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THE MOLECULES R_2CXCR_2 INCLUDING AZOMETHINE, CARBONYL AND THIOCARBONYL YLIDES. THEIR SYNTHESES, PROPERTIES AND REACTIONS

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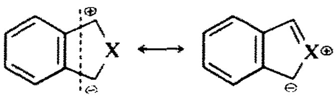
INTRODUCTION

The organic chemist must blend the rigor of theory with the art of synthesis. During the past several years an instructive demonstration of this pleasing and unique symbiosis has manifested itself in the development of the chemistry of the molecules R_2CXCR_2, X being a heteroatom. Interest in such molecules was reawakened about a decade ago as a result of new theory that posed problems and made predictions that could not be subjected to the test of experiment until the required synthetic methodology had been developed. This synthetic challenge has been significant and thus far only partially met; the state of affairs at this time reveals, however, a fascinating view of a portion of that subtle mozaic of theory and practice that is organic chemistry.

The *molecular fragment* C–X–C is a common one indeed, particularly for the cases where X is NR, O or S; for example, one need only consider the innumerable examples of the heterocycles **1a–c**. But the corresponding *molecules* R_2C–X–CR_2 wherein the molecular fragment has been excised from a ring system were comparative rareties 10 years ago. The potential chemistry of such entities had, however, already been partially unmasked in [benzo]-fused heterocycles like **2a–c**.

1 a: X = NR
b: X = 0
c: X = S



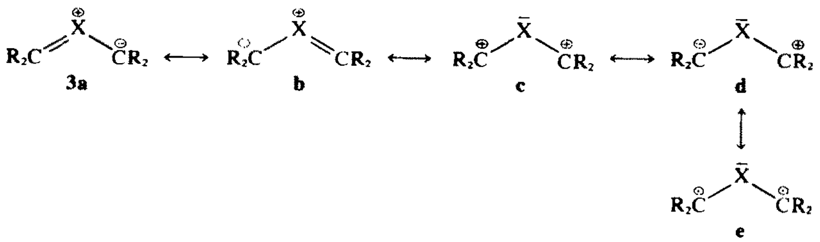
2a–c

Huisgen[1] recognized early that examples of **3** (X = NR, O or S) could (or did) exist and that for such cases the molecules would be 1,3-dipolar species of the "internal octet stabilization without double bond" type. Some potential resonance contributors are shown. (Before the formulation of the octet rule the consideration of such structures in the literature produced almost always impressive confusion).[2]† If X = NR the molecule is an azomethine ylide; if X = O a carbonyl ylide and for X = S a thiocarbonyl (more properly thione)[4] ylide.

Further reflection convinces one that there exists also a real potential for the existence of species with X = Se or PR (seleno carbonyl and phosphinomethine ylides, respectively). The bridging group X also could conceivably be $S\rightarrow O$ or $S\genfrac{}{}{0pt}{}{\nearrow O}{\searrow O}$ or the corresponding phosphorus derivatives; moreover, molecules bearing a formal charge like $R_2C{=}\overset{\oplus}{N}{=}CR_2$, $R_2C{=}\overset{\oplus}{P}{=}CR_2$, $R_2C{=}N{-}\overset{\ominus}{C}R_2$, are either known or reasonable structural possibilities. The electronic make-up of the latter species obviously can vary greatly from that of the uncharged 1,3-dipolar structures applicable for azomethine, carbonyl, or thiocarbonyl ylides.

Some seminal experiments and theories

Some events of recent history deserve extra mention. First the advent by Woodward and Hoffmann[5] of the concept of the conservation of orbital symmetry posed problems that required an experimental test. Particularly relevant was the following: cyclobutenes were predicted on thermal activation to open to 1,3-dienes with *conrotation* of the substituents, a non-least motion pathway. The prediction was assumed to apply to all systems containing



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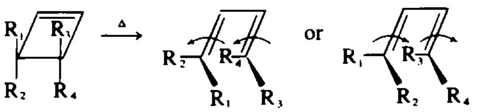
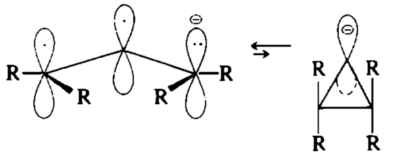
†But see, for example, the remarkably farsighted and cogent sorting out of this problem by Smith.[3]

4q participating electrons. This prediction had been amply verified[5] for the 1,3-butadiene-cyclobutene conversion (eqn 1). It was, however, by no means clear whether or not extrapolation was permissible to isoelectronic compounds having more or fewer atoms than butadiene but still the same number of electrons. Solid substantiation of the prediction would provide justification for wide-spread application to heterocyclic systems. The allyl anion (4) cyclopropyl anion (5) equilibrium, which usually lies entirely to the left, is a relevant, but non-heteroatom containing example (eqn 2). More pertinent, however, are the 1,3-dipolar species of general formula **6** recognized by Huisgen as having π-electronic systems isoelectronic with that of the allyl anion. Various cases wherein the 3-membered ring (**7**) and 1,3-dipole were in thermal equilibrium (eqn 3) were known. The opportunity to test the prediction of conrotation presents itself, however, only if *X* and *Z* in **6** are trigonal carbon atoms with their characteristic stereochemical integrity.



(1)



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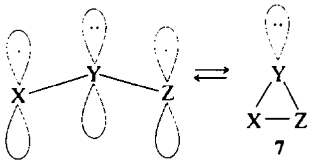
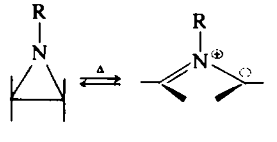
(2)



6 **7**

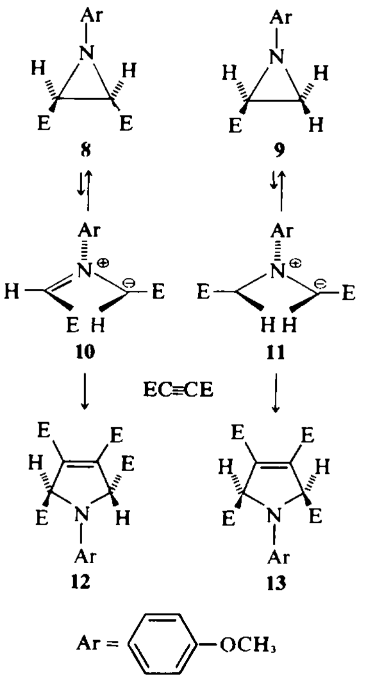
(3)

The desired reversible ring-opening (eqn 4) had long been known[2] with substituted aziridines though only recognized for what is at a considerably later date.[6] In an elegant exploitation of this observation of reversible valence isomerization Huisgen and his collaborators[7] prepared *cis*-**8** and *trans*-**9**, and demonstrated the stereospecific cycloaddition under thermal conditions to dimethyl acetylenedicarboxylate as shown in eqn (5). The stereochemistry of cycloadducts **12** and **13** demonstrates unequivocally that ring-opening to azomethine ylides **10** and **11** proceeds stereospecifically in the predicted conrotatory fashion followed by their capture by dipolarophile with retention of configuration (eqn 5). This clean and timely result provided impetus for further consideration of the chemistry of azomethine ylides as well as that of chemically related species.



(4)

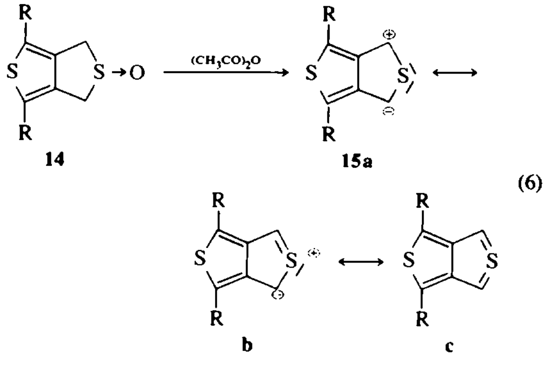
From a completely different angle a synthetic discovery raised anew an old and vexing problem. The neat synthesis (eqn 6) of the "non-classical" thiophene **15** by Cava and Pollack[8] in 1967 made topical once again the question of possible d-orbital participation in conjugation by elements of the third row; i.e. is uncharged **15c** an important resonance contributor? This question still continues to plague chemists since Pauling's original suggestion of the possibility in 1939.[9] More importantly, however, the very existence of **15** and related compounds and the demonstration that they reacted well as 1,3-dipoles made pertinent the question whether the parent thiocarbonyl ylide segment in **15** might have sufficient stability to be capable of existence.



8 **9** **10** **11** **12** **13**

(5)

$E = CO_2C_2H_5$



14 **15a** **b** **c**

(6)

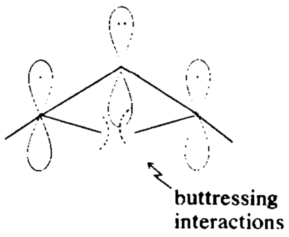
These two examples deserve mention because of their timeliness and simple elegance; themes drawn from these as well as other lines of thinking provided the incentive to a number of groups to attack with determination the problem of the R_2CXCR_2 molecules either as such or incorporated as a segment of a larger molecule but in such a way that their intrinsic properties are brought to the fore.

This review will have as theme almost exclusively the isolated R_2CXCR_2 molecules and in most cases only passing mention will be made of examples wherein the molecular fragment is a component of a larger heterocyclic system. For further details regarding "non-classical thiophenes" like **15** the interested reader is referred to the review by Cava and Lakshmikanthan,[10a] and for relevant literature on mesoionic structures containing these molecular fragments to Refs. 10*b,c,d*. Relatively more attention will be paid to those subjects that have not been reviewed previously in any detail.

STRUCTURAL AND ELECTRONIC PROPERTIES OF R_2CXCR_2

Walsh's[11,12] rules allow the prediction with qualitative accuracy of the ground state geometries of small molecules, even those too short-lived to be observed by direct methods. These rules consist of certain "magic numbers": for example, molecules H–X–H are linear if there are four or less valence electrons but bent if more are present; molecules H–X–Y are linear with 10 or less valence electrons but bent if this number is exceeded [HC≡N (10 valence electrons) is linear but CH_3OH (14 valence electrons) is bent]: molecules X–Y–Z are linear if they contain 16 or less valence electrons [linear CO_2 (16 valence electrons)] but nonlinear SO_2 (18 valence electrons). Molecules with three (not mutually bonded) ligands on the central atom Y are planar if they have less than 6 electrons for YH_3, 12 for AYH_2, 18 for ABYH, and 24 for ABCY. If these numbers are exceeded the molecule becomes pyramidal [for example $(CH_3)_3C^{\oplus}$ (24 valence electrons) is normally considered to be planar whereas NH_3 (8 valence electrons) is pyramidal]. On this basis the predictions shown are readily made. Cursory inspection convinces one that carbonyl and thiocarbonyl ylides **16** and **18** should be nonlinear but one could be led astray by an azomethine ylide (**17**), which is predicted to have planar rather than pyramidal nitrogen; the same applies for the as yet unknown phosphinomethine ylide **19**. For **20–23** (and one can devise many other interesting molecules) unambiguous demonstrations of existence remain to be given but we may predict, on the basis of impressive precedent, that should the species be generated that **20** and its derivatives will be linear, **21** and **22** will be planar, and **23** will have a pyramidal S atom.

As regards more detailed aspects of molecular geometry, we anticipate that for **16–19** the most stable structures will be those with sp^2-hybridized methylene groups lying in a common plane thereby allowing maximum overlap of the carbon 2p orbitals with a lone pair on the heteroatom giving the geometry of **24**. As already noted, this π-system is isoelectronic with that of the allyl anion or 1,3-butadiene. A potential problem in such a model will be the potential buttressing of the inner substituents in **24**, especially at smaller C–X–C interior bond angles.



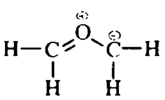
24

For more esoteric structures like **20–23** d-orbitals can well be involved in bonding. Models for the potential bonding situation in related compounds have been developed by Hoffmann *et al.*[13] Detailed discussion is not called for, however, until the interesting problems of synthesis have been successfully overcome.

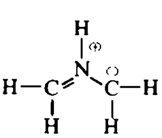
With some qualitative ideas of the structural features to be expected we now turn to the chemistry of the fairly commonly available moieties.

THIOCARBONYL YLIDES

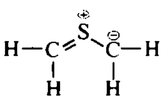
The thiocarbonyl ylide has been considered in the literature on various occasions. The first recognition of the structure appears to have been by Knott[14] in 1955 in conjunction with considerations of the contributions of this segment to the electronic make-up of certain dyestuffs. Knott very likely generated the unstable thiocarbonyl ylide (**25**) via the route of eqn (7).



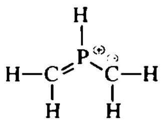
16
18 valence electrons
(non linear)



17
18 valence electrons
(planar)



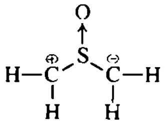
18
18 valence electrons
(non linear)



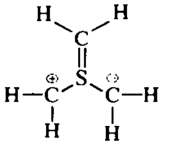
19
18 valence electrons
(planar)

HC≡S≡CH

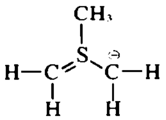
20
16 valence electrons
(linear)



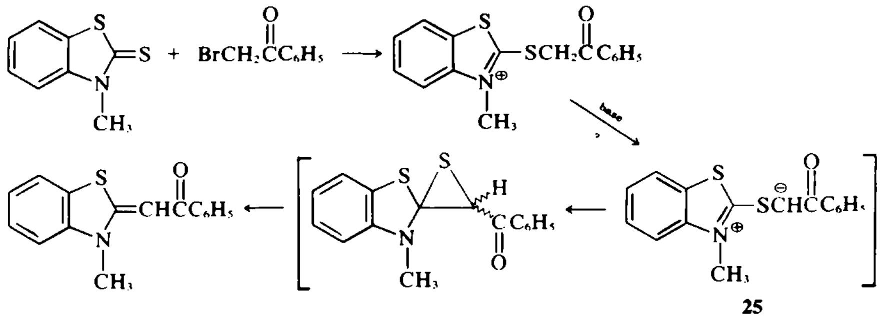
21
24 valence electrons
(planar)



22
24 valence electrons
(planar)

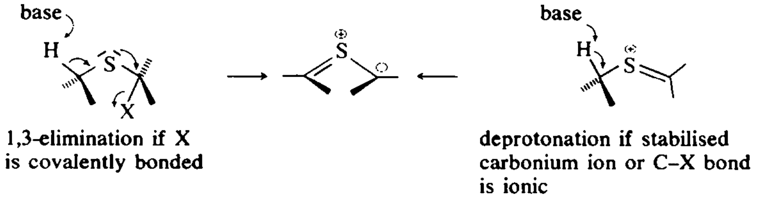


23
26 valence electrons
(pyramidal)



(7)

This synthetic approach, given in generalized form in eqn (8), has been subsequently followed by others. The fairly stable thiocarbonyl ylides **26** and **27**[15] have been prepared in this fashion. Less stable examples bearing an adjacent carbonyl group typically undergo the rearrangement shown in eqn (9).[16]



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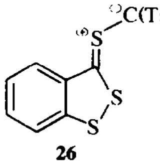

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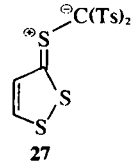

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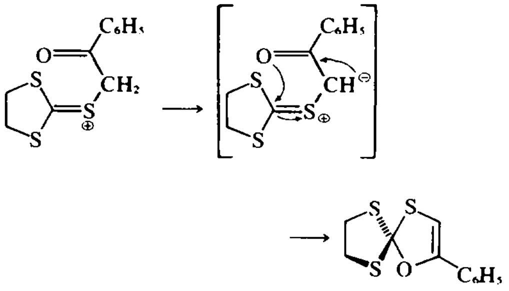
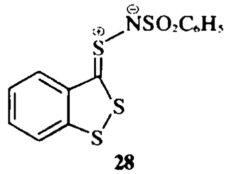


(9)

The 1,3-elimination route has been used also with success to prepare the related and stable thiocarbonyl (thione)-S-imides (**28**[17] and **29**)[2] as well as the well known sulfines, as exemplified by **30**.[18]†



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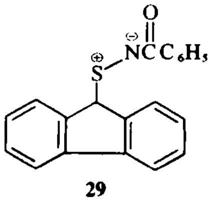

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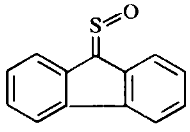
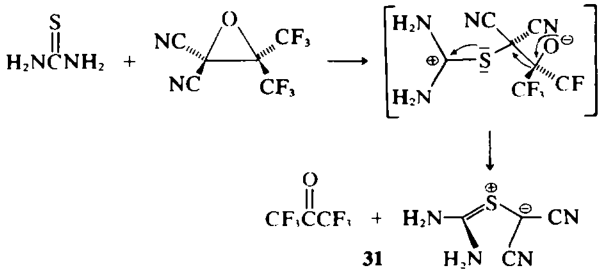


30

A fundamentally different concept is used in the synthesis of the very stable thiocarbonyl ylide (**31**) prepared by Middleton in 1966 (eqn 10);[20] tetracyanooxirane with thiourea was later found to give the same product.[21] The normal course of the reaction of thiourea with an oxirane is formation of a thiirane;[22] however in the reaction of eqn (10), owing to the unusual electronic properties of the oxirane, cleavage of the C–C bond intercedes.

The most flexible and general route to thiocarbonyl ylides as yet developed passes through the Δ^3-1,3,4-thiadiazoline ring system (**32**) as precursor; this on mild thermolysis smoothly releases nitrogen and produces the thiocarbonyl ylide **33**. The principle involved is that of a *retro*-1,3-dipolar cycloaddition. Two generalized routes to the precursor **32** are outlined in eqn (11).



(10)

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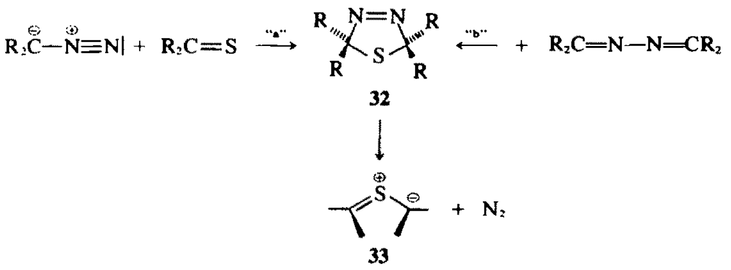
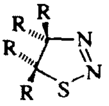
†Other examples of the 1,3-elimination route to (probable) thiocarbonyl ylides are available.[19]



(11)

Synthesis of examples of **32** through 1,3-dipolar addition of a diazo compound to a thioketone (route "a", eqn 11) appears first to have been attempted by Staudinger and Siegwart[23] and this was later followed up by Schönberg *et al.*[24] There was some dispute at the time as to the direction of cycloaddition since a Δ-1,2,3-thiadiazoline **34** is, of course, a possible product. However, in a typical experiment, the reaction of diphenyldiazomethane with thiobenzophenone, nitrogen evolution occurred immediately on mixing leading to tetraphenylthiirane as the only isolable product; the failure to isolate a cycloadduct made discussion of the direction of cycloaddition rather academic.

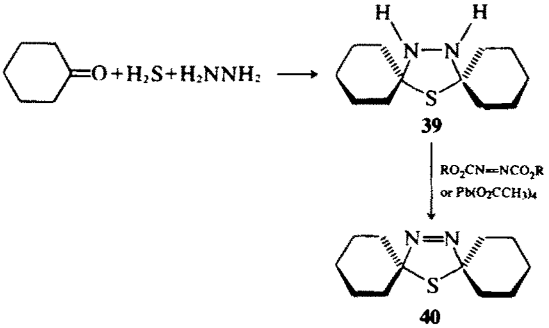


34

By using fluorinated components Middleton[25] was able to isolate the cycloaddition products **35** and **37** (eqn 12) and to establish the Δ^3-1,3,4-thiadiazoline structures. On mild warming loss of nitrogen occurred giving the thiiranes **36** and **38**, respectively.

A new attack on this ring system following in essence route "b" of eqn 11 was made simultaneously and independently by the groups of Prof. Barton at Imperial College and our own.[26,27] The key to the synthesis was a report in the literature that cyclohexanone (as well as some other aldehydes and ketones), hydrazine, and hydrogen sulfide condensed spontaneously at *ca.* −10 to −20° to form the 1,3,4-thiadiazolidine **39** (eqn 13).[28] The required dehydrogenation to give **40** was readily accomplished using a dialkyl azocarboxylate[29] or lead tetraacetate.[26]

On heating to 100° **40** smoothly loses nitrogen and produces in quantitative yield the thiirane **42**, which can be desulfurized to afford cyclohexylidenecyclohexane. The thiocarbonyl ylide **41** generated as a reactive and short lived intermediate can be trapped by a dialkylazodicarboxylate acting as a 1,3-dipolarophile; kinetic analysis of the scheme proposed in eqn (14) establishes unambiguously the transitory existence of intermediate **41**.[27]



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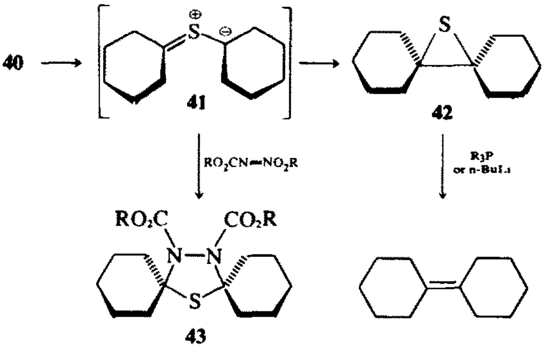
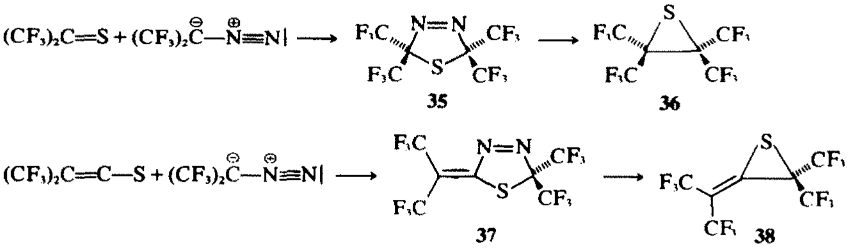
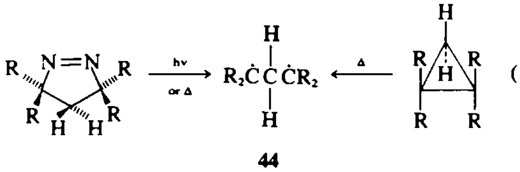


(14)

The thiocarbonyl ylide **41** represents to the best of our knowledge the first example of a R_2CXCR molecule having 1,3-dipolar characteristics and not stabilized by electron-withdrawing and/or conjugating groups. The basic chemistry is that indicated in eqn (14), valence isomerization of 1,3-dipolar cycloaddition. This parallels the chemistry already mentioned for azomethine ylides **10** and **11**, which are obviously well-stabilized 1,3-dipoles. But in fact intermediates like **41** could equally well be considered as close chemical relatives of the 1,3-biradicals (**44**) also intensively studied as potential intermediates in cyclopropane isomerizations or in the thermolysis and photolysis of Δ^1-pyrazolines (eqn 15).[30] One is provided in **41** and its relatives with the opportunity to study directly the effect of replacing the central

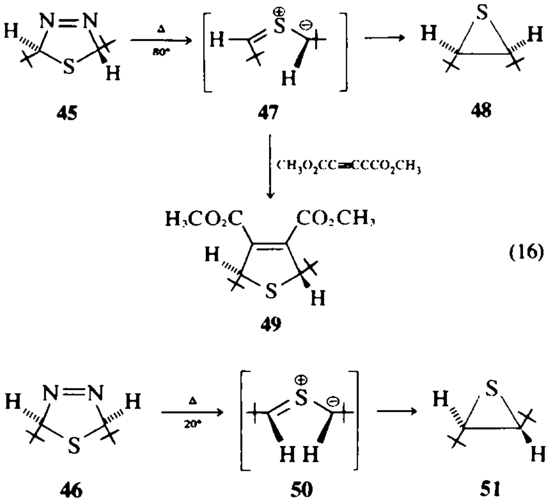


(12)



(15)

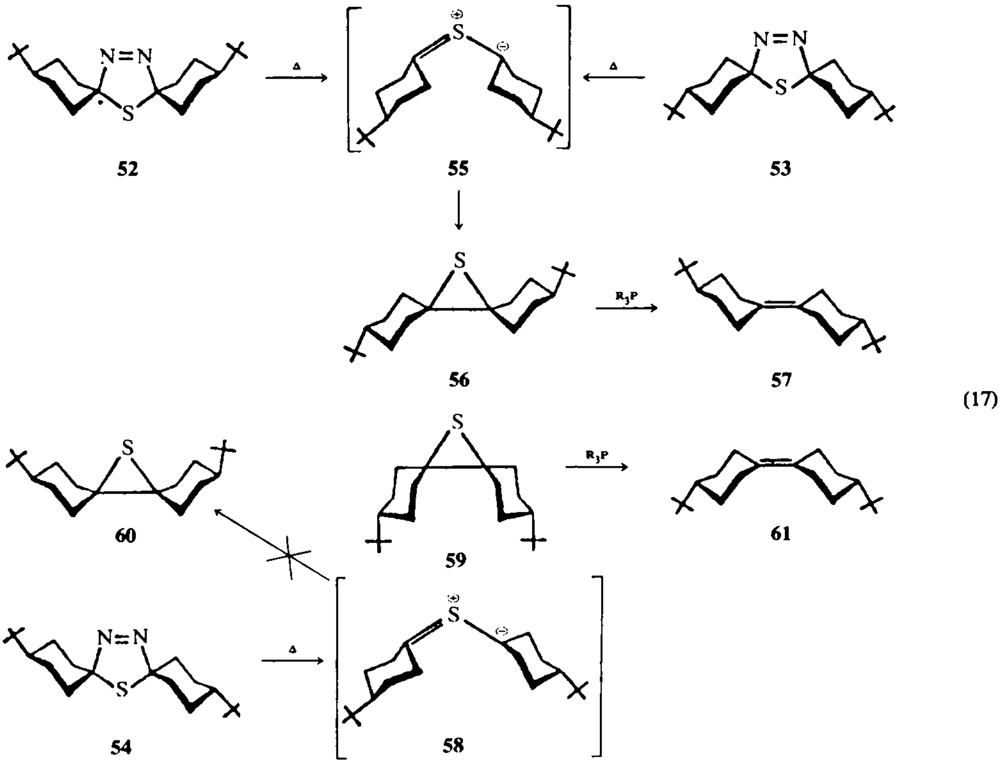
methylene of **44** with an atom containing a lone pair; in other words investigating the results of building in the opportunity for direct conjugation between the two radical centers in a system unbiased by the presence of substituents capable of distorting the electronic structure. (The allyl anion is, of course, also a model although the presence of a formal charge distorts the system; recently cycloadditions of the allyl anion derivatives have been demonstrated to go often in reasonable yield.)[31]



(16)

A significant problem was the degree to which such intermediates would follow the stereochemical predictions of the Woodward-Hoffmann rules. We were pleased to find in fact very rigid obedience to the Woodward-Hoffmann predictions as nicely demonstrated in the example shown in eqn (16).[32,33] The thiadiazolines **45** and **46** were made in the usual fashion; **45** is quite stable but **46** loses nitrogen slowly at room temperature. The predicted conrotatory ring-closure occurs with **47** to give thiirane **48** in 100% yield and 100% stereospecificity in a remarkable triumph of orbital symmetry effects over steric interactions. Cycloaddition of **47** proceeds with retention of configuration as predicted. The thiocarbonyl ylide **50** cannot be trapped but ring-closes in quantitative yield and 100% stereospecificity to thiirane **51**, the expected product of conrotation.†

Analogous stereochemical behavior has also been confirmed with ethyl rather than t-Bu substituents on the thiocarbonyl ylide.[33] Another interesting example is provided by the readily separable isomers **52**–**54** (eqn 17).[34] Isomers **52** and **53**, both having reflection symmetry of the two cyclohexyl rings, must give the same thiocarbonyl ylide **55** on pyrolysis. Brief thought reveals that conrotatory ring-closure of this intermediate must destroy the mirror symmetry; hence it is reasonable—but striking—that thiirane **56**, wherein the new carbon–carbon bond is axial-equatorial, is formed exclusively and in quantitative yield. Thiocarbonyl ylide **58**, on the other hand, must give a product(s) having reflection symmetry of the cyclohexyl rings; both **59** and **60** are allowed from orbital symmetry considerations but for reasons that are not entirely clear



(17)

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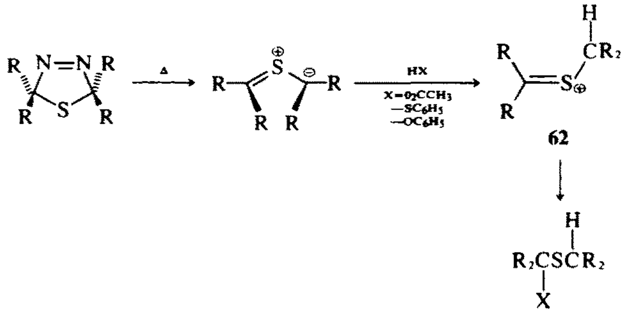
†Thiocarbonyl ylide **47** is not likely to be completely planar as indicated because of the difficulty of accommodating the "inside" t-Bu group. The methylene groups are likely tilted with respect to each other; the consequences of this are discussed in detail in Ref. 33.

only **59** is formed. Desulfurization affords the unique olefin isomers **57** and **61**, which have been used as rigid stereochemical frameworks upon which to test certain ideas concerning the mechanism of singlet oxygen reactions with olefins.[35]

Such simple thiocarbonyl ylides bearing only alkyl groups or hydrogen atoms as substituents can be trapped efficiently by 1,3-dipolar cycloaddition only with very potent dipolarophiles like dialkyl azodicarboxylates, dialkyl acetylenedicarboxylates, dicyanoacetylene, tetracyanoethylene and N-phenylmaleimide. Cycloadditions with diphenyl ketene also occur.[36] This requirement of active trapping agents need not indicate that such thiocarbonyl ylides are "poor" 1,3-dipoles but only that the efficiency of trapping must be very high indeed to compete successfully with *intra*molecular valence isomerization to a thiirane.†

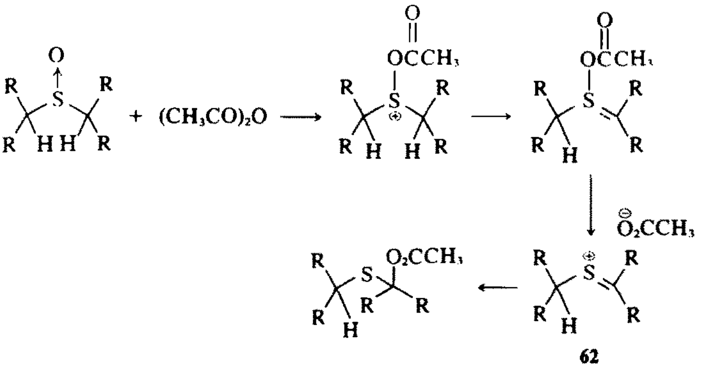
The most commonly encountered chemistry of thiocarbonyl ylides is, as has been seen, a competition between valence isomerization to a thiirane or 1,3-dipolar cycloaddition. One other type of reaction has been uncovered, however, which gives insight into the electronic make-up of the species. Simple thiocarbonyl ylides react well with various organic acids to give (often unstable) 1,3-addition products most likely via the pathway shown in eqn (18). This implies that the thiocarbonyl ylides are fairly potent carbon bases, i.e. that they readily manifest their potential to behave as sulfur ylides. This observation is pertinent for understanding a long-known reaction, the Pummerer rearrangement of a sulfoxide to an α-acetoxysulfide in the presence of acetic anhydride (eqn 19). The mechanism shown is believed to apply for this rearrangement.[38c] The reaction schemes of eqns (18) and (19) have in common the carbonium intermediate **62**. If this assumption is true one has, at least in theory, the possibility of devising a method to deprotonate **62** derived from the Pummerer reaction to obtain via the dehydration of a sulfoxide the thiocarbonyl ylide generated by pyrolysis of a Δ^3-1,3,4-thiadiazoline in eqn (18).‡ This would provide a considerable expansion of synthetic potential for thiocarbonyl ylides. This conversion can indeed be realized in specialized cases like that of eqn (20)[38] (also eqn 6); the key to success, however, seems to be that the proton to be removed be sufficiently acidic to be accepted by acetate ion more rapidly that coupling to the classical Pummerer product occurs.



(18)

Various ways to accomplish the deprotonation with simpler (and less acidic) sulfoxides suggest themselves but a satisfactory and general experimental solution to the problem remains to be delivered.

In practice the thiadiazoline route to thiocarbonyl ylides has been thus far the most practicable. In our experience[33] the addition of hydrogen sulfide to an azine following in essence path "b" of eqn (11) to form a 1,3,4-thiadiazolidine addition product (for example **39**, eqn 13) often leads to complications owing to the ready



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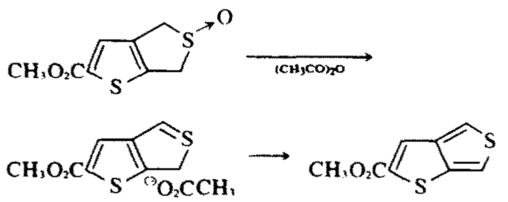

(20)

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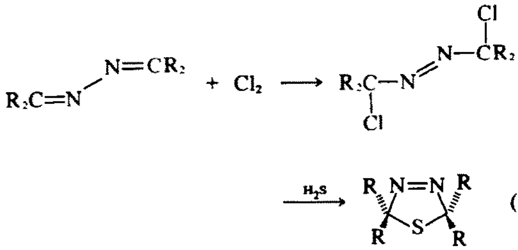
† Considerable attention has been given recently to questions of reactivity and regioselectivity with 1,3-dipoles using reasonably simple frontier orbital approaches.[37] There are unfortunately too few examples available and too little data on regioselectivity of cycloaddition to make at this time an analysis of thiocarbonyl ylide reactivity worthwhile.

‡ The Pummerer reaction does take place, however, even when deprotonation of the carbonium ion intermediate is impossible for structural reasons, i.e. with phenylmethylsulfoxide. Routes involving sigmatropic rearrangement of the ylidic intermediate are considered by most authors[37] not to be important.

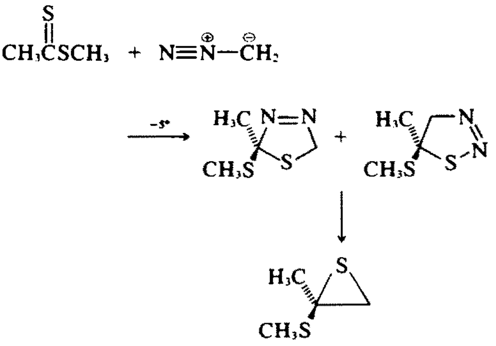
reversal (particularly in the presence of acid) of this reaction. A solution to this problem has been to avoid the thiadiazolidine stage by "oxidizing" the azine prior to reaction with hydrogen sulfide. This is accomplished readily by allowing the azine to react with chlorine in the cold to give the 1,4-dichloroazo addition products,[39] which on treatment with excess hydrogen sulfide provide the desired thiadiazoline and two equivalents of hydrogen chloride (eqn 21). In practice the synthesis is restricted to azines derived from aliphatic aldehydes and ketones—the ring-closure, in our hands at least, fails when aromatic groups are present—and to symmetrical azines owing to the difficulties in preventing nonsymmetrical azines from disproportionating under the conditions of the experiment.



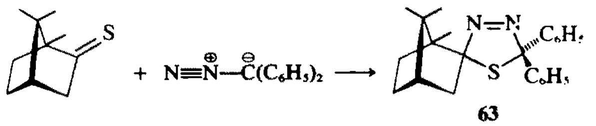
(21)

An alternative attack on the problem of thiadiazoline synthesis via route "a" of eqn (11) by the group of Sir Derek Barton has led to the elegant syntheses of a number of very strained alkenes.[40] The heterocyclic precursors have been assembled by a 1,3-dipolar cycloaddition of a thioketone and diazo compound, a typical example being shown in eqn (22). The Δ^3-1,3,4 rather than Δ^2-1,2,3-thiadiazoline structure for **63** was firmly established. Pyrolysis followed by desulfurization with triphenylphosphine gives in good yield **64**. In a similar fashion highly strained olefins like **65** and **66** were secured. The success of the approach hinges on the fact that the bulky substituents are first brought into the same molecule but held far enough apart so that steric hindrance is not severe; subsequent fragmentation of the molecule is exothermic and likely allows the new carbon–carbon bonds to be well joined before steric interactions develop to a high degree. A synthetic advantage of the approach is the fact that aliphatic thiones become more tractable to handle and easier to prepare as the amount of steric hindrance increases.†

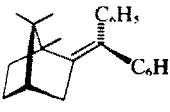
The addition of diazo compounds proceeds also with other thiones although the possibility of the formation of the alternative Δ^2-1,2,3-thiadiazoline structure becomes very real. A representative example is that shown in eqn (23).[43]



(23)



63 (22)



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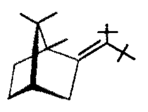

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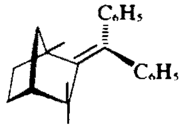

66

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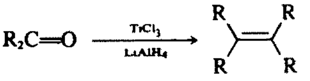
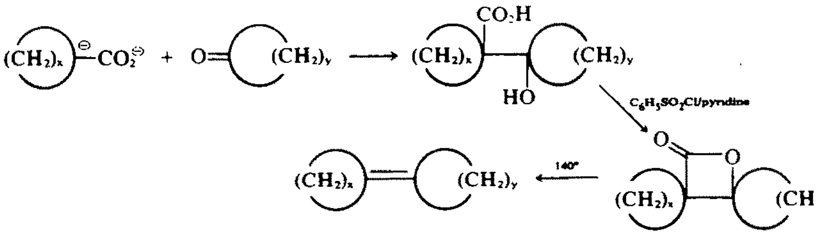
† If one is interested in a direct and effective route to a not especially hindered *symmetrical* alkene, the McMurry and Fleming synthesis (eqn i) is to be recommended.[41]



(i)

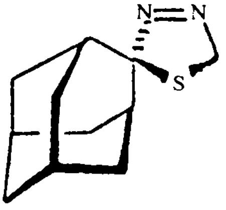
Nonsymmetrical as well as symmetrical cycloalkylidenecycloalkenes can be obtained by means of the method of Krapcho and Jahngen (eqn ii).[42]



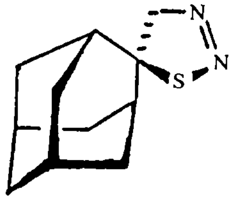
(ii)

The thiocarbonyl route to alkenes has the greatest utility for the preparation of strained compounds or in cases where the potential for stereochemical control during synthesis is required.

A solvent induced competition between the two modes of cycloaddition is also seen with adamantanethione and diazomethane; both products **67** and **68** are obtained.[44] The cycloaddition route has also been used to prepare remarkable spirocyclic compounds like **69**, which can be desulfurized to give **70** (eqn 24).[45] The thiadiazoline route to alkenes (in some cases starting from the azines) has been used with success for the solution of other synthetic problems.[46]



67



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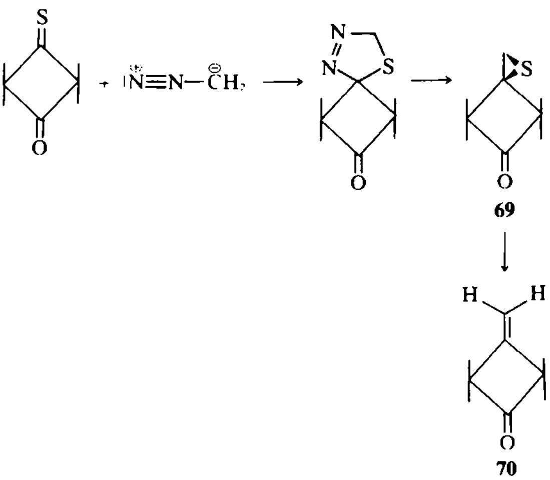
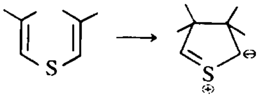


(24)

Thiocarbonyl ylides as well as other 1,3-dipolar species should in principle be obtainable via electrocyclic ring-closure of divinyl sulfides (eqn 25). A nice application of this principle, which may have reasonable generality, is seen in eqn (26) wherein the desired cyclization is brought about photochemically.[47] The successful subverting of the **71**→**72** conversion by N-phenylmaleimide giving **74** points clearly to the presence of thiocarbonyl ylide **75** as an intermediate; a 1,4-hydrogen shift in **75** leads to the product **72**. It is not clear how **73** originates; the formation of both **72** and **73** bears, however, striking resemblance to the photochemically induced low yield rearrangement of eqn (27) discovered earlier by Groen, Kellogg, Buter and Wynberg.[48]



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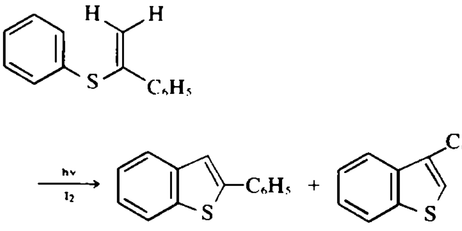
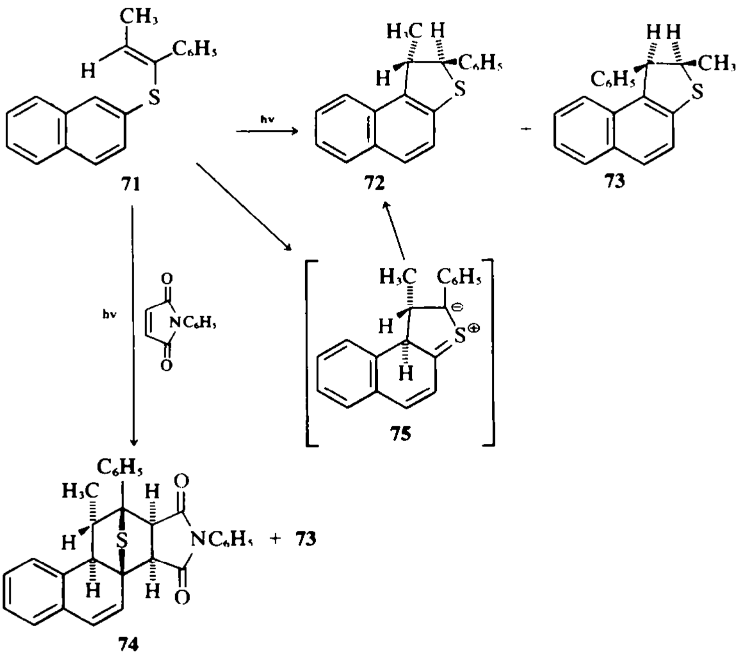


(27)

Essentially the same reaction sequence lies at the heart of eqn (28), wherein an aryl group is, in effect, added in a Michael fashion to an enone.[49]

Thiocarbonyl ylides may possible be involved as intermediates in some other reactions. The formation of thiirane **77** could well proceed through **76** (eqn 29).[50]

Ring-opening of a thiirane remains an attractive possibility for generation of a thiocarbonyl ylide although this approach thus far has met with little success. A colored intermediate formed during low temperature irradiation of



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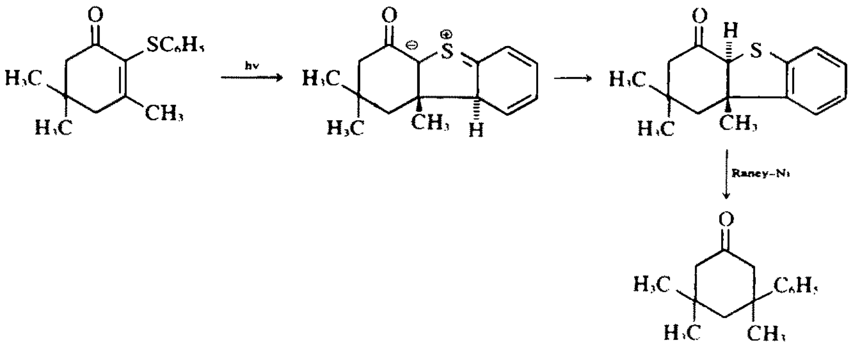

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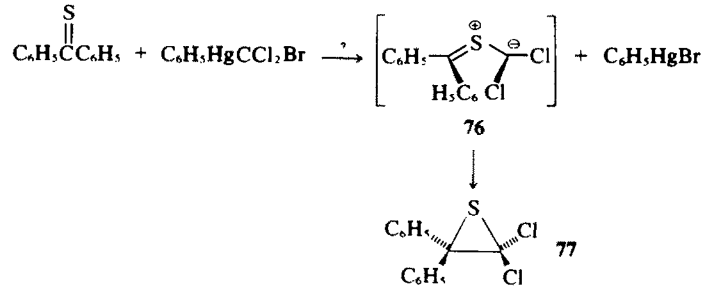
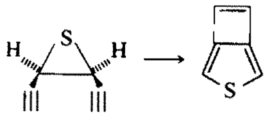


76

77

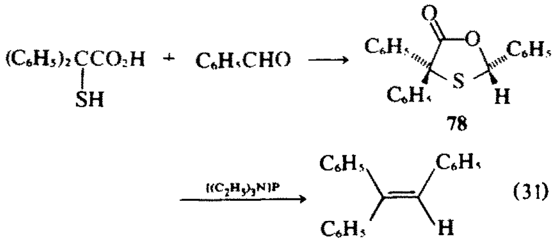
(29)

tetraphenylthiirane might be a thiocarbonyl ylide.[51] The rearrangement of eqn (30) could conceivably also involve a thiocarbonyl ylide.[52]



(30)

The condensation of thiobenzilic acid with benzaldehyde (other reactive aldehydes and ketones can be used) provides **78** (eqn 31), which, on pyrolysis in the

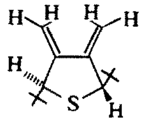


78

(31)

presence of a phosphine, provides the alkene in good yield.[26] One can well imagine that a thiocarbonyl ylide is formed by loss of carbon dioxide in analogy to thiodiazoline pyrolysis. The synthesis is hampered by the fact that one appears to be limited in the components that can be used for the condensation reaction leading to the ring system of **78**.

As a final point we mention that products obtained from thiocarbonyl ylide chemistry have been used as starting materials for the synthesis of such chemical rarities as tautomers of 3,4-dimethylthiophene, for example **79** (also the corresponding sulfoxides and sulfones) and the biradical **80**.[53]



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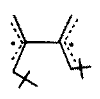
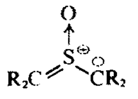


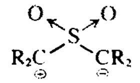
80

Intermediates structurally related to thiocarbonyl ylides

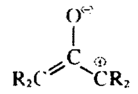
Various attempts have been made to obtain intermediates like **81** and **82**. Examination of **82** reveals in electronic make-up a certain similarity with oxallyl **83**; there is no available lone pair on sulfur leaving only two electrons in the π-skeleton. First order principles allow



81



82

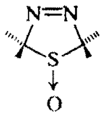


83

prediction that **82** should tend toward *disrotatory* ring-closure for a thiirane-S-dioxide and cycloaddition with 4π-electron components, *ergo* dienes.

Predictions for **81**, a valence tautomer of a thiirane-S-oxide, are less clear-cut from first principles because one is not sure to what extent the lone pair on sulfur will be available for conjugation (the S atom is expected to be pyramidal).[11]

An obvious route to intermediates **81** and **82** would be through Δ^3-1,3,4-thiadiazoline-S-oxide and S-oxides, respectively (**84** and **85**).



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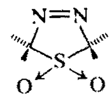
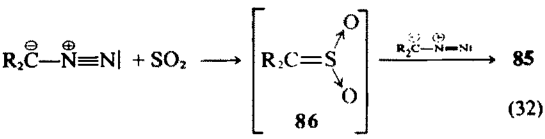


85

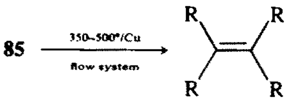
The latter ring system has been known for some time as a product of the reaction of diazo compounds with sulfur dioxides; a sulfene is likely involved as an intermediate (eqn 32).[54]



86

(32)

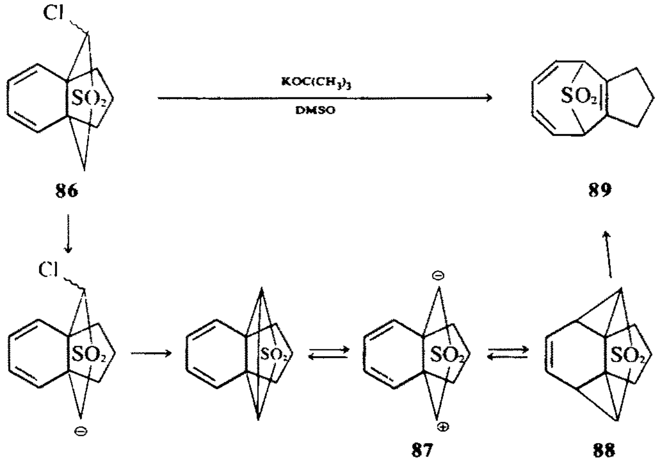
However, one anticipates difficulties on pyrolysis of **85** since the desired intermediate **82** has only 2π electrons causing the required fragmentation to be no longer a thermally allowed *retro*-Diels–Alder process but rather a forbidden *retro* 2+2 cycloaddition. This anticipation is well in accord with fact. At high temperatures derivatives of **85** afford low yields of *tetra*-substituted alkenes (eqn 33).[55] Derivatives of **85** formed by oxidation of available



(33)

Δ^3-1,3,4-thiadiazolines on pyrolysis under milder conditions or photolysis[26,56] afforded azine and sulfur dioxide and no alkene or thiirane-S-dioxide.

There are, however, indications that derivatives of **82** may exist. The rearrangement of eqn (34), uncovered by Paquette *et al.* during an attempt to bring about a Ramberg–Bäcklund[58] reaction on **86** (the normal course of the Ramberg–Bäcklund reaction being that shown in eqn (35) can readily be understood by postulating the formation of **87**, which is quickly trapped by intramolecular 4+2 cycloaddition to the diene system present followed by rearrangement through **88** to product **89**.



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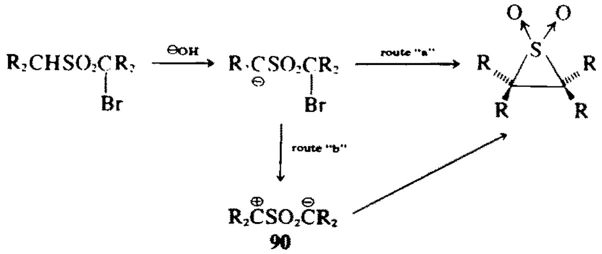
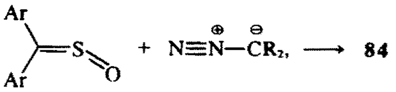


(35)

The dipole **90** had, however, earlier been discounted by the same author as a general intermediate in the Ramberg–Bäcklund rearrangement.[59]

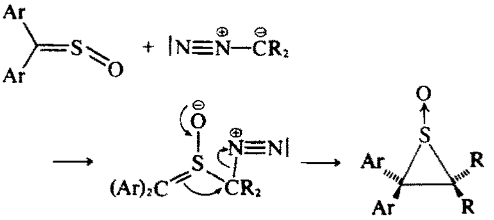
On the other hand all attempts to date to generate examples of **81** have been inconclusive, at least to the present author's mind. Oxidation of a Δ^3-1,3,4-thiadiazoline with a single equivalent of a peracid affords the S-oxides **84** in good yield. However, on either pyrolysis or photolysis at best only small quantities of azine are obtained.[26,56]

Another route to the ring system of **81**, whereby aryl substituents are introduced, is through addition of a diazo



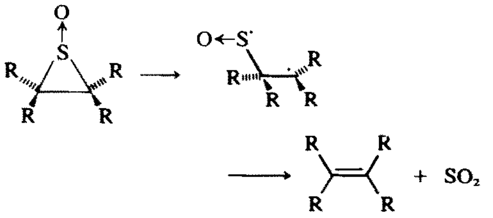
(36)

compound to a sulfine (eqn 36). Although the claim has been made[60] that pyrolysis of such compounds produces the intermediate **81**, it seems more likely that another path is followed. The normal course of thermal decomposition is usually a *retro*-1,3-dipolar cycloaddition regenerating sulfine and diazo compound although in some cases episulfoxides can be isolated.[61] However, as suggested by Zwanenburg[62] there is sufficient reason to believe that these products are arrived at via the route of eqn (37).



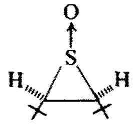
(37)

Nor has success been forthcoming in attempting to cleave the C–C bond of a thiirane-S-oxide. In all cases studied thus far nonstereospecific loss of sulfur monoxide is the usual result (eqn 38); in certain cases an "ene" reaction may compete.[63]



(38)

Steric strain has also proved ineffective as a driving force for breaking the carbon–carbon bond of a thiirane. *cis*-2,3-di-t-Butylthiirane (**48**) fails to undergo either thermally or photochemically induced ring-opening.† One could imagine that withdrawal of an electron from sulfur or creation of a sulfonium center would lead to more ready cleavage of the C–C bond; an analogy for this anticipation is the ready *disrotatory* ring-opening of cyclopropyl halides on solvolysis.[64] Derivatives **91–94** show, however, neither in chemical reactivity nor in spectroscopic properties any tendency to undergo C–C bond cleavage.[65]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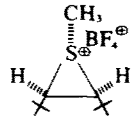
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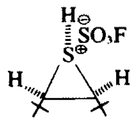
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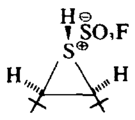
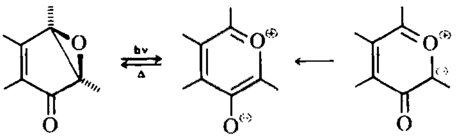
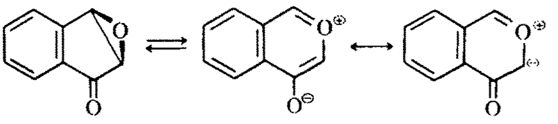

94

Carbonyl ylides

One of the first unambiguous demonstrations of a carbonyl ylide was the discovery of a reversible photochemically induced valence isomerization in cyclopentadienone oxide (**95**) and indenone oxide (**97**) (eqn 39).[66] The ring-opening of **95** or **97** must be disrotatory to prevent formation of a *trans*-double bond.

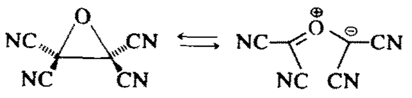


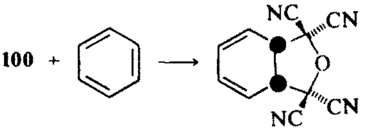
95 **96a** **96b** (39a)

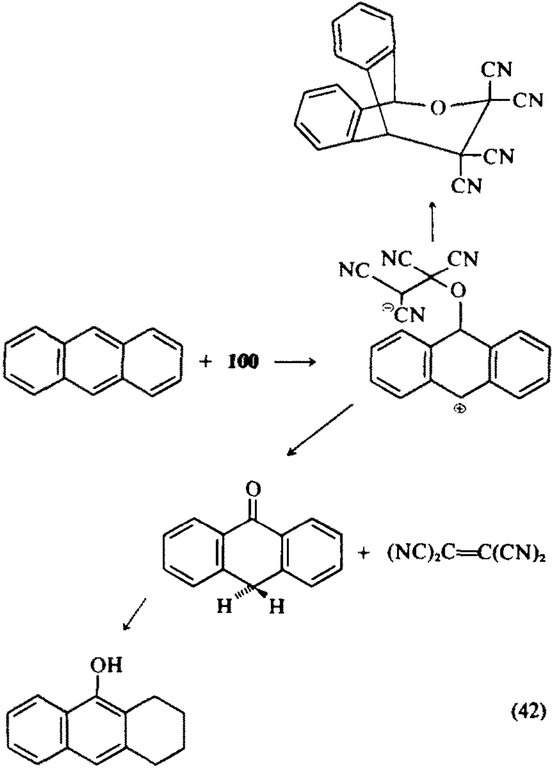

97 **98a** **98b** (39b)

The disrotatory motion is an allowed photochemical process for 4π-electron systems. By the same token the dipolar intermediates **96** and **98** enjoy a certain stability since the thermal ring-closure back to starting material is allowed only for a conrotatory rather than disrotatory motion. The ring-closure does occur, however, but the rate is slower than might have been anticipated, owing to the necessity of overcoming the forbiddenness. One notes also that the ring-opening of indenone oxides may, under the proper conditions, be accomplished by means of a formally nonallowed thermal process.[66d]

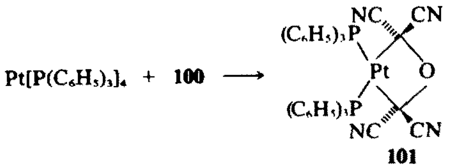
Likely the best-known carbonyl ylide is **100** derived from already mentioned tetracyano oxirane (**99**).[67] This extraordinarily reactive oxirane on heating to about 100° is in equilibrium with a low concentration of the carbonyl ylide (eqn 40). The potency of **100** as a 1,3-dipole[68] is demonstrated by its ability to react with benzene itself (eqn 41).[69] On the other hand with aromatics of greater nucleophilicity oxygen transfer may occur in the fashion shown in eqn (42).[70]


99 **100** (40)

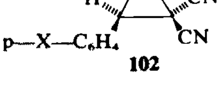

(41)


(42)

The carbonyl ylide has also been trapped as the metal complex **101** (eqn 43).[71]


101 (43)

Thermally induced C–C bond cleavage of an oxirane will also occur with other permutations of electron withdrawing groups on the ring. Representative structural types are **102–105**.[72] For the pair of isomers **106** and **107** Huisgen and Hamburger[72a] established the operation of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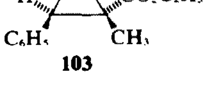
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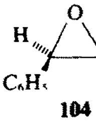
†An earlier report[32] by us claiming that isomerization of **48** to the *trans* isomer (**51**) can be brought about photochemically is incorrect; we have been unable to reproduce this result on repeating the reaction.



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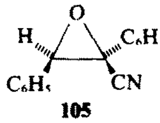
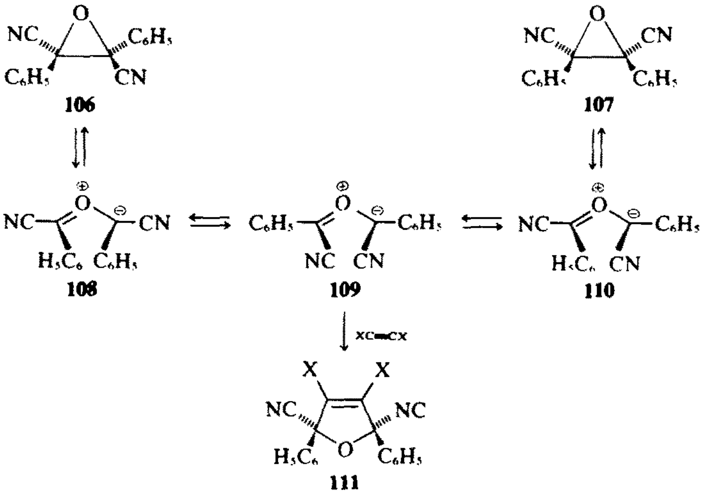


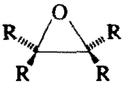
105

the scheme indicated in eqn (44). For the conversion of **106** to **107** $\Delta H^{\neq} = 27.2$ kcal mole^{-1} and $\Delta S^{\neq} = -8$ e.u. It is striking that both **106** and **107** give the same 1,3-dipolar cycloaddition products **111**. Bond rotation about the C–O bond in the ylide **110** must be faster than trapping (**109** is probably for steric reasons the most stable of the three geometrical isomers **108**–**110**).



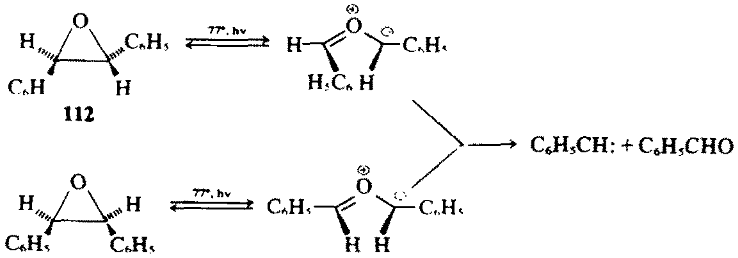
106 **107** **108** **109** **110** **111** (44)

In some cases oxiranes can be converted into carbonyl ylides by photochemical techniques. A well-known result of the irradiation of oxiranes is the formation of a carbene and carbonyl compound as convincingly demonstrated by Griffin *et al.* (eqn 45).[73] However, if two or more of the substituents of the oxirane ring are aryl irradiation affords



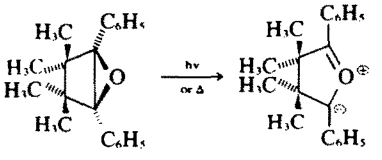
$\longrightarrow R_2C{=}O + R_2C:$ (45)

colored intermediates detectable at 77°K; these intermediates from the 2,3-diphenyloxiranes **112** and **113** on warming to 140°K fragment into phenylmethylene and benzaldehyde presumably via the course depicted as eqn (46).[74]



112 **113** (46)

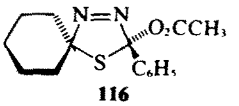
An even more pronounced example of such behavior is found with **114** which, on irradiation, opens to the colored (λ_{max} 540 nm in benzene) intermediate **115** (eqn 47). The same intermediate is formed on heating **114** at 100° ("forbidden" disrotatory ring-opening); **115** is readily trapped by 1,3-dipolar cycloaddition.[75]



114 **115** (47)

In the light of this observation several surprising reports in the literature wherein the central C–C bond of a 5-oxabicyclo[2.1.0]pentane is cleaved become better understandable. For example, lithium aluminumhydride reductions of derivatives of this ring system involve a degree of C–C bond cleavage,[76] as do some thermal reactions.[77] Also the monooxide of dewarbenzene on thermolysis rearranges to oxepin via cleavage of the C–C bond of the oxirane ring.[78]

An attractive route to carbonyl ylides would be through the Δ^3-1,3,4-oxadiazoline ring system in analogy to the Δ^3-1,3,4-thiadiazoline route to thiocarbonyl ylides. Unfortunately no general synthesis of the oxadiazoline system exists. The only pertinent examples of these compound types appear to be **116** and **117** formed by addition of pentamethylenediazo methane and ethyldiazoacetate, respectively to the appropriate electron deficient carbonyl compounds.[79] The carbonyl ylide **118** formed on pyrolysis of **116** can be trapped by 1,3-dipolar cycloaddition with acrylonitrile;[80] in the absence of trapping agent extensive rearrangement of **118** occurs.[79a]



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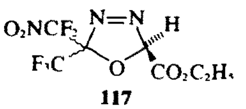

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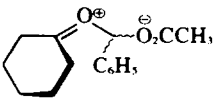
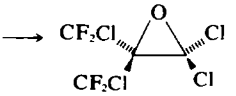
A different and little exploited route to carbonyl ylides



118

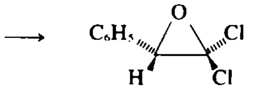
is the addition of a carbene or carbenoid to the oxygen of a carbonyl compound. Examples of such reactions wherein a carbonyl ylide may well be formed are shown in eqns (48) and (49).[81,82]

$C_6H_5HgCCl_2Br + (CF_2Cl)_2C{=}O$



$+ C_6H_5HgBr$ (48)

$C_6H_5HgCCl_2Br + C_6H_5CHO$



$+ C_6H_5HgBr$ (49)

One anticipates that the carbonyl ylide **120** is an intermediate in the photochemically induced rearrangement of **119** to **121** (eqn 50).[83]

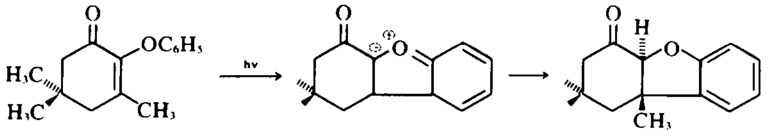
The stereochemical assignment (by the present author) for **121** is tentative. The conversion **119** to **121** bears close resemblance to the reaction sequence depicted in eqn (26).[47]

AZOMETHINE YLIDES

The most abundant of the molecules R_2CXCR_2 are azomethine ylides (X = NR). These will, however, despite their plentifulness be treated briefly here because of the availability of the excellent and thorough review of Lown[84] as well as Stukwisch.[85]

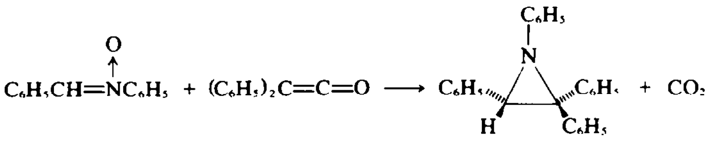
Azomethine ylides are fairly readily available through the thermally induced ring-opening of aziridines which bear electron-withdrawing or conjugating substituents. Some synthetic routes to suitable aziridines are shown in eqns (51)–(54).

Both older reports[90] in the literature as well as a large number of recent investigations[91] have established that aziridines of the structural types indicated can serve as precursors of azomethine ylides. The stereochemical aspects of this valence isomerization have already been discussed.[7] The azomethine ylides appear to be fairly potent dipolarophiles and thanks to the reversible ring-opening of the aziridine precursor, the azomethine ylide can be trapped in good yield. This contrasts sharply with

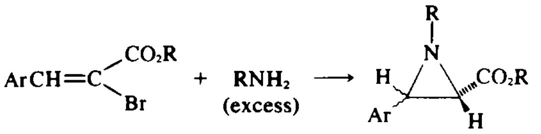


119 **120** **121**

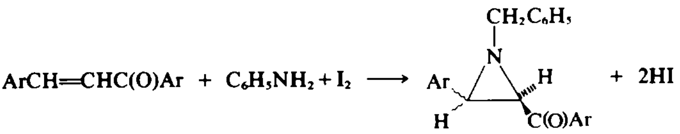
(50)



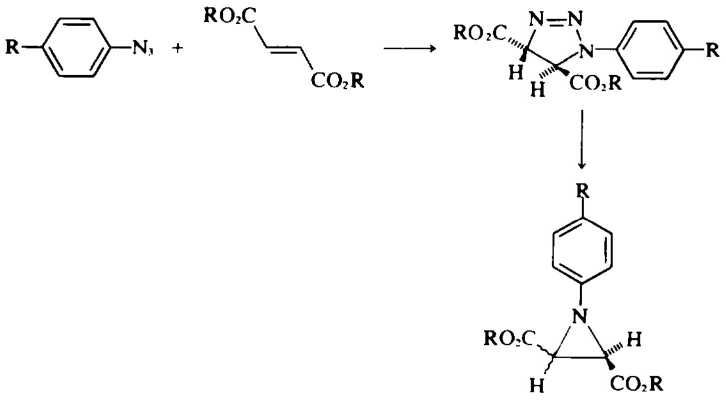
(51)[2]



(52)[86]



(53)[87]

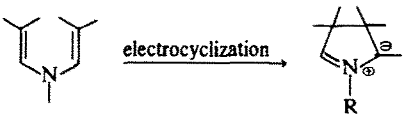


(54)[88,89]

the situation for thiocarbonyl ylides where valence isomerization to the 3-membered ring causes irreversible loss of the intermediate.

There appear to be few other workable routes to azomethine ylides. One obvious approach is the deprotonation of an immonium salt as indicated in eqn (55); the immonium salt will perforce require structural features that prevent the alternative possibility of deprotonation to afford an enamine (an azomethine ylide is a potential tautomer of an enamine). This possibility has been realized by Huisgen *et al.*[92] who have succeeded in bringing about the sequence of alkylation of dihydroisoquinoline followed by deprotonation to give, for example **122** (eqn 56); several other examples have also been obtained. However, the rather rigid structural requirements needed to circumvent enamine formation preclude extensive application of the route of eqn (55).

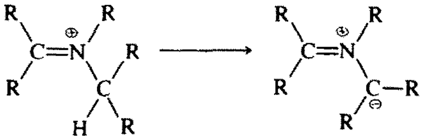
A fair amount of success has, however, been realized through application of the generalized scheme of eqn (59). For example the enamine **124** is transformed on irradiation



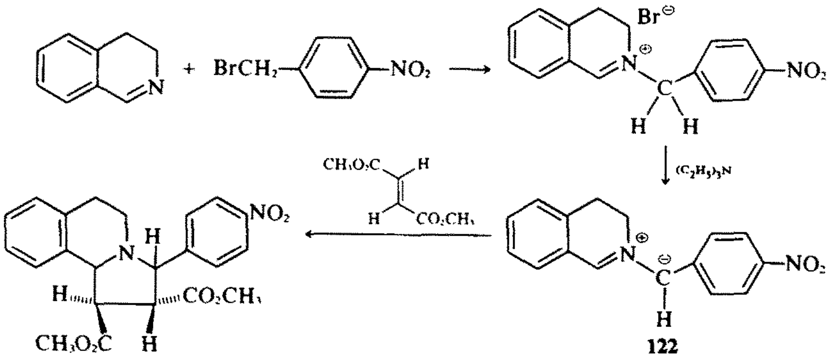
(59)

to **126**; the reaction almost certainly involves the formation of azomethine ylide derivative **125**, which stabilizes itself by an orbital symmetry allowed hydrogen shift (eqn 60).[94]

The azomethine ylide system is well-known as a component of various reactive heterocyclic systems. A nice example is provided by the betaines **127**, which react with 1,3-dipolarophiles adding the azomethine ylide unit iso-

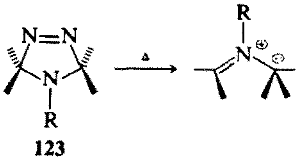


(55)



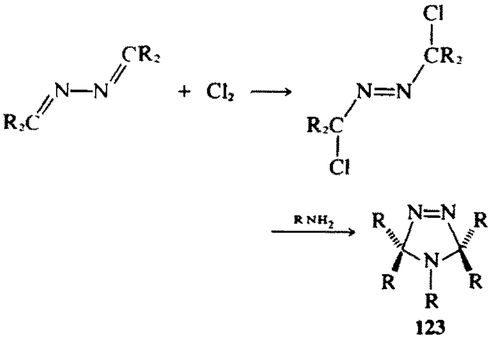
(56)

There appear to be no synthetic routes to Δ^3-1,3,4-triazolines (**123**), which, in analogy to the reactions of Δ^3-1,3,4-thiadiazolines and oxadiazolines, would be expected to afford azomethine ylides (eqn 57). Numerous attempts



(57)

to carry out the logical synthesis of eqn (58) using various aromatic and aliphatic amines have thus far resulted only in mono-substitution reactions without subsequent closure to the heterocycle.[93]



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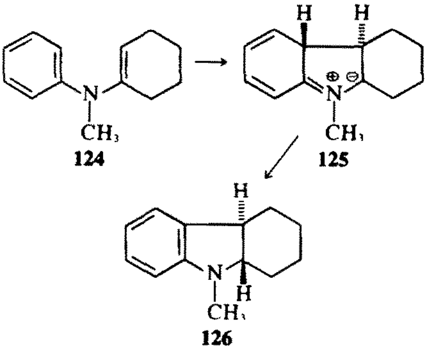

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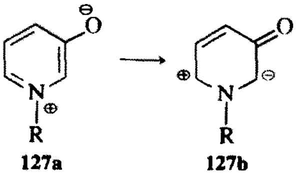
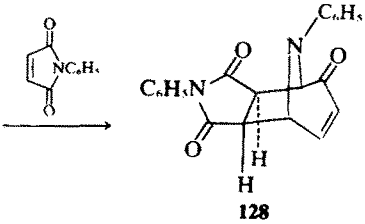
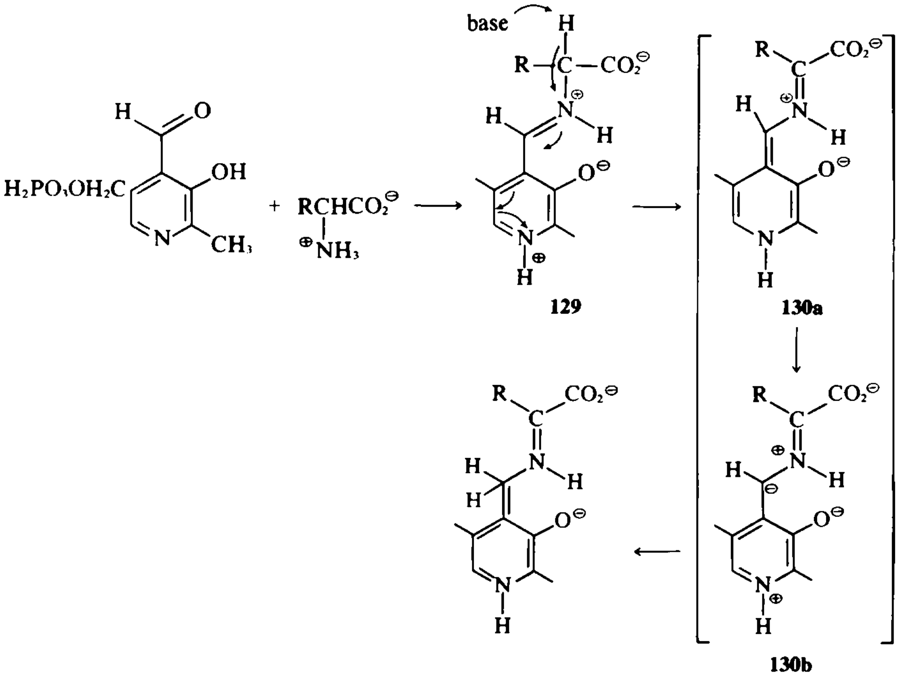




(61)

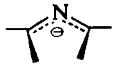
lated in resonance structure **127b** to, for example, N-phenylmaleimide to give **128** (eqn 61). Katritzky's group has examined numerous aspects of these types of reactions.[95]

Although the point is rarely made in fact an azomethine ylide is the critical intermediate in transamination reactions between an amino acid and an α-ketoacid mediated by pyridoxalpyrophosphate coenzymes. After initial imine formation between pyridoxal and the amino acid to give **129**, a base is presumed to remove the acidic proton generating **130**, which is readily recognized as being a stabilized azomethine ylide (eqn 62).[96]



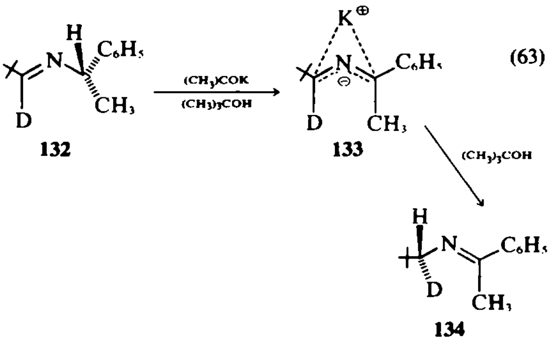
(62)

Intermediates related to **130** are the 2-azaallyl anions (**131**), which are the conjugate bases of 2-H azomethine



131

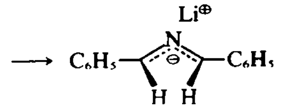
ylides. These species obviously can intercede—at sufficiently high pH values—as intermediates in the transformation of eqn (62). The 2-azaallyl anion is surely an intermediate in base-catalyzed imine isomerizations, the example of eqn (63), uncovered by Cram and his collaborators,[97] being a nice example. During the isomerization of optically active **132** by potassium t-butoxide in t-butanol the proton is transferred with essentially complete stereospecificity across the face of the imine to generate **134**; the intermediate **133**, most likely with a potassium ion complexed in some fashion to the same face of the system from which the proton was originally removed, would seem to be involved. In an effort to rationalize the suprafacial shift of hydride one could speculate about the possible formation of aziridines by conrotatory closure of **133** during the reaction; this would provide an additional mechanism for retention of configuration. There appears, however, to be no convincing evidence for the formation of aziridine anions during the reaction.



(63)

Various 2-azaallyl anions have been generated under aprotic conditions using diisopropylamide with an appropriate imine or by deprotonation and subsequent ring-opening of a 1-H-aziridine;[98] this is illustrated in eqns (64) and (65). The reactive intermediate **135** (*trans*-**136**; if formed, isomerizes under the experimental conditions to **135**) undergoes cycloaddition reaction with a wide variety

$C_6H_5CH{=}NCH_2C_6H_5 + LiN[CH(CH_3)_2]_2$



135

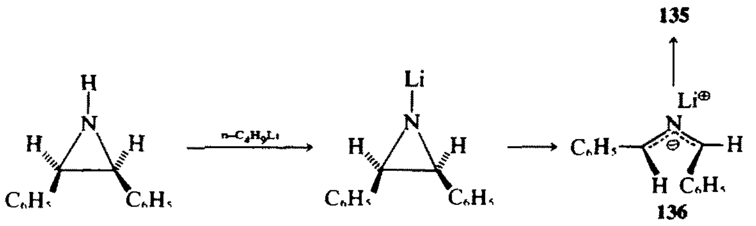
(64)

of activated alkenes, azo-compounds, nitriles, and similar potential acceptors; the general course of the reaction is depicted in eqn (66).

Other R_2CXCR_2 *species*

There are strong reasons to suspect that many other R_2CXCR_2 molecules can—or in fact do—exist.

(a) *2-Azaallyl cations* (*2-azoniaallenes*). It seems now well established that 2-azaallyl cations (generic type **138**)



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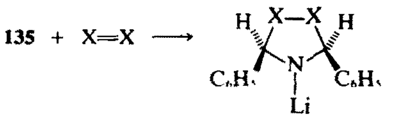
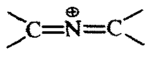


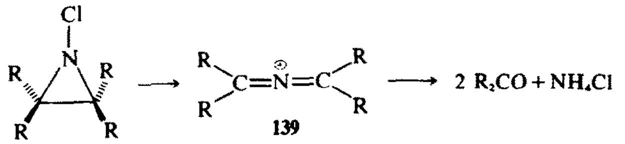
(66)

can be formed. One impetus for the generation of such species came from carbonium ion chemistry; the preparation of heteroanalogs of the allyl cation was obviously an appreciable challenge. One must realize, however, that the chances for existence of a true aza structural analog of the allyl cation as implied by both the commonly used name, 2-azaallyl cation, and the implied structure, **138**, are slim; Walsh's rules[11] predict the linear geometry of **137** and, if the terminal methylenes are turned at an angle of 90° with respect to each other (which point has not been proven) the species are allene analogs, 2-azoniaallenes, rather than relatives of an allyl cation.


137


138

Gassman *et al.*[99] have demonstrated that N-chloroaziridines undergo solvolytic rearrangements as indicated in eqn (67); the solvolysis rates as function of substituents on the carbon atoms suggest the expected orbital symmetry allowed disrotatory ring-opening to **139**, which suffers subsequent hydrolysis.



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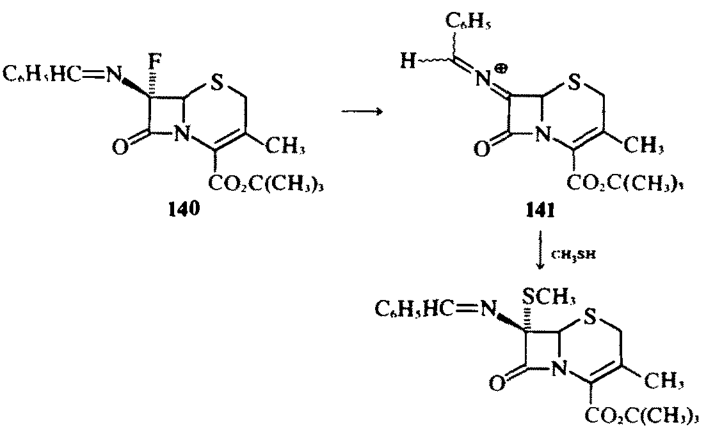
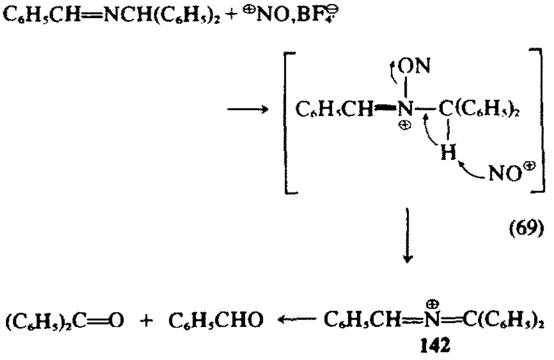


(68)

A fundamentally different approach to (most likely) the same type of intermediate is illustrated in eqn (68); solvolysis of the fluorinated cephalosporin **140** produces the reactive intermediate **141**, which is rapidly attacked by thiolate (and other nucleophiles) from the least hindered side of the molecule.[100] A similar approach has also been used in the penicillin series to introduce methoxy substituents, the bromide rather than fluoride is used and solvolysis is carried out with silver oxide in methanol.[101]

The transformation of eqn (69) becomes understandable if one grants the formation of **142** as an intermediate.[102] Following the same general synthetic principle



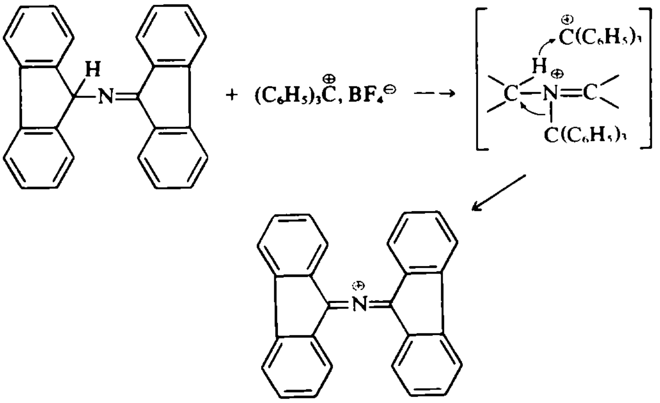
$C_6H_5CH{=}NCH(C_6H_5)_2 + {}^{\oplus}NO,BF_4^{\ominus}$

$(C_6H_5)_2C{=}O + C_6H_5CHO \leftarrow C_6H_5CH{=}\overset{\oplus}{N}{=}C(C_6H_5)_2$

(69)

as indicated in eqn (69), Barton *et al.*[103] have succeeded in isolating **143** as a hygroscopic red crystalline material (eqn 70); other examples of 2-azoniaallenes having however less stability were also generated.

(b) *Other intermediates.* One can think of many other R_2CXCR_2 molecules potentially capable of existence. In the present author's judgment good bets are the phosphinomethine ylides **19**, the corresponding anions **144**, and possibly the cation **145**. The problem of generating species like **146** is probably chiefly one of devising the proper synthetic strategy; there seems to be no fundamental



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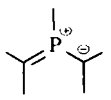

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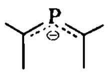

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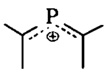

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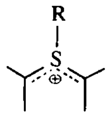

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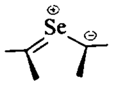
reason to doubt that this, or other intermediates mentioned should be incapable of existence.

In regard to this point one is encouraged to note that selenocarbonyl ylides **147** appear now to belong to the list of known species. The transformation of eqn (71) implies strongly the selenocarbonyl ylide **148** occurs on the



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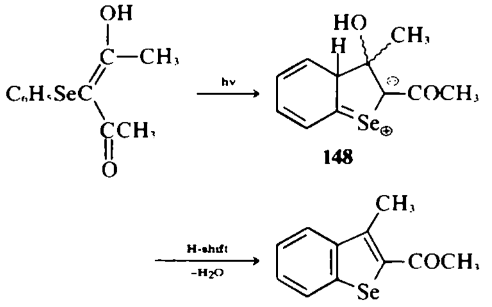
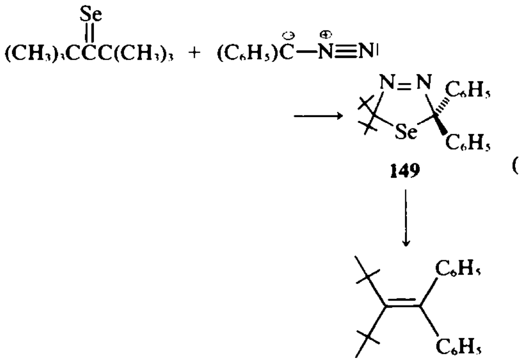
reaction path.[104] One can also speculate whether a selenocarbonyl ylide in the conversion of **149** to **150** (eqn 72); analogous conversions have been carried out with selenofenchone.[105]

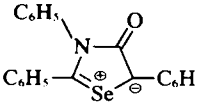


(71)

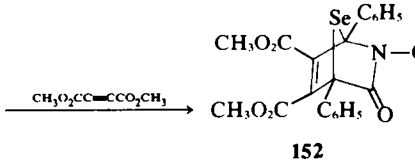


(72)

150



151



(73)

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The properties of a selenocarbonyl ylide are also revealed in the mesoionic compound **151**, which undergoes sluggish reaction with dimethylacetylenedicarboxylate to give apparently **152**, which quickly loses selenium (eqn 73).[106]

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