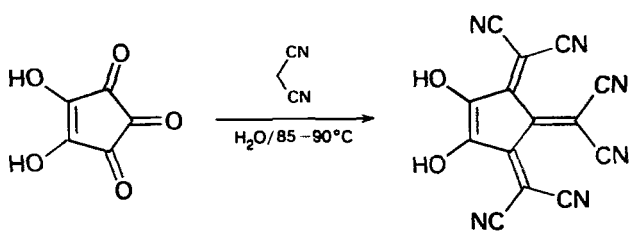
Malononitrile anion reacts with the tosylate of oximinomalononitrile yielding the highly stabilized tetracyano-2-azapropenide anion[196] (equation 135).

(135)

Further examples of polycyanocarbon anions or acids are the trimethylenecyclopropane dianions produced by the reaction of tetrachlorocyclopropene and malononitrile (or cyanoacetic ester etc.) in the presence of sodium hydride[197] (equation 136) and the 1,2,3-tris(dicyanomethylene)croconates, obtained from croconic acid and malononitrile in aqueous solution[198] (equation 137).



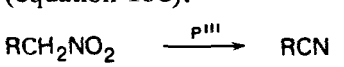
(136)



(137)

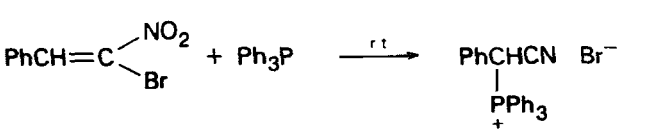
VII. PREPARATION OF NITRILES BY MISCELLANEOUS METHODS

Useful sources for the preparation of nitriles may be aliphatic nitro compounds, which can under certain conditions be reduced to yield the cyano function. Mainly compounds with phosphorus in lower valence state are used, such as tris(dimethylamino)phosphine[199], phosphorus trichloride[200] or diphosphorus tetraiodide[201] (equation 138).



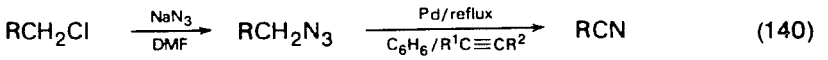
(138)

1-Bromo-1-nitro-2-phenylethylene reacts with 3 moles of triphenylphosphine to give a cyano-substituted phosphonium cation[202] (equation 139).



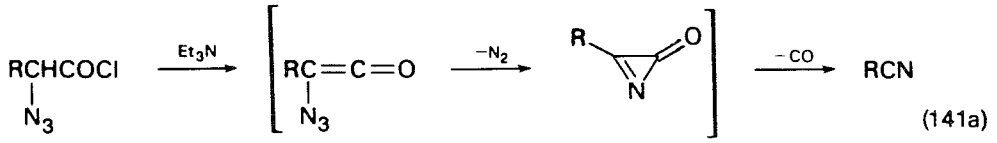
(139)

The decomposition of suitably structured azido compounds has been used to prepare nitriles. Primary azides are decomposed under the catalytic influence of palladium metal in refluxing benzene, a dialkylacetylene serving as a hydrogen acceptor[203] (equation 140).

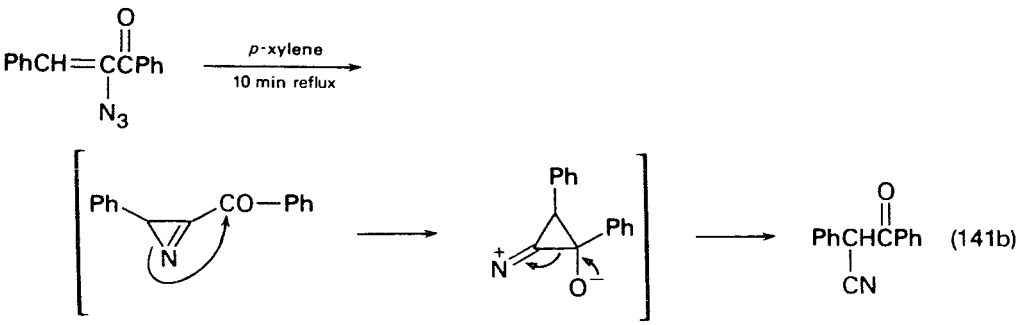


(140)

α-Azidocarbonyl compounds on decomposition yield nitriles via azirines, for example azidocarboxylic acid chlorides[204] (equation 141a) or azidoketones[205] (equation 141b).

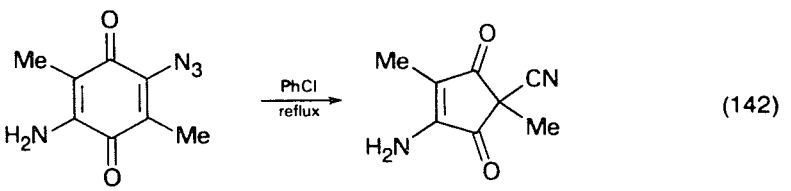


(141a)

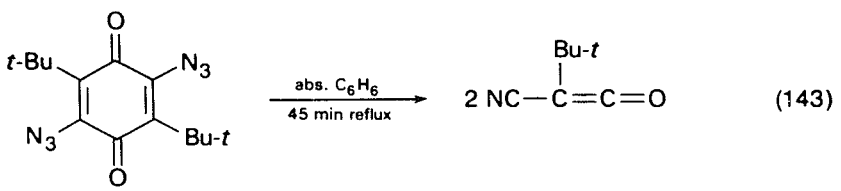


(141b)

2-Azidocycloheptatrieneone decomposes in boiling cyclohexane to give 2-cyanophenol[206]. Monoazidobenzoquinones give, on thermal decomposition, ring-contracted products[207] (equation 142) whereas 2,5-diazido-3,6-di(*t*-butyl)-benzoquinone is split into 2 moles of *t*-butylcyanoketene[208] (equation 143).

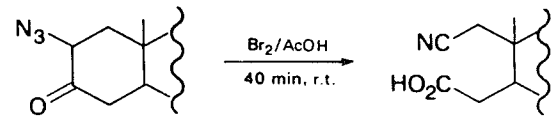


(142)



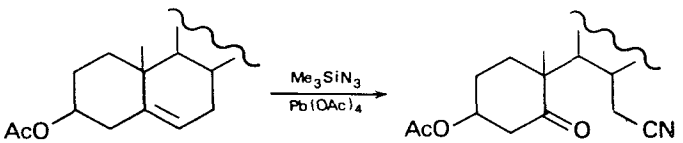
(143)

With bromine in acetic acid, cyclic α-azidoketones undergo ring-cleavage to produce dicarboxylic acid mononitriles[209] (equation 144).



(144)

The combination of lead tetraacetate and trimethylsilyl azide produces a reagent $Pb(OAc)_{4-n}(N_3)_n$ which cleaves olefinic bonds via the corresponding azidoaziridine to a ketone and a nitrile group[210] (equation 145).



(145)

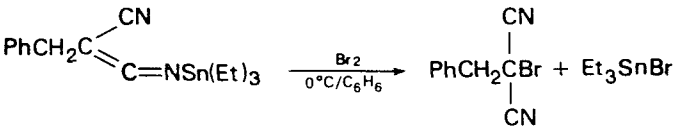
Amines or imines, on direct oxidation or on halogenation–elimination, may yield nitriles. *N,N*-Dichlorobutylamine reacts with caesium fluoride as a base in acetonitrile to give butyronitrile[211]. Triphenylphosphine acts as a defluorinating agent on polyfluoroalkylamines[212] (equation 146).

$$CFCl_2CF_2NF_2 \xrightarrow[-196°C \rightarrow r.t.]{2\ Ph_3P} CFCl_2CN + 2\ Ph_3PF_2 \qquad (146)$$

The autoxidation of benzylamine in the presence of an active cobalt oxide gives benzonitrile[213]. The reaction of benzaldehyde with ammonia in methanol/methylate anion followed by oxidation with iodine has been found to produce benzonitrile[214]. Bis(trifluoromethyl)-*N*-*t*-butylketenimine decomposes at 145°C to isobutene and the corresponding acetonitrile[215]. Benzaldimines on treatment with diisopropyl peroxidocarbonate generate benzimidoyl radicals which subsequently decompose to give nitriles[216] (equation 147).

$$PhCH{=}NBu\text{-}t \xrightarrow[60°C/C_6H_6]{(i\text{-}PrOCOO)_2} PhCN \qquad (147)$$

N-Trialkylstannylketenimines may be transformed to bromonitriles with elementary bromine[217] (equation 148).

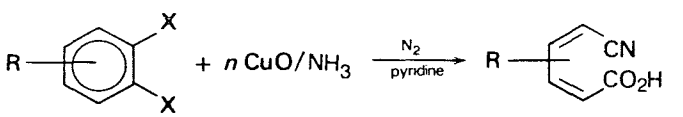


(148)

A generally applicable method for the conversion of nitrile oxides into nitriles under very mild conditions consists in reacting them with trimethyl phosphite[218] (equation 149).

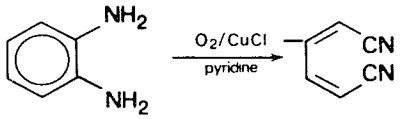
$$ArC{\equiv}NO \xrightarrow[100°C]{(MeO)_3P} ArCN \qquad (149)$$

O-Benzoquinones, catechols or phenols are starting materials for the Cu(II)-induced cleavage of C—C bonds in the presence of ammonia which furnishes mononitriles of muconic acids[219] (equation 150).



(150)

cis, *cis*-Muconononitrile is produced by the Cu(I)-catalysed oxidation of 1,2-diaminobenzene[220] (equation 151).

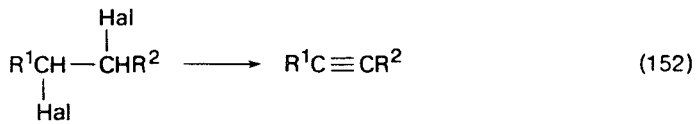


(151)

VIII. PREPARATION OF ACETYLENES BY ELIMINATION REACTIONS

A. Dehydrohalogenations

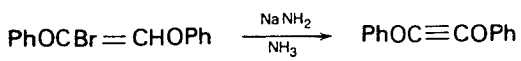
When starting from alkanes or alkenes mainly potassium hydroxide or alkoxides are used as bases. Therefore potassium *t*-butylate[221] or solid potassium hydroxide/glyme[222] convert vicinal dihalogeno compounds into the corresponding acetylenes (equation 152).



(152)

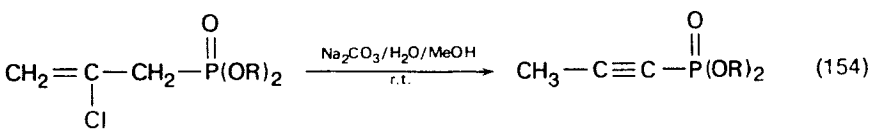
Hal = Br, I

Solid potassium *t*-butylate in ligroin is also effective in the presence of 18-crown-6[223]. The conversion of methylene ketones into acetylenes may be accomplished by treatment with phosphoryl chloride in DMF followed by dehalogenation of the chloroethene with potassium hydroxide in aqueous DMF[224]. Diphenoxyethyne is produced by dehydrobromination of the corresponding alkene with sodium amide in liquid ammonia[225] (equation 153).



(153)

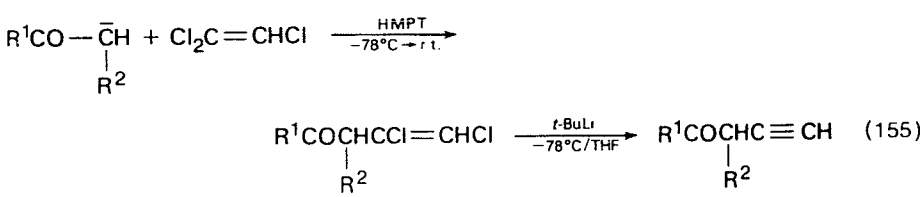
Activation of the hydrogen by a phosphonate group allows the use of weak bases for dehydrohalogenations[226] (equation 154).



(154)

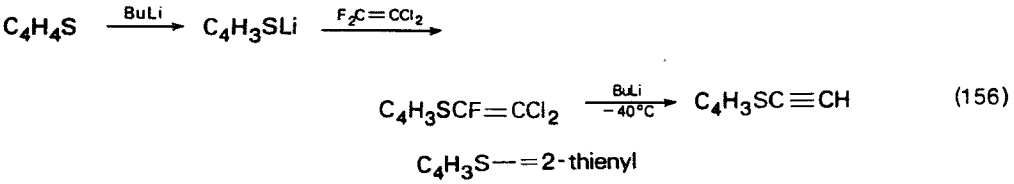
B. Dehalogenations

The dichlorovinylation of enolates with trichloroethene in HMPT at low temperatures yields α-dichlorovinyl ketones which may be dehalogenated by *t*-butyllithium to give the corresponding alkynes[227] (equation 155).



(155)

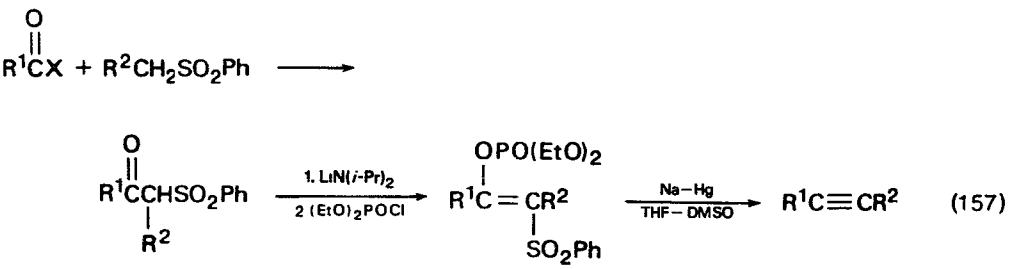
The ethynyl group may be introduced into the thiophen ring by reacting the 2-lithio derivative with 1,1-dichloro-2,2-difluoroethene followed by a reductive dehalogenation of the perhaloethene function with *n*-BuLi[228] (equation 156).



(156)

C. Miscellaneous β-Eliminations

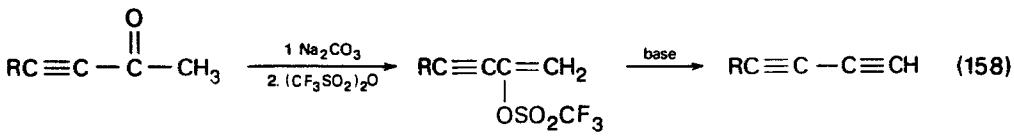
The acylation of aralkyl sulphones and the subsequent formation of the enol phosphate esters from the resulting β-keto sulphones yields alkenes which may be used as precursors for acetylenes[229] (equation 157).



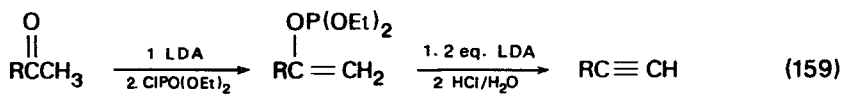
(157)

β-Chloro. ethers can be dechloroalkylated with lithium alkyls giving the corresponding acetylenes[230]. A method for the transformation of an alkynyl methyl ketone into a conjugated diyne uses β-elimination from the enol triflate[231] (equation 158).

Terminal acetylenes are obtained by a similar method via the enol phosphate esters[232] (equation 159).



(158)



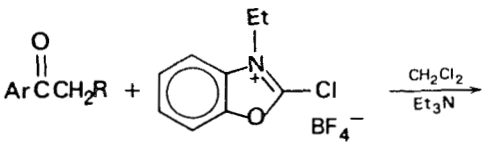
(159)

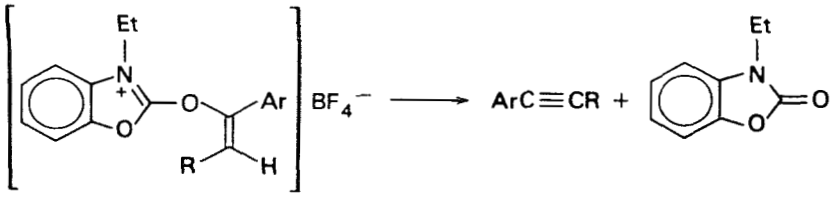
LDA = Lithium diisopropylamide

Reaction of methylene ketones with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in the presence of triethylamine converts them directly into acetylenes, the corresponding enol ether being an intermediate[233] (equation 160).

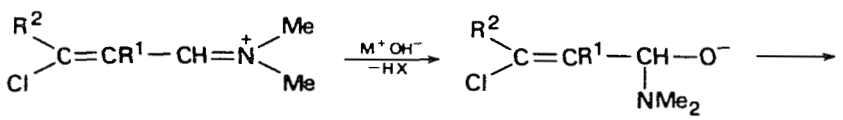
3-Chloro-2-propeneiminium salts add hydroxide ions, the adducts then fragmenting to alkynes, formamides and chloride anion[234] (equation 161).

Benzoylation of hexaphenylcarbodiphosphorane yields an adduct which on thermolysis, in analogy to the final step of the Wittig synthesis, decomposes to an





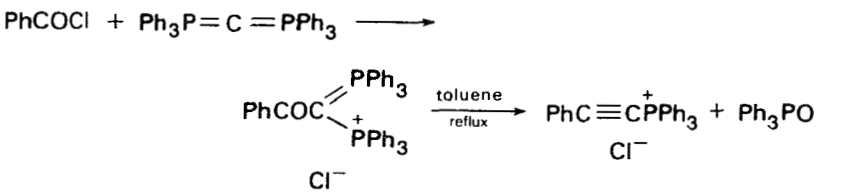
R = H, Br, PhS, Et

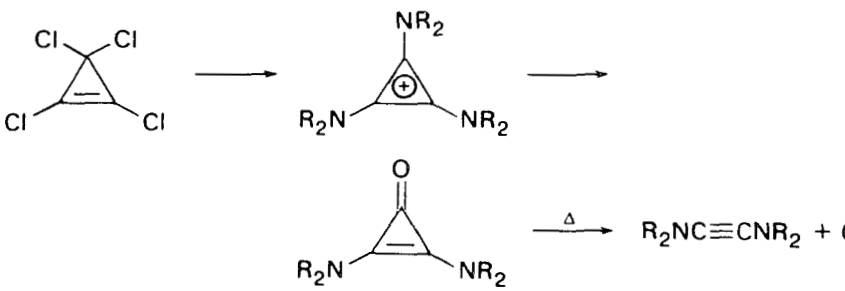


$$R^2C{\equiv}CR^1 + HCONMe_2 + M^+Cl^- \qquad (161)$$

arylethynyl triphenylphosphonium cation and triphenylphosphine oxide[235] (equation 162).

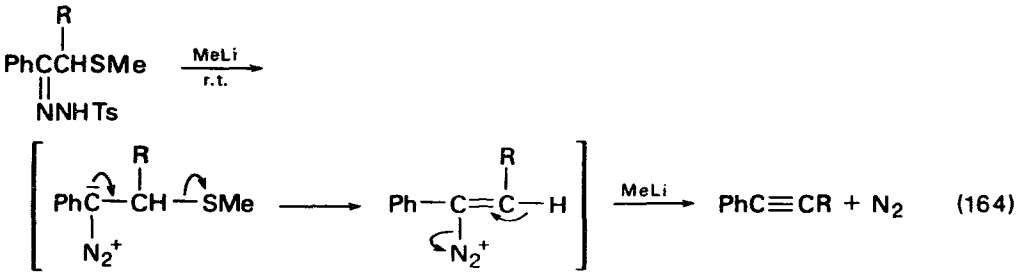
The pyrolysis of bis(dialkylamino)cyclopropenones, obtainable from tris(dialkylamino)cyclopropenium cations, affords bis(dialkylamino)acetylenes[236] (equation 163).





D. Elimination of Nitrogen from Hydrazones

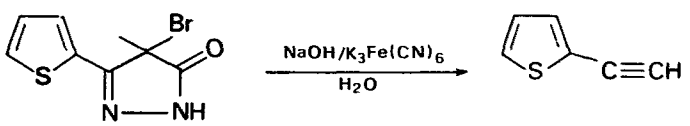
Some additional examples for this method have been reported during the last years, such as the oxidation of bishydrazones of 1,2-diketones by lead tetraacetate[221] and the reaction of tosylhydrazones with methyllithium to give a diazo compound, which in the presence of a suitable leaving group such as a thio ether, may fragment [237] (equation 164).



(164)

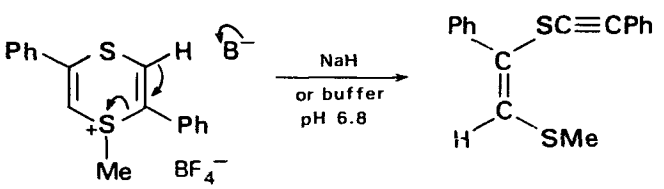
E. Ring-cleavage of Heterocycles

The reactions in this section are in fact eliminations, a C_2 moiety of the heterocyclic system producing the acetylene unit. Flash pyrolysis of 4-arylmethylene-5(4*H*)-isoxazolones at 700–800°C yields acetylenes[238]. 1,2,3-Selenodiazoles, obtainable from ketones via the semicarbazones with selenium dioxide, on pyrolysis give acetylenes[239]. This method continues to be applied to the synthesis of cyclic acetylenes[221,240]. A new acetylene synthesis is the reaction of 3,4-disubstituted 4-halo-2-pyrazolin-5-ones with aqueous sodium hydroxide in the presence of potassium ferricyanide[241] (equation 165).



(165)

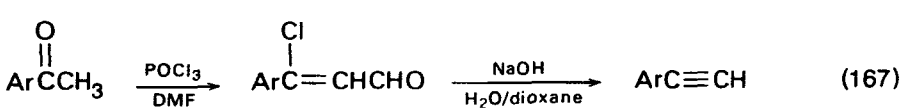
The selective abstraction of the hydrogen in position 3 of 1-methyl-2,5-diphenyl-1,4-dithiinium tetrafluoroborate in aqueous phosphate buffer leads to ring-cleavage and formation of an acetylenic thio ether[242] (equation 166).



(166)

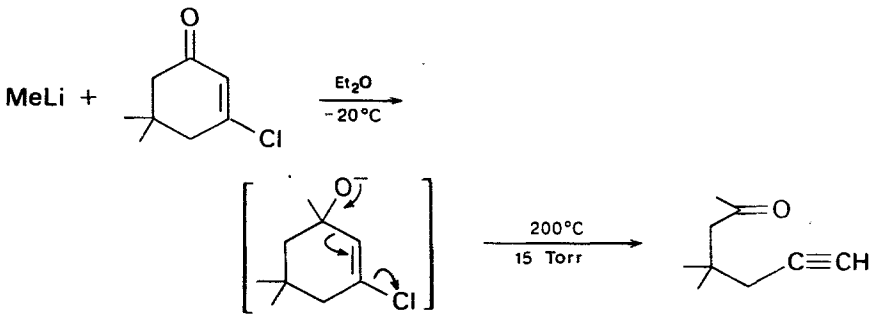
F. Fragmentations

Besides the Eschenmoser method[243], which has found further use[244], other fragmentations yielding acetylenes have been published. The conversion of methyl ketones into substituted β-chloroacroleins with phosphoryl chloride/DMF provides an access to acetylenes by reaction of the aldehyde with sodium hydroxide in aqueous dioxan[245] (equation 167).



(167)

The reaction of 3-chlorocyclohex-2-enones with methyllithium at −20°C gives the 1,2-addition product which fragment at 200°C to the corresponding acetylenic ketone[246] (equation 168).

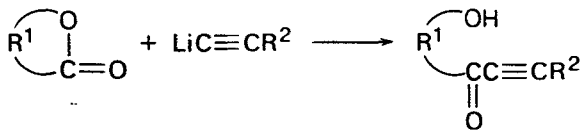


(168)

IX. PREPARATION OF ACETYLENES BY SUBSTITUTION REACTIONS

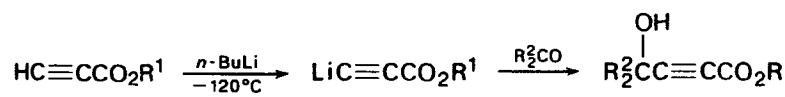
A. Alkali and Alkaline Earth Metal Acetylides

Lithium derivatives of terminal acetylenes have been used in reactions with five-[247] and six-ring lactones[248], yielding the corresponding acetylenic ketones (equation 169).



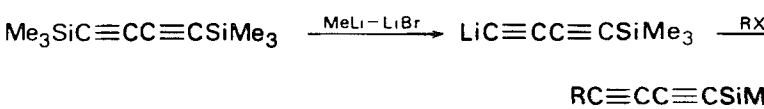
(169)

2-Butynoic acid is transformed with *n*-BuLi at −78°C into the dianion which can be γ-alkylated with haloalkanes, while metalation with LDA and alkylation in the presence of cuprous iodide at −78°C gives the α-alkylation product instead[249]. At −120°C propiolic esters may be alkylated with *n*-BuLi and the acetylide anions added to a variety of carbonyl compounds to give ethyl or methyl 4-hydroxy-2-alkynoates[250] (equation 170).



(170)

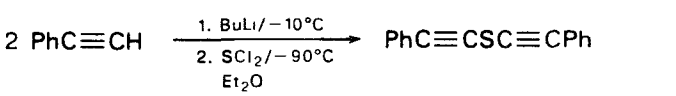
Cleavage of bis(trimethylsilyl)butadiyne with the methyllithium–LiBr complex[251] gives the monometalated diyne which may be reacted with primary haloalkanes[252] (equation 171).



(171)

The enantioselective addition of monosilylated acetylene to benzaldehyde in the presence of *n*-BuLi with (2*S*, 2′*S*)-2-hydroxymethyl-1-[(-methylpyrrolidin-2-yl)-methyl]pyrrolidine as a chiral ligand has been reported[253].

Di(1-alkynyl) sulphides are obtained by reaction of lithiated phenylacetylene with sulphur dichloride at −90°C[254] (equation 172).



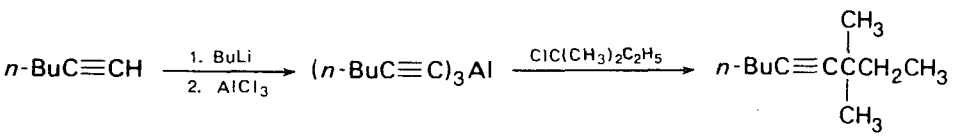
(172)

The dianion prepared from phenyl propargyl selenide with LDA can be used as a synthetic equivalent of acrolein dianion[255]. The reaction of an acetylenic Grignard reagent with methanephosphonic acid methyl ester chloride has been used to prepare acetylenephosphinic ester[256]. An improved synthesis of 1,4-diynes uses 3-tosyloxypropyne instead of the corresponding bromide for the reaction with acetylene Grignard reagents[257] (equation 173).

$$HC{\equiv}CCH_2OTs + BrMgC{\equiv}CR \xrightarrow[THF]{CuBr} HC{\equiv}CCH_2C{\equiv}CR \qquad (173)$$

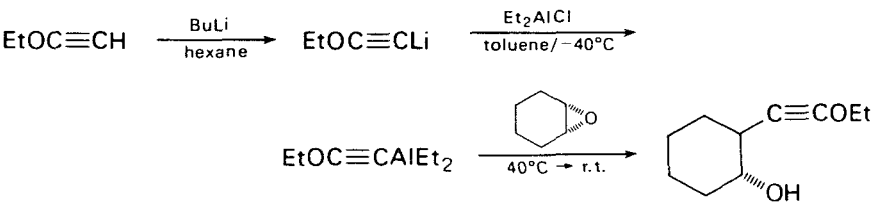
B. Aluminium and Silicon Acetylides

Lithiation of terminal acetylenes with *n*-BuLi followed by reaction with aluminium chloride yields the corresponding aluminium compound, which can be used for the coupling with tertiary alkyl groups[258] (equation 174).



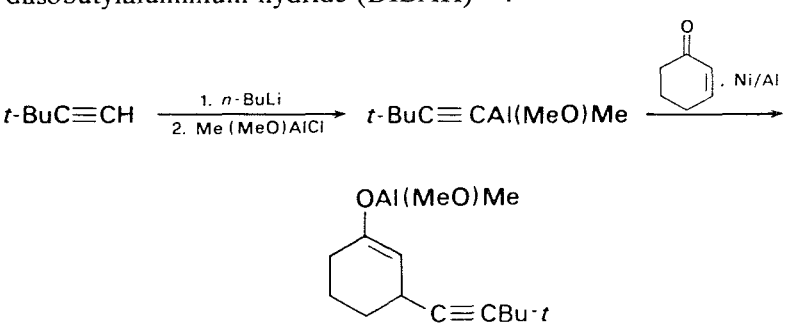
(174)

Ethoxyacetylene may be converted into the diethylaluminium derivative via the lithium compound. These aluminium derivatives have been found useful for the opening of oxidocycloalkenes[259] (equation 175).



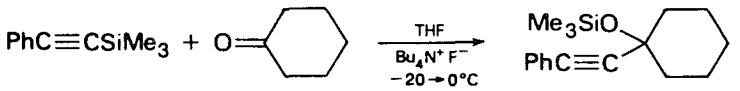
(175)

Aluminium acetylides have also been used for the nickel-catalysed conjugate addition to α,β-unsaturated ketones, either with a nickel–aluminium catalyst[260] (equation 176) or with a complex formed by reaction of $Ni(acac)_2$ and diisobutylaluminium hydride (DIBAH)[261].



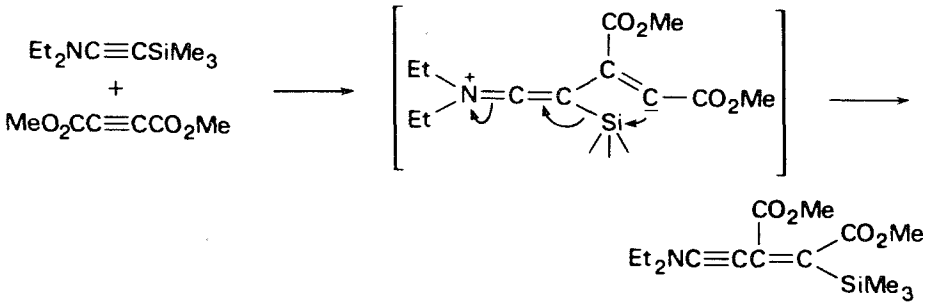
(176)

Silylated acetylenes can be added to carbonyl compounds in a fluoride-ion-catalysed reaction[262] (equation 177).



(177)

Silylynamines will add across active triple bonds such as in acetylenedicarboxylic esters. The product is the result of an 1,3-anionic rearrangement of the trialkylsilyl group from carbon to carbon[263] (equation 178).

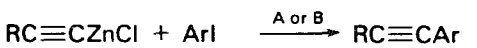


(178)

C. Zinc, Copper and Palladium Compounds

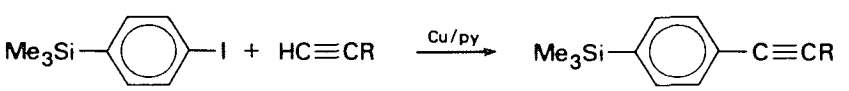
Alkynylzinc reagents undergo a palladium-catalysed reaction with aryl halides to give terminal or internal arylalkynes[264] (equation 179).

A copper acetylide is an intermediate in the reaction of aryl iodides with terminal acetylenes[265] (equation 180).



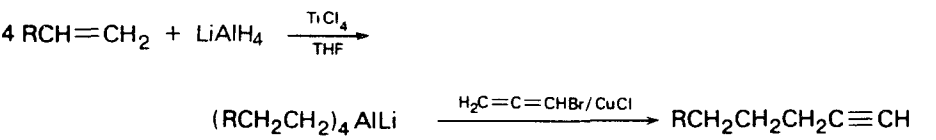
(179)

A = $Pd(Ph_3P)_4$, B = $Cl_2Pd(Ph_3P)_2$ + $(i\text{-}Pr)_2AlH$



(180)

The reaction of tetraalkylalanates, prepared by hydroalumination of 1-alkenes with lithium alanate in the presence of titanium tetrachloride, with bromopropadiene/CuCl has been found to be a convenient route to add the acetylene moiety to the terminal double bond[266] (equation 181).

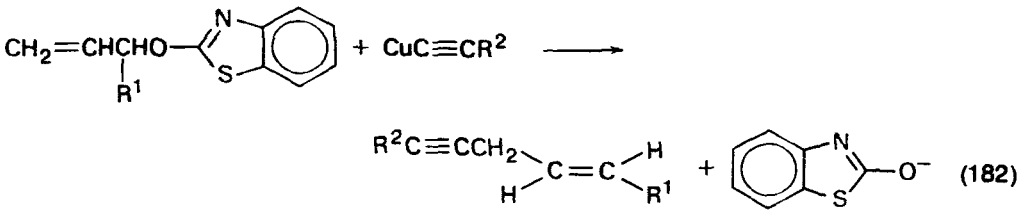


(181)

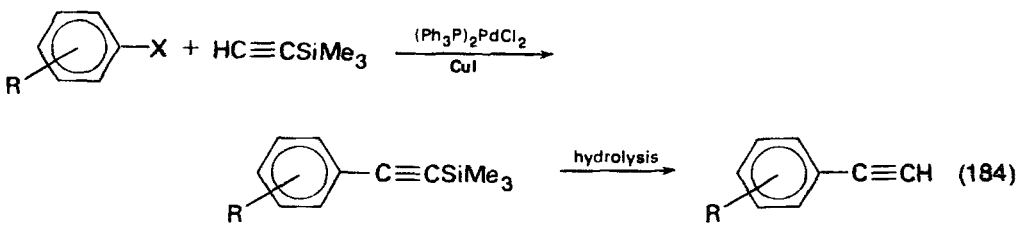
Allylic ethers of benzothiazole react with Cu(I) acetylides to afford 1,4-enynes under complete regio- and stereo-selective control[267] (equation 182).

The synthesis of acetylene carboxylates is possible by oxidative carboxylation of terminal acetylenes catalysed by $PdCl_2$ without reducing the triple bond[268] (equation 183).

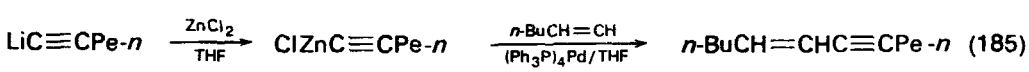
The alkylation of terminal acetylenes by aryl or vinyl halides induced by palladium compounds continues to attract interest[269]. Aryl bromides or iodides have been



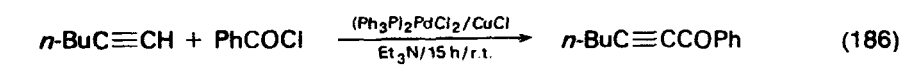
reacted with monosilylated acetylene in the presence of a palladium complex and copper(I) iodide (equation 184). The method is also applicable to dihalides.



Reaction of an alkynylzinc chloride, readily obtainable from the corresponding alkynyllithium compound and zinc chloride, with an alkyl bromide or iodide in the presence of a catalytic amount of a palladium–phosphine complex provides the corresponding terminal or internal enynes[264,270] (equation 185).

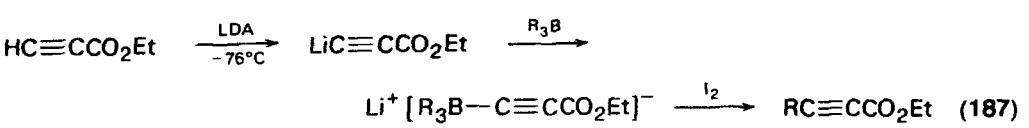


Dichlorobis(triphenylphosphine)palladium(II) together with cuprous chloride catalyses the formation of 1-alkynyl ketones from terminal acetylenes and benzoyl chloride[271] (equation 186).



D. Boranes

The iodine oxidation of alkynyltrialkylborates[272] has found further use. The preparation of lithium acetylides with LDA avoids the competitively occurring addition to other functional groups by BuLi[273] (equation 187).



The use of dicyclohexyl(methylthio)borane allows the synthesis of unsymmetrical 1,3-diynes by the route shown in equation (188)[274].

$$(C_6H_{11})_2BSMe \xrightarrow{LiC\equiv CR^1} (C_6H_{11})_2\bar{B}(C\equiv CR^1)(SMe)Li^+ \rightleftharpoons$$

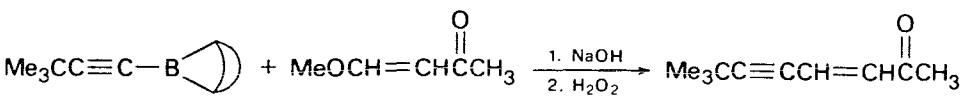
$$(C_6H_{11})_2BC\equiv CR^1 + LiSMe \xrightarrow{LiC\equiv CR^2}$$

$$(C_6H_{11})_2\bar{B}(C\equiv CR^1)(C\equiv CR^2)Li^+ \xrightarrow{I_2} R^1C\equiv CC\equiv CR^2 \quad (188)$$

(*E*)-1-Alkenyldisiamylboranes and (*E*)-1-alkenyl-1,3,2-benzodioxaboroles are obtainable via hydroboration of 1-alkynes. They react with 1-alkynyl halides or 1-alkenyl halides in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium and base to give the corresponding (*E*)-enynes[275] (equation 189).

$$\begin{matrix} R^1 & & H \\ & C=C & \\ H & & BX_2 \end{matrix} + R^2C\equiv CBr \xrightarrow[NaOEt/reflux]{(Ph_3P)Pd/C_6H_6} \begin{matrix} R^1 & & H \\ & C=C & \\ H & & C\equiv CR^2 \end{matrix} \quad (189)$$

A route to conjugated enynones consists in reacting alkynylboranes like 3,3-dimethyl-*B*-1-butynyl-9-borabicyclo[3.3.1]nonane as THF complex with 4-methoxy-3-buten-2-one and related derivatives[276] (equation 190).



(190)

The alkynyltrialkylborate formed by reaction of propargyl chloride with tricyclopentylborane adds acrolein to yield 3-hydroxy-6-cyclopentylhex-1-en-5-yne[277] (equation 191).

$$ClCH_2C\equiv CH + (C\text{-}C_5H_9)_3B \xrightarrow[THF,\ -90\text{ to }-80°C]{BuLi}$$

$$[(C\text{-}C_5H_9)_3BC\equiv CCH_2Cl]^-\ Li^+ \xrightarrow[2.\ [O]]{1.\ CH_2=CH-CHO} C\text{-}C_5H_9C\equiv CCH_2\underset{OH}{CH}CH=CH_2 \quad (191)$$

E. Haloacetylenes

A convenient synthesis of internal acetylenes uses the reaction of alkynyl bromides with trialkylalanes in the presence of bis(*N*-methylsalicylaldimine)nickel as a catalyst[278] (equation 192).

$$(i\text{-}Bu)_3Al + BrC\equiv C\underset{CH_3}{CH}C_2H_5 \xrightarrow{0°C/pentane} \left[\text{Ni-chelate}\right]_2 \quad i\text{-}BuC\equiv C\underset{CH_3}{CH}C_2H_5 \quad (192)$$

X. PREPARATION OF DIAZONIUM CATIONS

Only a few publications concerning the synthesis of diazonium cations have appeared since the last review article[279]. The chemistry of alkenediazonium salts has been reviewed[280] and another review deals with the diazotation of heterocyclic amines[281].

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