SUMMARY OF KATRITZKY RESEARCH GROUP SCIENTIFIC RESULTS (1954-1993)

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I. Overview of Research Areas

The five- and six-membered ring heteroaromatics are, I firmly believe, the core and heart of heterocyclic chemistry, and the comprehension of their aromaticity and tautomeric relationships is vital to their proper understanding. Accordingly, major efforts have been made to measure experimentally, and to rationalize theoretically, the aromaticity and tautomerism of heterocycles.

I have divided my treatment of heteroarmatic reactivity into two main classes: (i) reactions of the rings and the mode in which such reactions are influenced by substituents, and (ii) the ways in which the nature of the rings influence the reactivity of substitutents. Of all the ring reactions, electrophilic substitutions are the most important and preparative and quantitative aspects of this have been intensively studied. Another major area of research has been the cycloadditions of six-membered heteroaromatic compounds, particularly betaines. Lithiation at ring carbon atoms of heteroaromatic compounds and the way in which such metallation can be activated, and other sensitive parts of the molecule protected, have formed a further area of research. Finally, nucleophilic attack at ring carbon, which leads to ring opening and ring interconversion has been studied, particularly with respect to pyrylium to pyridinium transformations.

My work on the chemical behavior of substituents attached to heterocyclic rings has been especially concerned with substituents attached to ring nitrogen. As regards substituents attached to pyridine-like nitrogen atoms, we have made extensive studies of N-oxides, of N-imides, of N-N linked heterocycles and of carbon linked substituents, particuarly those attached to pyridinium rings. More recently, the behavior of substituents attached to the nitrogen atoms of azoles, and above all to benzotriazole, have received intensive study. As regards C-linked substituents, these have been considered particularly where they can induce a rearrangement at the heterocyclic ring, particularly a ring opening/ring closure rearrangement. The mechanisms of ring closures to form 5- and 6-membered heterocycles, including those involving both C-C and C-N bond forming reactions, have been studied.

As regards 5- and 6-membered non-aromatic heterocycles, two major areas have received attention: the non-aromatic azoles and their relationship to their more familiar aromatic counterparts on the one hand, and on the other, 6-membered non-aromatic heterocycles, particularly as regards their conformational analysis.

The application of heterocycles in organic synthesis has been a major leit-motif. The chemistry of primary amines has been extended by many novel transformations available by the application of pyrylium and pyridinium cation chemistry. More recently, the chemistry of N-substituted benzotriazoles has uncovered a vast new armory of synthetic methods. Several novel protection methods have been developed.

Parallel to the discovery and documentation of facts, and to the development of methods, my work has been driven by the desire to understand and rationalize. Frequently work initiated in heterocyclic chemistry has enabled the better understanding of general problems of organic and physical organic chemistry. Thus, the concept of nucleophilic substitution at saturated carbon atoms has been illuminated by intensive investigations both in solution and in the gas phase. Similarly, understanding has been gained as to the factors underlying the stability of free radicals. Extensive work with infrared spectroscopy, and particularly infrared intensities, has shed light on the nature of intramolecular interactions in aliphatic and benzenoid as well as heterocyclic compounds. NMR methods have been fully utilized in a variety of applications. Work in strongly acid solutions required more detailed knowledge of acidity functions and particularly their variations with temperature than was previously available. Finally, the experience of statistical methods in considerations of heteroaromaticity encouraged further development, particularly into quantitative structure activity and quantitative structure property relationships.

Finally, assistance has been provided in applications of heterocycles to society. Significant amounts of work have been conducted in the fields of dyestuffs, polymers and surfactants. A completely new field of "aquathermolysis" was entered in the investigation of the behavior of organic molecules in general and heterocycles in particular under the influence of water at temperatures ranging upwards from 250°.

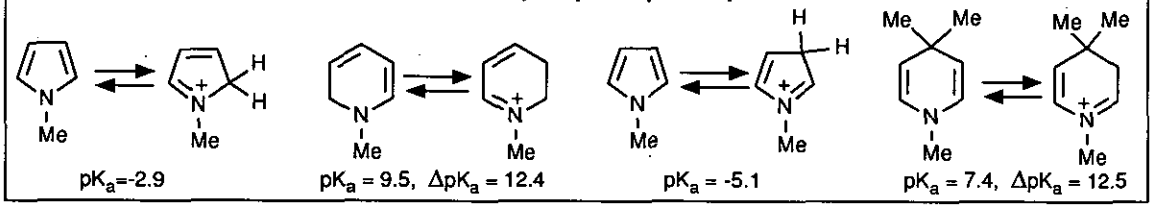
Each of these areas is now considered in more detail, but before doing so I must acknowledge that none of this work could have been accomplished without the devoted and skilful work of a large number of research students, visiting students and postdoctoral associates whose names are mentioned in the reference list. Much work has been in collaboration with other groups, only some of the most important of these are specifically mentioned, but due acknowledgement is again made in the reference list. I would like to acknowledge here long and happy collaborations at East Anglia particularly with Drs A. John Boulton, Mike Cook, C. David Johnson and Richard A. Y. Jones.

II. Five- and Six-Membered Heteroaromatics

A. *Heteroaromaticity*

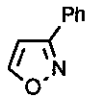
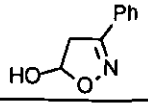
The classical methods of combustion or hydrogenation are notoriously difficult to apply to the accurate determination of the aromatic stabilization energies of many heterocycles.[427] Although nmr coupling constants can give valuable indications,[287] it is difficult to relate the results to the energy scale. In this situation several new methods capable of providing quantitative data were developed.[394,400] Thus the basicity method depends on the measurement of the pKa values of an aromatic compound in which the aromaticity is lost on protonation and comparison with the basicity of suitable models which on protonation do not lose aromaticity: the method is illustrated for pyrrole in Scheme 1. The method has also been applied to various benzopyrroles, and to furan.[555]

Scheme 1. Aromaticity of Pyrrole by Basicity Method

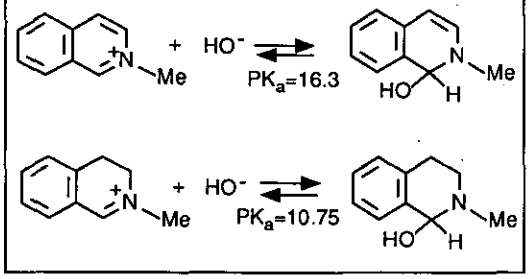


Another method is to determine the heat of dehydration of a compound which when dehydrated gives an aromatic ring and to compare this heat of dehydration with that for a suitable model in which no aromaticity is obtained. This is illustrated for isoxazole in Scheme 2. In this method the heats of solution of the starting materials and products have to be measured and the heats of vaporization are estimated. The method has also been applied to pyrazole.[609]

Scheme 2. Resonance Energy of Isoxazole from Heat of Dehydration

	Crystal to H_2SO_4	Crystal to $CHCl_3$	Estimate of Vapors to H_2SO_4
	-22.7	4.0	-26.7
H_2O	-	-	-8.2
	-15.5	-0.9	-14.6

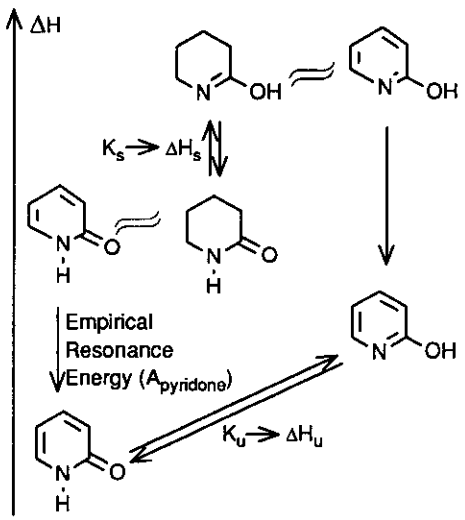
Scheme 3. Aromaticity and Pseudo-base Equilibria



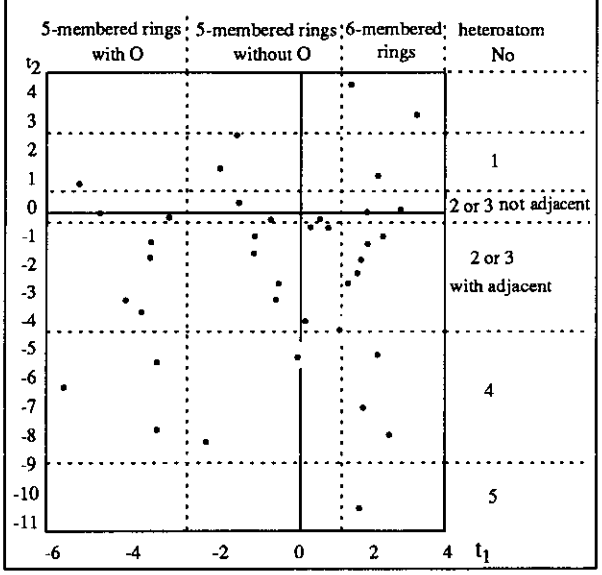
For the aromatic stabilization energy of a six-membered ring, psuedo base equilibria can be applied as shown for isoquinoline in Scheme 3. Again, the comparison is with a non-aromatic model. The method has also been applied to thiazole.[556]

Tautomeric equilibria can be used to relate the aromaticities of compounds like pyridones to the parent heterocycles,[356,386] in this case pyridine, by the use of a thermodynamic cycle as shown in Scheme 4. This method has been applied to pyridones and to sulphur, nitrogen, and carbon analogues and to the corresponding bicyclic compounds.[416]

Scheme 4. The Enthalpy of Tautomeric Equilibria for the Resonance Energy Calculation of 2-Pyridone



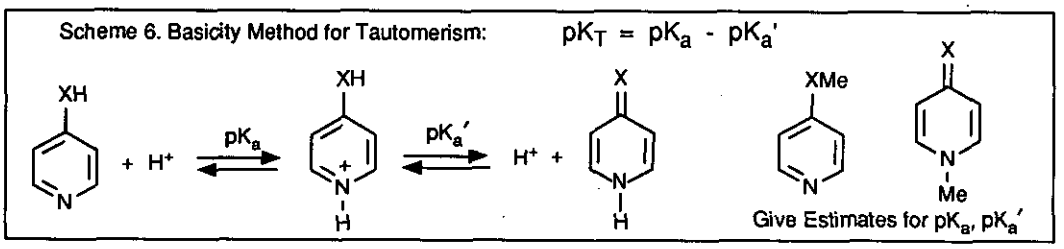
Scheme 5. Scores for the Total Set of Monocyclic Heteroaromatics



Although this work related well to the overall picture of thermodynamic stability and led to significant extension of the conclusions from combustion analysis, the overall picture in the mid-80's was, nonetheless, one of confusion and complication. In particular, many other measures of aromaticity were incompatible with each other. In this situation a statistical approach was applied in which (initially for a set of sixteen familiar monocyclic aromatic nuclei) twelve different variables were collected from the literature and examined by principal component analysis. The results indicated[1041] that at least two types of aromaticity were to be distinguished, of which we called one "classical aromaticity" and the other "magnetic aromaticity". Using these two measures, three quarters of the varience could be explained[1151] and the approach was successfully extended to bicyclics[1152] and to a much larger set of monoheterocyclic nuclei.[1153] Semi-empirical methods have been compared for the calculation of molecular geometries and aromaticity indices.[1177] As has been recently reviewed,[1192] the field of heterocyclic aromaticity can now be considered to be at least much better understood.

B. Heteroaromatic Tautomerism

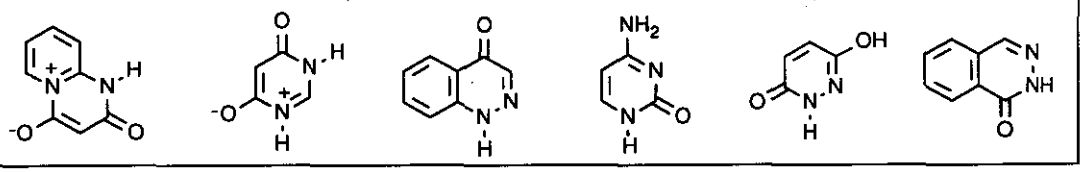
The importance of heteroaromatic tautomerism can hardly be overestimated. It is vital to a proper understanding of the chemical and physical behavior of a large proportion of heterocycles. It lies at the heart of the genetic code and the understanding of spontaneous mutation which is responsible for evolution. Thirty years ago this importance was not at all realized; tautomeric structures were written haphazardly and there was little understanding or rationalization. Thus, the discovery of the genetic code was held up significantly because of the way in which uracil was generally depicted. The situation was considerably improved by our early reviews[103-106,154,268,300] and then by our comprehensive monograph of the subject:[514] the importance of the basicity method to obtain quantitative estimates of tautomerism constants (Scheme 6) was emphasized. We have recently reviewed later developments.[1193] Dangers in the misapplication of nmr to problems of tautomerism were indicated.[84,268,401]



Tautomeric equilibria in pyridines have been extensively investigated and rationalized in terms of dependence on bond energies and aromaticities. We have investigated pyridones,[47] pyridinethiones,[26] acylamino-,[31] sulfonamido-,[72] benzyl-,[420] phosphorylmethyl-,[186] ethoxycarbonylmethyl-,[128] sulfonylmethyl-,[160] and phenacyl-pyridines.[161] Pyridones were shown to undergo O-protonation[62,113] and the cation structures of thiopyridones and acylaminopyridines were confirmed.[162,586] The effect of substituents on the pyridine tautomeric equilibria has been considered[184,216] and rationalized in terms of the differential effects on the acidity of the two alternative protons that can be lost from the common cation.[251] The effect of intramolecular hydrogen bonding has been shown to be of considerable importance[346,603]. Changes of state can have a drastic effect on the tautomeric equilibrium of a pyridine as we have shown by studying the change of solvents on UV spectra in solution[271,548] and by studies of heats of solution.[558] In the gas phase, mass spectra of mercapto-[482] and hydroxy-pyridine[483,615,627] ion-cyclotron resonance[529,586] and photoelectron spectra[583] have elucidated these equilibria. We have applied AM1 to successfully correlate the tautomerism of pyridones and thiones[1057] and, in combination with reaction field theory, to rationalize solution equilibria.[1061,1334]

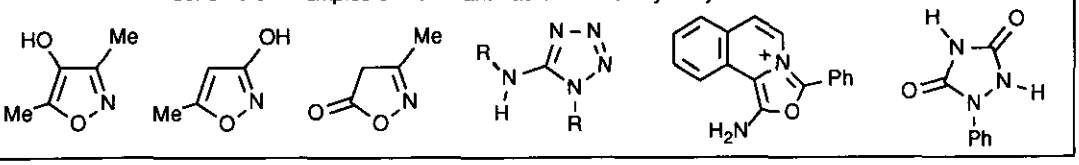
Prototrophic tautomerism has been investigated for amino and hydroxy,[13] and for mercapto- and aminoacyl-pyridine 1-oxides,[54] for 3-ethoxycarbonylquinolones,[726,729] for bridged aza[10]annulenes,[1339] for acridine N-oxides,[200] for hydroxy N-nitroimides,[428] and for pyridine 1-benzimide cations.[926] Among diazines we have elucidated the tautomeric structures of maleic hydrazide,[135] "malonyl-α-aminopyridine",[86] 2,6-dihydroxypyrimidine,[185] 4-cinnolone,[347] and phthalazinone.[581] Particular attention has been given to the tautomerism of the nucleic acid bases in view of their biological importance. We have shown that it is possible to use basicity measurements to deduce the tautomeric equilibria of uracil[85] and of cytosine[114] derivatives, and of thiouracil.[1048] Molecular orbital methods have been applied: the AM1 method gives excellent results for the gas phase[1049] (in agreement with photoelectron spectra[1134]) and with suitable corrections for solvent polarity[1085] very good estimates for solution phase equilibria[1194] (this theoretical work was in collaboration with Professors Karelson and Zerner).

Scheme 7. Examples of the Dominant Tautomeric Form of Hydroxy Azines



We have studied the tautomerism of a variety of azoles including aminoisoxazoles,[81] 3-,[149] 4-,[365] and 5-hydroxyisoxazoles,[80,97] hydroxypyrazoles,[147,148,174] hydroxytriazoles,[203] aminotetrazoles,[319,349,359] N-hydroxyimidazoles,[429,348] hydroxyoxadiazoles[173] and Reissert salts.[571] Theoretical treatment including solvent effects gives results in agreement with experimental data.[1133] Examples of the dominant tautomeric form for azoles are given in Scheme 8.

Scheme 8. Examples of Dominant Tautomers for Hydroxy and Amino Azoles

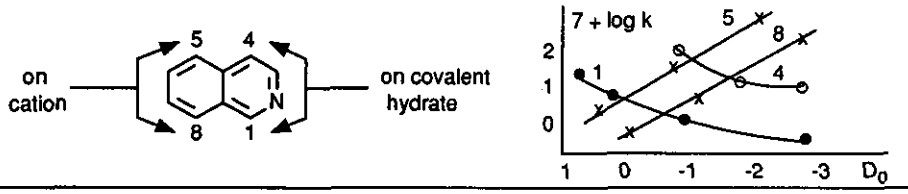


In our reviews of heteroaromatic tautomerism,[393,514,1193] it has been emphasized that it is now relatively easy to predict the tautomeric structure of the vast majority of heterocycles and that this knowledge enables a far easier understanding of their chemical and physical behavior.

C. *The Electrophilic Substitution of Heteroaromatics*

The objectives of our work in electrophilic substitution can be summarized as the elucidation of reaction mechanisms and the determination of the quantitative effects of the replacement of one or more carbon atoms in benzene by heteroatoms, the correlation of rates with theory leading to a better understanding of preparative work, the optimization of reaction conditions, and the prediction of new reactions. We have attempted to reach these objectives using mainly hydrogen exchange and nitration reactions of a wide variety of heteroaromatic compounds.[206]

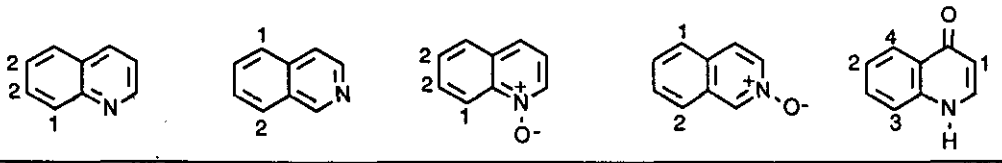
Scheme 9. Dependence of the Isoquinoline Hydrogen Exchange Rate on Acidity of the Medium at 245 °C



Hydrogen exchange can easily be followed by proton nmr and conveniently studied in aqueous media where acidity function behavior is well understood. Dependence of the rates on acidity[223] (for an example see Scheme 9) indicate which species is undergoing reaction, whether it be cation, free base, covalent hydrate, etc. Kinetic salt effects on these rates were investigated.[486]

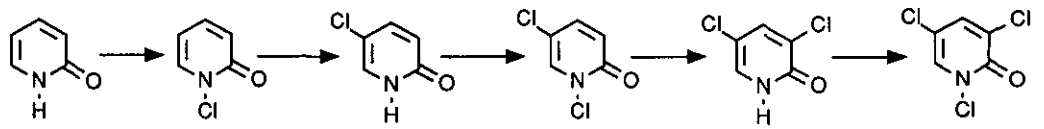
For the quantitative comparison of hydrogen exchange rates, we worked out a procedure[413] for extrapolating rates to an acidity of pH = 0 and a temperature of 100°C. We applied this to monosubstituted benzenes[415] and to rates that we measured[462] for methylpyridines,[118,92,115] aminopyridines,[351] pyridones,[155,225] and pyrones and thiopyrones.[233] Hydrogen exchange has also been quantitatively determined in pyridazines,[256] pyridine 1-oxides,[131,224] and quinolones,[225,245] and studies as an intramolecular reaction at the 3-position of pyridines.[950] In pyrimidines, reaction can proceed via a covalent hydrate.[262,264] Hydrogen exchange rates were compared with those of p-substituted anilines[254] and with phenols.[255]

Scheme 10. H-Exchange for Bicycles (Successive Positions for H-Exchange in Strong Acid Are Indicated)



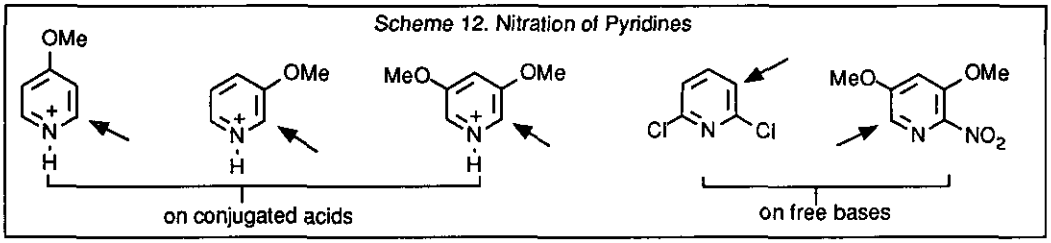
Among bicyclic compounds (cf Scheme 10), we have studied quinoline and isoquinoline and their N-oxides,[334] and 2-[245] and 4-quinolones,[225] and compared the results with beta-naphthol;[335] the immonium group in indolenium cation was shown to direct para.[150] In the azole series we investigated pyrazoles,[418] isoxazoles and isothiazoles,[352,454] and azaindoles.[414] For comparison purposes we measured benzene and naphthalene.[453]

Scheme 11. Chlorination of 2-Pyridone



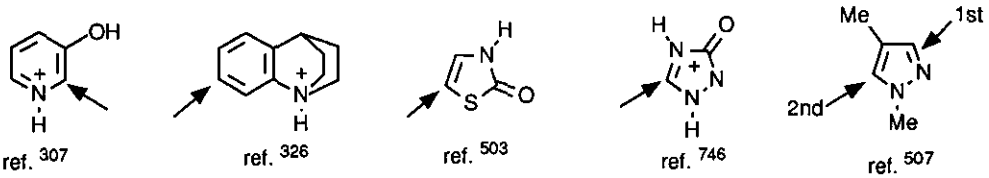
The bromination was studied of 2-aminopyridines;[308] pyridones are chlorinated first on nitrogen; the N-chloro derivatives then rearrange to 3- and 5-chloropyridones[851] (see Scheme 11).

Scheme 12. Nitration of Pyridines



In our studies of nitration we have shown that pyridines are normally nitrated in the beta position as their conjugate acids; however if the basicity of the nitrogen is sufficiently reduced, nitration can occur in the beta-position also on the free base.[220] Again, nitration can be directed to the alpha-position[221] and depending on the particular compound, can occur on the conjugate acid or the free base (see Scheme 12). Nitration has been studied for aminopyridines,[388] and their 1-methyl cations,[389] pyridones,[261,368,390] 3-hydroxypyridines,[307] benzoquinuclidine,[326,361] pyrimidinones,[333] thiazoles,[503] isothiazoles,[504] pyrazoles in the 3- and 5-positions,[507] and triazolones.[746]

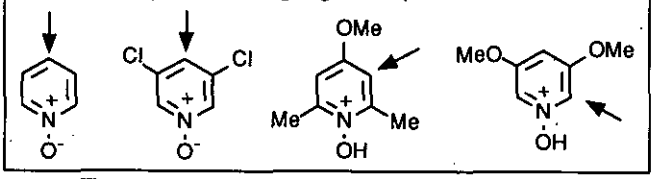
Scheme 13. Nitration of Heterocycles: Orientation and Species Undergoing Electrophilic Substitution



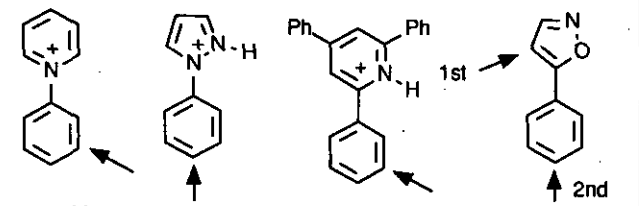
In the case of pyridine 1-oxides, nitration normally occurs in the gamma position on the free base, or in the beta position in the conjugate acid. In addition, we have found cases where nitration can occur in the alpha position of a pyridine 1-oxide both on the free base and on the conjugate acid.[222]

We have also studied the nitration in phenyl groups of phenyl- and benzyl-substituted pyridines and their 1-oxides,[19,253] pyrazolones,[451] pyrazoles,[452] 3-hydroxypyrazoles,[501] isoxazoles,[506] 4-pyrones,[873] and 1-phenylpyridinium cations.[894] The orientation of electrophilic substitution in phenyl substituted heterocycles has been rationalized theoretically.[894]

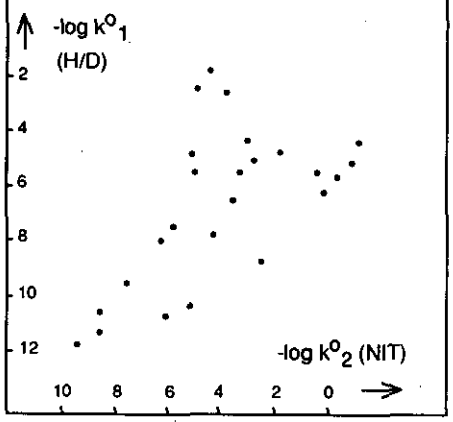
Scheme 14. Nitration of Pyridine 1-Oxides: Orientation and Species Undergoing Electrophilic Substitution



Scheme 15. Orientation and Species for Nitration of Phenyl-substituted Heterocycles



Scheme 16. Plot of Rate Data for Hydrogen Exchange vs Rate Data for Nitration of Substituted Pyridines



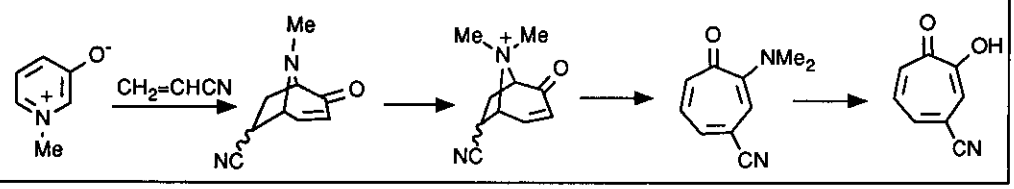
We developed[502] an extrapolation procedure to allow the comparison of nitration rates under standard conditions, i.e., 35% sulphuric acid and 25°C, and processed the data from approximately 130 compounds to show the quantitative effects of heteroatoms and substituents. Hammett treatments showed linear behavior within closely related classes of compounds.[505] However, a comparison of standard rates for hydrogen exchange with those for nitration showed[601] no clear pattern indicating clearly that no unique order of the susceptability of individual ring positions towards electrophilic attack by different reagents exists.[513] Hence no single reactivity index can be used as such a measure.

Our work in electrophilic substitution was first reviewed in 1967,[206] and an account in Italian appeared soon after.[266] Quantitative effects of the electrophilic substitution of heterocycles were covered in 1977 for our own work,[566] and then for the whole field in a comprehensive monograph.[1086] A recent article has presented a historical survey.[1249]

D. Cycloadditions of Six-Membered Heteroaromatic Betaines

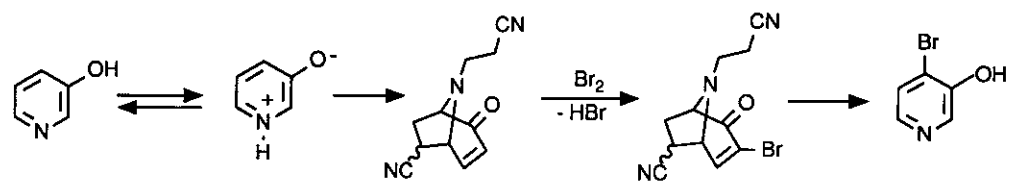
We discovered[353] that 1-methylpyridinium-3-oxide reacts regiospecifically across the 2-, 6-positions with a variety of electron-deficient olefins to give, in most cases, mixtures of diastereo isomers. Kinetic rates were determined.[550,596,857] Useful syntheses of tropones and tropolones[302] using these cycloadducts were developed[354] (Scheme 17) and the route extended to benzotropones,[379] to analogues with further substituents,[543] and to benzoanulated azines.[493,538] Interesting further transformations occur: thus, the 1-phenacyl substituent gave a double addition,[485] the 1-oxidophthalazinium adducts rearrange to benzdiazocenes,[557] a novel pyridine to quinoline ring annulation was achieved,[599,668] and photooxidation investigated.[527] Cycloadditions were achieved with 1,ω-bis-(3-oxidopyridium)alkanes[595] and with 3-hydroxypyridine-2-thione derivatives.[711]

Scheme 17. Cycloadditions and Tropone Preparation[354]



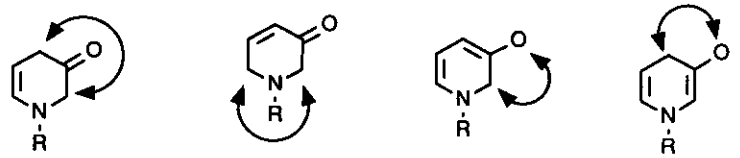
3-Hydroxypyridine itself undergoes this cycloaddition in its zwitterionic tautomeric form. The cycloadducts can again be transformed into tropolones[644] and can also serve as a form of protection because the cycloaddition readily reverts. In this way, 4-bromo-3-hydroxypyridine could be prepared.[544] 3-Hydroxypyridines and 4-hydroxyisoquinoline also react with two molecules of benzyne to yield the expected products of N-phenylation and cycloaddition.[539] We also found syntheses of benzopyranopyridones.[378,438]

Scheme 18. Preparation of 4-Bromo-3-hydroxypyridine[544]



1-Phenyl-3-oxidopyridinium readily undergoes cycloadditions with electron-deficient olefins,[540] benzynes,[377] and also with styrenes.[437] The adducts can cyclize further.[554,637] We found that 1-arylpyridine-3-oxides undergo photochemical interconversion with bicyclic isomers.[545] Mass spectra of these compounds were recorded.[553,604]

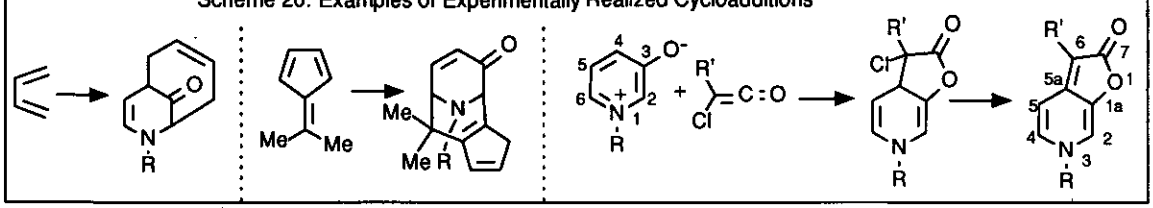
Scheme 19. Predicted Thermal and Photochemical Cycloadditions to 3-Oxidopyridiniums



Δ with 4 π; hv with 2π Δ with 2π; Δ 6π Δ, with 2π Δ, with 2π

When an electron-withdrawing substituent was placed on the pyridine-nitrogen atom, then cycloadditions also succeeded with unactivated olefins. We used 2,4-dinitrophenyl[405,441,484] and 5-nitro-2-pyridyl as the substituents. In the latter case reversible dimerization of the betaine now occurred.[435] The unsymmetrical dimer had formed by reaction of the 2,6-positions of one ring and the 2, 4-positions of the other. This demonstrated the orbital symmetry control and led to several predictions (Scheme 19), which could then be achieved experimentally: (i) 4π components form adducts across the 2, 4-positions (we used 1,3-dienes),[542] (ii) 6π components give adducts thermally across the 2, 6-positions (we used fulvenes),[542] (iii) 2π components yield adducts thermally across the 2-position and oxygen atom, and across the 4-position and oxygen (we used chloroketenes),[561,659,674] and (iv) 2π components give adducts photochemically across the 2, 4-positions (we used photochemical dimerization of 1-phenyl-[492] and other[645] pyridine-3-oxides - some of the dimers cyclize to diazadiamantanes).[572] Some of the products fragment to furans.[784,985]

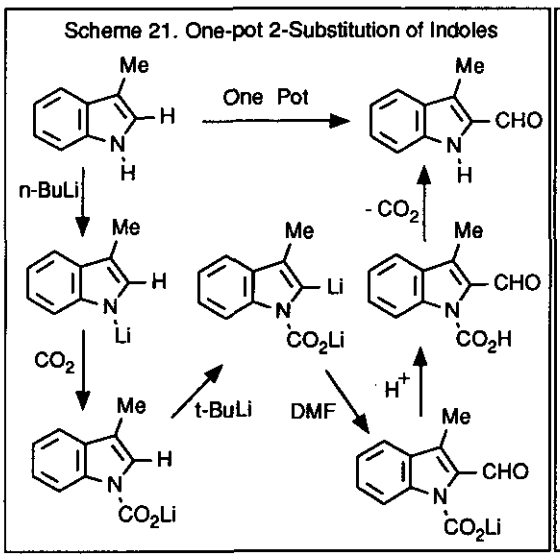
Scheme 20. Examples of Experimentally Realized Cycloadditions

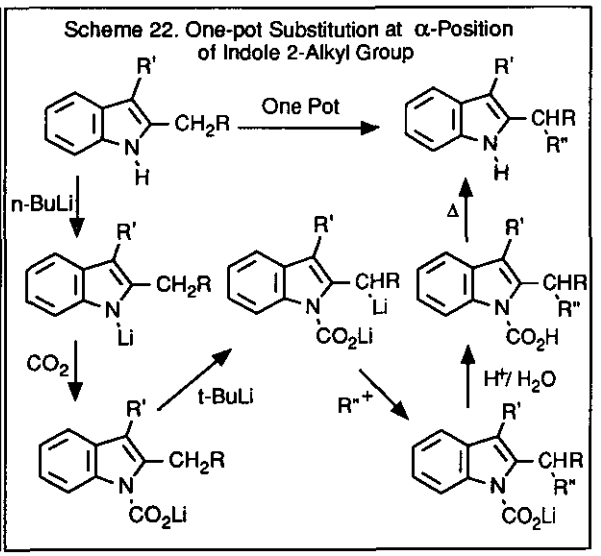


A further increase in reactivity was obtained by using the 4,6-dimethyl-2-pyrimidinyl substituent.[491] In this case two dimers were formed, one under kinetic and one under thermodymic control.[541] It was possible to rationalize all the site and regio and part of the stereoselectivity, of these addition reactions using molecular orbital methods.[629] The FMO energies could be directly correlated with rate constants. We have also studied as N-subsitutents in 3-oxidopyridiniums the following groups: 1,3,5-triazinyl,[579] acylvinyl,[655,671] nitrophenylvinyl,[728] pyridyl,[669] quinoxolinyl,[669] and others.[628,664] Several 3-iminopyridines were prepared and their structures studied.[582] Our work on the cycloadditions of six-membered betaines has been reviewed.[517,652,653,1030,1221]

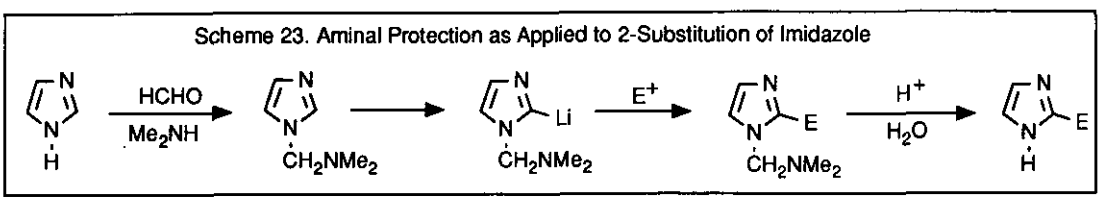
E. Metallation at Ring Carbon: Strategies for Protection, Activation, and Direction in Lithiation Chemistry

The activation to proton loss of a CH group in the presence of a heterocyclic NH group has been a classical problem in heterocyclic chemistry which we have tackled by a variety of methods. Our first approach was to use CO_2 which allows[882] a one-pot[1017] conversion of indoles into 2-substituted indoles (Scheme 21). The reaction involves a carbanic acid intermediate and at the end CO_2 is lost by gentle heating. This method was extended to pyrroles,[1013] to tetrahydroquinoline[1043] and tetrahydroisoquinoline,[915] and to thiazolidine.[974] The method also works well for phenothiazine[1018] and phenoxazine.[932] In the case of 2-pyridone, the activation surprisingly occurs[964] at the 4-position. When applied to 2-alkylindoles the CO_2 protection method enables substitution in the 2-alkyl group[898] (Scheme 22).



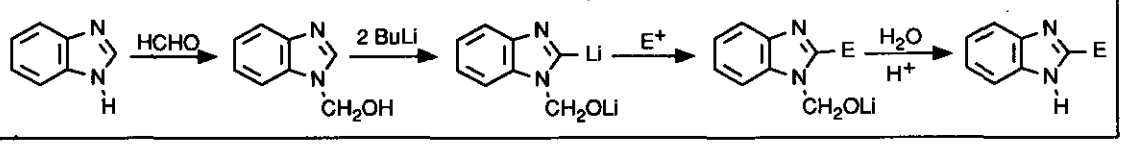


As an extention we developed the aminal protecting group which has enabled the selective lithiation of carbazoles and benzocarbazoles,[996] of imidazoles, benzimidazoles, and pyrazoles,[1001] and of triazoles.[1169] It also works well for indole.[1147] This method is illustrated for imidazole in Scheme 23; the aminal formation requires a separate step but the remained of the reaction can be carried out in one pot although the substituted aminal can be isolated if desired.



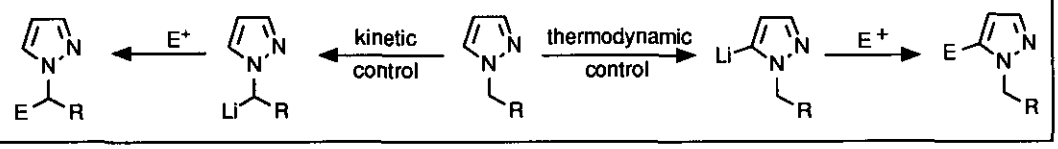
The third strategy was the use of hemiaminal anion intermediates illustrated in Scheme 24 for benzimidazole.[1058] The method has been extended to pyrazole;[1081] it goes in one pot, the CH_2OH group is lost by gentle heating with excess H_2O.

Scheme 24. Hemiaminal Procedure for One-pot 2-Substitution of Benzimidazole



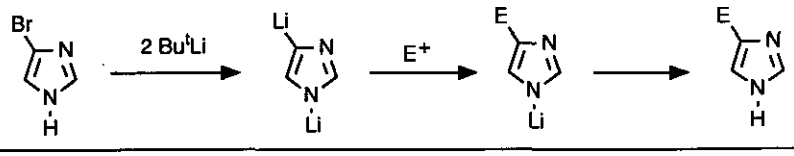
We have also studied the selective lithiation at ring CH groups for various other five- and six-membered heterocycles in the search for synthetically useful transformations. 2-Carbamoyl-[730] and 2-benzothiazolylthio-pyridines[928] are readily lithiated in the 3-position. 2-Substituted thiazoles,[976] and 3,4-disubstituted thiazole-2-thiones,[695] are lithiated in the 5-position. In alkylpyrazoles, lithiation was shown to occur at N- or C-alkyl group or at a ring carbon atom depending on the conditions[810] (Scheme 25). In all cases reactions of the lithiated derivatives with electrophiles gave convenient synthesis of the corresponding substituted heterocycles.

Scheme 25. Lithiation of 1-Methyl and 1-Benzyl Pyrazole under Kinetic and Thermodynamic Control



4-Bromoimidazole gives 1,4-dilithioimidazole which provides a general route to 4-substituted imidazoles[1046] (Scheme 26). 4- and 4,6-Di-substituted dibenzothiophene have been obtained via lithiation.[1142] In the course of the above work, the first examples of the imino-Wittig rearrangement were uncovered.[735]

Scheme 26. General Route to 4-Substituted Imidazoles from 4-Bromoimidazole

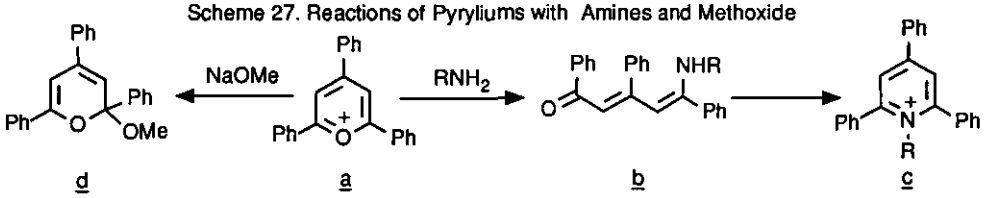


Our work on protection and activation to lithiation by the CO_2 method was first reviewed in 1987.[961] A more general account of the lithiation of heterocycles was presented in 1988 under the title *activation of* α-sp^3 *centres toward electrophilic substitution in alcohols and amines.*[1014] In 1989, strategies for protection, activation and direction in lithiation chemistry were covered.[1075] Finally, a comprehensive review *Generation and Reactions of* sp^2*-Carbanionic Centres in the Vicinity of Heterocyclic Nitrogen Atoms* appeared in 1993.[1281]

F. Ring Opening/Ring Interconversion: Pyrylium to Pyridinium

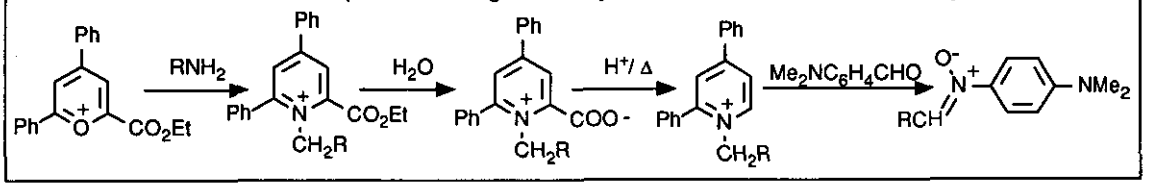
The pyrylium to pyridinium ring transformation represents the first step of our two stage conversion of amino group to other functionality (see later, Scheme 83), the second stage of which is described in Section IV A).

Scheme 27. Reactions of Pyryliums with Amines and Methoxide



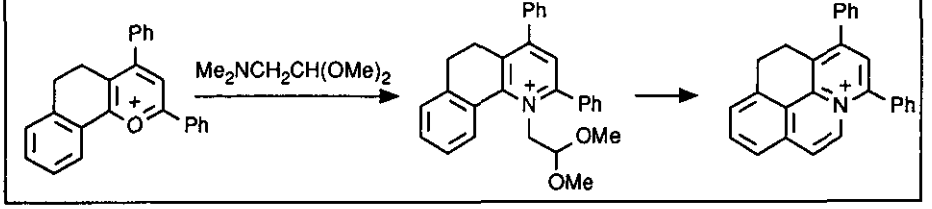
We have studied in detail the mechanism of the reaction of primary amines with pyrylium salts to give pyridinium cations, both by UV and nmr. Assignment[697] of all the carbon signals in starting materials and intermediates[706] showed (cf Scheme 27) that the primary and secondary alkylamines react with pyrylium salts **a** by fast ring opening to yield vinylogous amides **b** which in the former case slowly cyclize to pyridinium cations **c**. This ring closure requires acid catalysis and the kinetic investigation[722] has allowed correct preparative conditions to be determined[662] for the transformations of many types of amines by pyrylium salts into pyridiniums.[750] The dependence of the rates of reaction on the structure of the amine and the pyrylium salt has been investigated in detail.[867] Pyrylium cation conversion to pyridines by NH_3 has been studied in the gas phase by mass spectra.[850] Pyrylium cations and methoxide give 2-methoxypyrans **d** without ring opening.[616]

Scheme 28. Sequence Including Decarboxylation to Produce 2-Unsubstituted Pyridinium



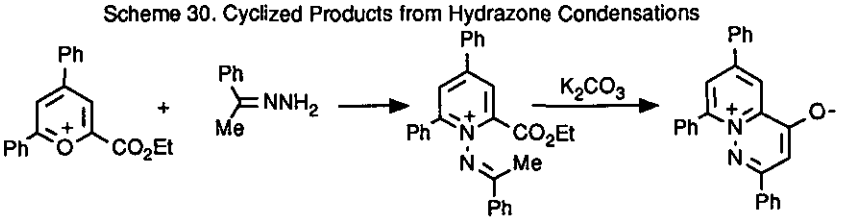
2- and 2,6-Di-ethoxycarbonylpyryliums have been reacted with amines to give, after hydrolysis and decarboxylation, pyridinium cations with unsubstituted 2-, or 2,6-positions,[731,808] alternatively de-ethoxycarbonylation can be achieved by direct treatment with amines.[765] The products can then undergo Kroehnke reactions with nitroso compounds (Scheme 28).[807]

Scheme 29. Preparation of Condensed Quinazoliniums



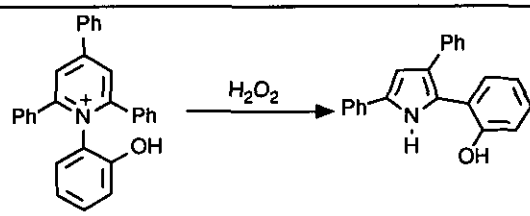
Aminobenzoic acids are converted by pyrylium cations into N-arylpyridinium betaines,[592] and dimethyl p-aminoethylacetal gave products which readily cyclized (Scheme 29) to condensed quinolizinium systems.[707] Sulfonium ylides of type $ArCOCH^{-}S^{+}R_2$ react with pyrylium cations to induce ring - contraction and produce furans.[487,494] Pyryliums react readily with hydrazine derivatives to give pyridiniums which cyclize (Scheme 30) if they contain a reactive 2-substituent.[718] Chelidonic acid is converted by amines into the corresponding 4-pyridone-2,6-dicarboxylic acid.[847]

Scheme 30. Cyclized Products from Hydrazone Condensations



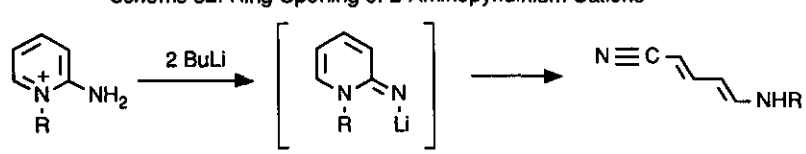
Thiopyrylium cations react with amines in part by hydrogen abstraction, and in part by conversion to pyridiniums.[675] Ring interconversions of pyrone-imines with isomeric pyridones, and corresponding ring interconversions of their sulfur analogs, have been elucidated with the help of mass spectra.[532,577]

Scheme 31.
Pyridinium into Pyrrole Conversion



Pyridinium betaines are converted by H_2O_2 into pyrroles[622,676] (Scheme 31) and 2-aminopyridinium cations are ring opened by BuLi into ϖ-alkylaminopentadiene nitriles[768] (Scheme 32).

Scheme 32. Ring Opening of 2-Aminopyridinium Cations

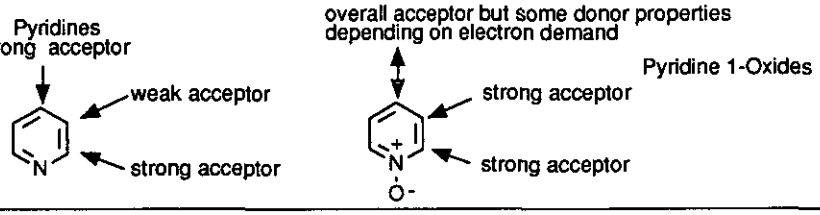


Much of this work on ring interconversion has been reviewed together with the corresponding reactions of pyridinium cations with nucleophiles in accounts of amino group transformation to other functionality: for references see Section IVA.

G. *N-Oxides*

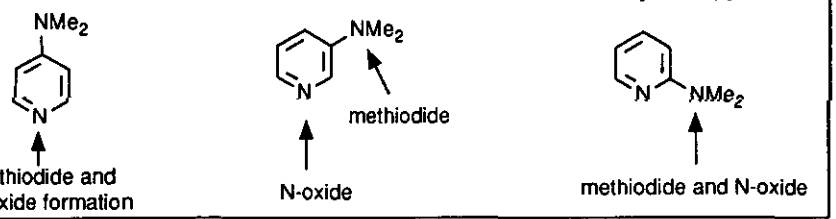
The fact that the N-oxide group in pyridine-N-oxide could act as both an electron source and an electron sink was an early fascination. This diverse polarizability was demonstrated by various physical methods including dipole moments[12] involving comparison with BCl_3 derivatives and BH_3 analogues,[16,17] and by infrared and ultraviolet[27] spectroscopy. Infrared spectra were used to show that carbonyl groups[20] could gain electron density from the 4-position of the ring and methoxy groups could donate electron density to this position. The cyano group[45] also withdrew electron density and an infrared method was developed for comparing the electronic properties of two aryl groups by placing them at the ends of an acetylenic bond.[51] Proton chemical shifts of 4-substituted pyridine 1-oxides[71] offer confirmatory evidence that the electron density at various ring positions decreases Ph > 3Py > 3PyO > 2Py > cationic rings. The conclusions from this work are shown in Scheme 33.

Scheme 33. Conclusions from Spectroscopic Evidence Regarding Electron Donor /Acceptor Ability

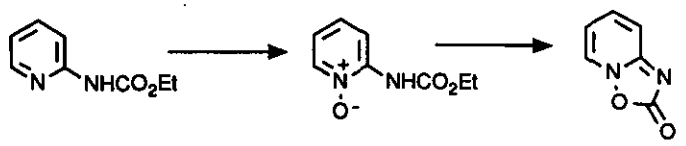


In addition to the aspects of aromaticity, tautomerism and electrophilic substitution discussed (in Section II, 1-3), our investigations of pyridine oxides have encompassed: preparation[9,15] (including the use of PhCN-H_2O_2 for aminopyridines[983]), displacement reactions of 2-chloro and 2-chloromethyl,[605] diazotization of the 2-amino,[11] selective reduction of other groups,[18] a color test,[41] pyridoxine analogs,[119] basicity[49] and UV spectra[57] of amino- and nitro-phenyl derivatives, and basicity,[50] dipole moments[188] and UV spectra[60] of 4-styryl and 4-phenylethynyl derivatives. Steric and electronic effects rationalized the orientation of the N-oxidation and N-methylation of the isomeric (N,N-dimethylamino)pyridines[362] (Scheme 34).

Scheme 34. Orientation of N-Oxidation and Methiodide Formation in Dimethylaminopyridines

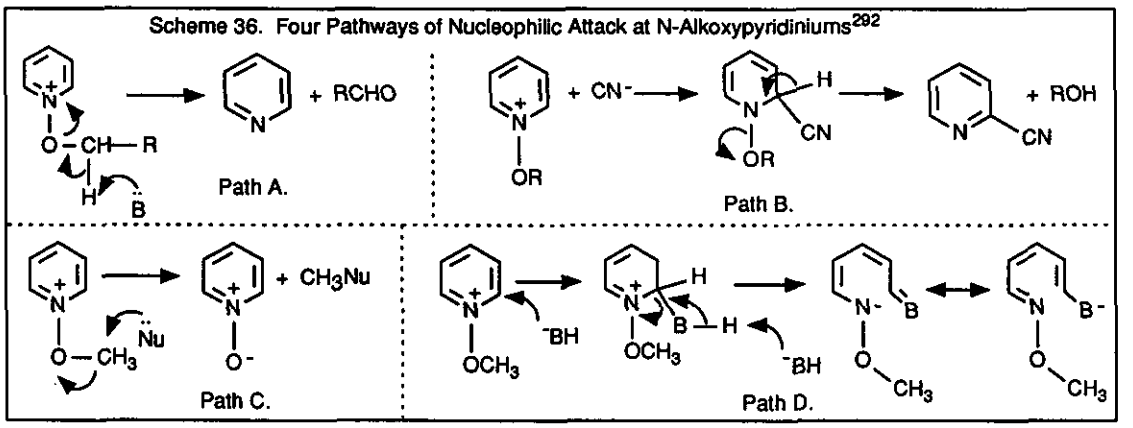


Scheme 35. Cyclization of 2-Ethoxycarbonylaminopyridine 1-Oxide



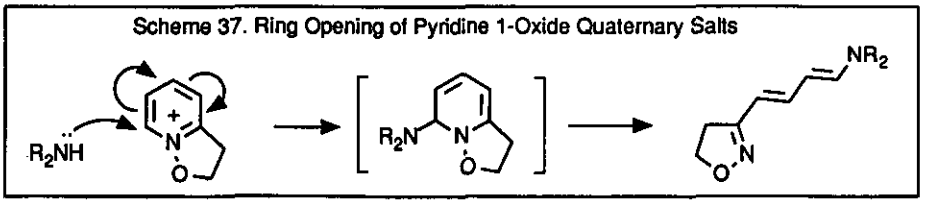
The radical ion pair mechanism of rearrangment of 2-methylpyridinium 1-oxide with Ac_2O to give 2-acetoxymethylpyridine suggested by Oae was confirmed by O-18 studies.[252,269] 2-Ethoxycarbonylaminopyridine 1-oxides cyclize to bicycles[8,14] (Scheme 35). Substituent ring interactions in pyrazines and their N-oxides were elucidated by dipole moments.[383] Stabilized radicals from 1-hydroxybenzimidazole 3-oxides were studied.[246]

Scheme 36. Four Pathways of Nucleophilic Attack at N-Alkoxypyridiniums[292]

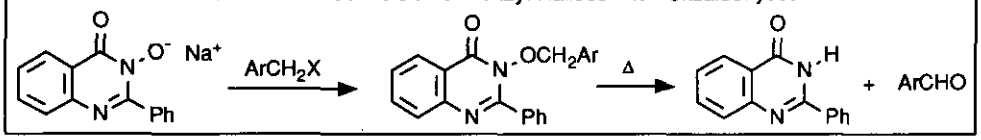


The reactions of N-alkoxypyridinium cations with nucleophiles has been intensely investigated and shown to proceed in diverse ways by attack on the ring, directly on the substituent or on an atom removed in the substituent.[292] An early idea of this ease of ring opening was found[175] in a UV investigation the reaction N-methoxypyridinium cation with base. Later, secondary amines were found to give ring open products which could be isolated[235] (Scheme 37).

Scheme 37. Ring Opening of Pyridine 1-Oxide Quaternary Salts

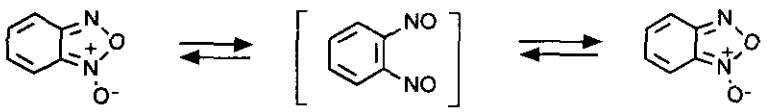


Scheme 38. Conversion of Benzyl Halides into Benzaldehydes



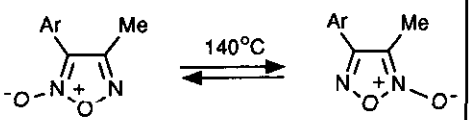
Sodium 4,6-diphenyl-1-oxido-2-pyridone converts primary halides into aldehydes by thermolysis of intermediate 1-alkoxyl-2-pyridones;[569,642] corresponding quinazolinones are reagents for conversion of benzyl halides into benzaldehyde[608,642] (Scheme 38) and for transformation of phenacyl halides into arylglyoxals.[704] N-Aryloxy- and N-alkoxy-2-pyridones thermally rearrange the RO group to the 3-position.[623] Other novel rearrangements of 1-substituted derivatives of 4,6-diphenyl-2-pyridone include loss of CH_2O from 1-(OCH_2CH_2Ph) and 1-($OCH_2CH_2CH{=}CH_2$) groups and transposition of the remainder of the substituent to the 3-position, rearrangement of 1-(OCOR) groups to the 3 and 5 positions, and of 1-[OC(:NH)R] to 3-NHCOR derivatives.[684]

Scheme 39. Valence Bond Tautomerism of Benzofuroxan

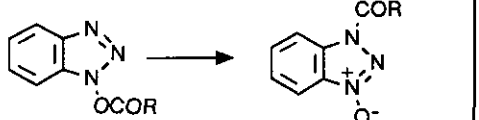


A quite different N-oxide is embodied by the case of benzofuroxan. We demonstrated[67] that the benzofuroxan equilibriation is slow at low temperatures and rapid at high temperatures on the nmr time scale (Scheme 39). We studied the influence of substituents,[112,219] and of heteroatoms in the benzene ring,[314] on the rates and equilibrium constants for this rearrangement (further work on benzofuroxans is mentioned under rearrangements; see Section II-11). 5-Amino- and 5-hydroxybenzofuroxans have been studied.[193] Isomerism in simple furoxans has been clarified[282] (Scheme 40). Work on the acyl-N-oxides has included M.O. study of rearrangements of 1-acyloxybenzotriazoles,[1258] shown by cross over to be intermolecular[1197] (Scheme 41).

Scheme 40. Isomerization in Furoxans



Scheme 41. Rearrangement of 1-Acyloxybenzotriazoles

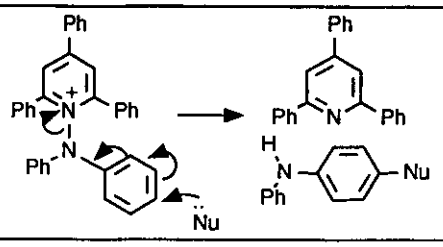


N-Oxide chemistry was first reviewed in 1956.[10] We later published a comprehensive monograph[327] and recently another review.[1248]

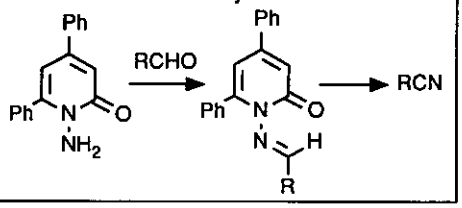
H. N-Imides and N-N Linked Heterocycles

Our interest in pyridine 1-oxides led naturally to a preoccupation with the corresponding N-imides. Thus, reactions of 1-amino-2,4,6-triphenylpyridinium salts have been studied,[710,749] and systematic investigations on heterocyclic N-imides conducted.[324] N-Diarylaminopyridinium cations undergo S_NR' type reactions with nucleophile (Scheme 42),[863] and 1-amino-4,6-diphenyl-2-pyridone was shown to convert aldehydes into nitriles (Scheme 43).[590,640]

Scheme 42.
S_NR' Reaction of
N-Aminopyridinium

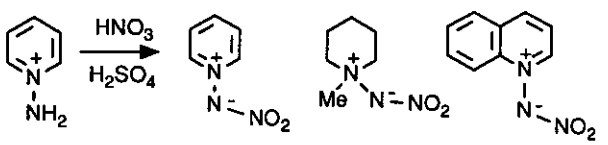


Scheme 43. Aldehydes into Nitriles

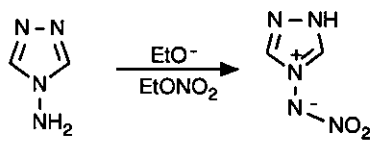


Nitration of 1-aminopyridinium cation[293] was shown to form stable pyridine N-nitroimide[474] and such behavior is typical of hydrazidium salts[408] (Scheme 44). N-Aminoazoles can be nitrated in the amino group by base catalysis[409] (Scheme 45). We have compared the chemical and physical properties of pyridine 1-nitroimides with M.O. theoretical predictions[547] and studied their nmr behavior.[509] Hydroxy-pyridine and -quinoline 1-nitroimides were prepared.[428]

Scheme 44. Examples of Amine N-Nitroimides

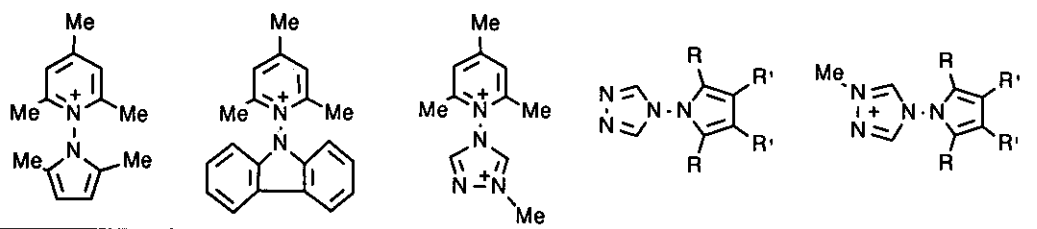


Scheme 45. Base-catalyzed Nitroimide Preparation



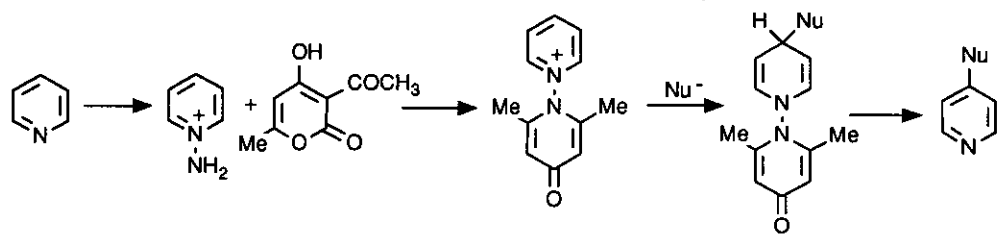
The chemistry of N-N linked biheterocycles has been investigated systematically.[511] The reactions of a variety of N-amino heterocycles with bielectrophiles were exploited to prepare diverse N-N linked biheterocycles: neutral species, monocations and dications[475,576] as illustrated in Scheme 46.

Scheme 46. Examples of N,N-Linked Biheterocycles



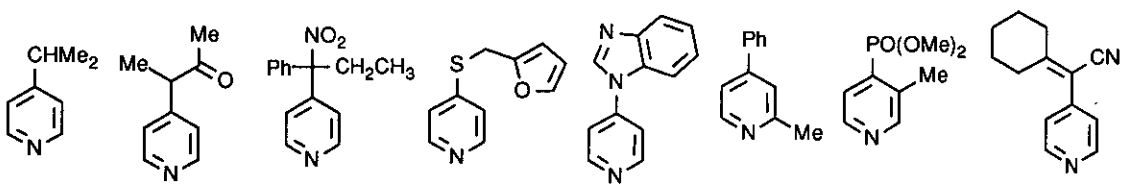
Pyridoniopyridinium cations prepared from 1-aminopyridinium cations and pyrones[489] have considerable synthetic potential. They are converted by $POCl_3$ into 4-chloropyridiniopyridinium dications which can be transformed into 1-arylpyridinium salts, pyridine disulfones, cyanopyridines,[574] and into 4-pyridyl(aryl)amines.[787]

Scheme 47. Regiospecific Preparation of 4-Substituted Pyridines



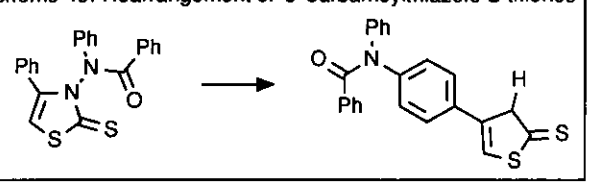
Use of the related 1-(2,6-dimethyl-4-pyridone-1-yl)pyridinium has been developed into a general method for the preparation of 4-substituted pyridines[614,617] (Scheme 47). The 2,6-methyl groups shield the 2 and 6 positions from nucleophilic attack as shown by the X-ray geometry.[868] Nucleophiles thus introduced have included the cyano group,[638] aryl and alkyl groups[682] from Grignard reagents, alkyl- and aryl-thio groups,[719] nitroalkyl groups,[713] acylalkyl groups,[681] alkylcarboxyalkyl,[720] and phosphorus containing[715] groups (Scheme 48). However, while carbanions from carbon acids of pK_a 7-14 attack the 4-position, those from weaker acids cause ring opening at the 2-position.[721] This work was extended to benzpyridines[708] and to the use of N-pyrryl groups.[709] Aminopyridones react with pyrrones to give N,N-bispyridones.[607]

Scheme 48. Examples of 4-Substituted Pyridines Prepared

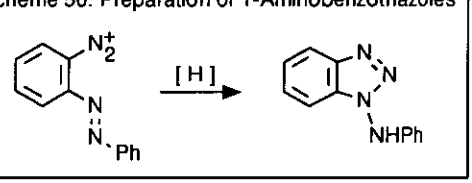


3-Carbamoylthiazole-2-thiones undergo a thermal benzidine-like rearrangement[860] (Scheme 49). The so-called "dihydrobenzo-1,2,3,4-tetrazines" were shown to be 1-aminobenzotriazoles[137] (Scheme 50).

Scheme 49. Rearrangement of 3-Carbamoylthiazole-2-thiones



Scheme 50. Preparation of 1-Aminobenzotriazoles

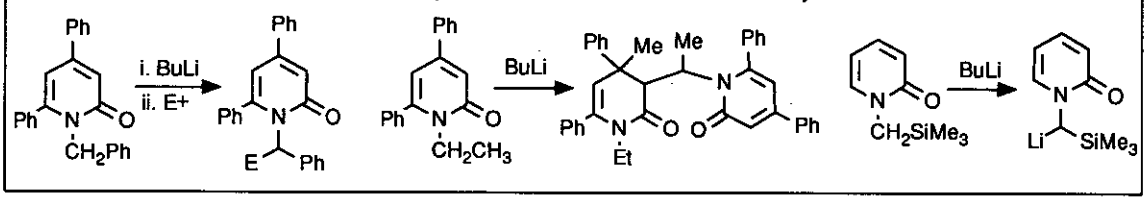


Our work on N-imides has been reviewed along with that on N-oxides.[1248]

I. Substituents Attached to Nitrogen of Six-Membered Rings

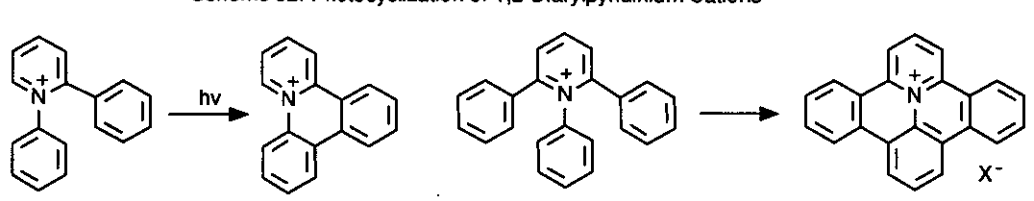
The majority of our work on N-alkyl and N-aryl substituted pyridinium cations has been concerned with synthetic methods not necessarily dealing with heterocyclic chemistry, and is accordingly considered later in section IV.1. Considerable further work has dealt with mechanistic aspects of the scission of the N-C bond of an N-alkyl substituent at a pyridinium ring with regard to the detailed mechanism as is also considered later (section V.1). We consider here the metallation of N-substituents their photocyclization, and reactions of ylids and N-vinylpyridiniums, but initially mention that the first N-(t-alkyl)pyridinium cations were prepared by silver-assisted solvolysis.[833]

Scheme 51. Examples of Lithiation of N-Substituents in Pyridones



N-Alkyl-[701] and N-benzyl-groups[685] in 4,6-diphenylpyridones are C-lithiated : the former spontaneously add to a second molecule of the substrate, while the latter give normal substitution products with electrophiles[754] (Scheme 51). Similar work has been carried out with simple 1-methyl- and 1-benzyl-pyridones.[802] 1-Trimethylsilyl-2-pyridone provided stable CH_2-lithiated intermediates[969] (Scheme 51) as did 1-benzylpyrimidinones.[755]

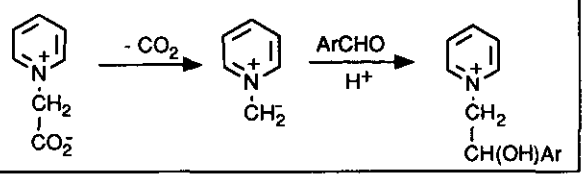
Scheme 52. Photocyclization of 1,2-Diarylpyridinium Cations



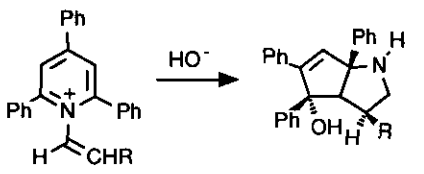
1,2-Diarylpyridinium cations undergo photocyclization[620] and corresponding photobicyclization are known[677,852] (Scheme 52). The cyclized products easily form pseudo bases by water addition.[806] The photochemistry of pyridinium salts has been reviewed.[931]

1-Methylpyridinium ylide was formed from 1-carboxymethylpyridinium betaine, and trapped (Scheme 53).[578] Pyridinium ylides cycloadd chalcones to give tetrahydroindolizines[716] and react with aldehydes[836] and Michael acceptors.[804] Cyano-stabilized ylides show analogous reactions.[779] We have rearranged ylides into azepines[927] and obtained tetrazole-stabilized ylides.[537]

Scheme 53. Preparation and Trapping of 1-Methyl Ylide

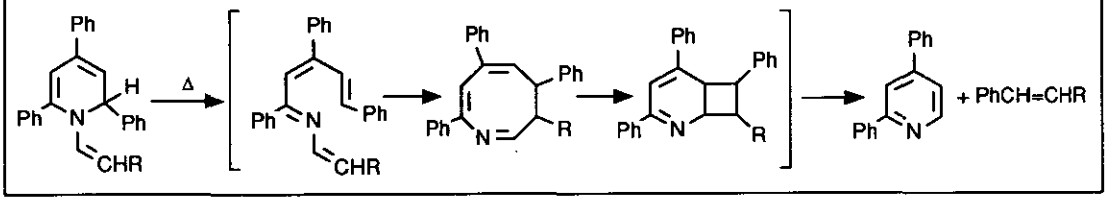


Scheme 54. Rearrangement of N-Vinylpyridiniums



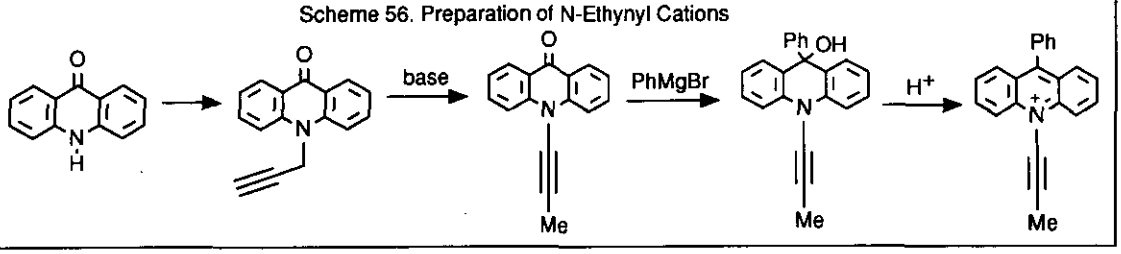
N-Vinylpyridinium salts have been prepared via β-chloroethylamine and pyrylium cation reactions,[597] and by other satisfactory preparative methods.[745,828] N-Vinylpyridinium salts act as Michael acceptors[803] and undergo a remarkable rearrangement with base (Scheme 54).[829,849] The reduced 1-vinyl-1,2-dihydropyridines undergo a different general rearrangement and fragmentation to give pyridines and olefins cf Scheme 55.[764] We prepared N-cyclohexenylpyridinium salts.[934]

Scheme 55. Rearrangement of N-Vinyl-1,2-dihydropyridines



N-(2-Propynyl)pyridinium cations rearrange to the N-allenyl isomers.[827,874] The first heterocyclic ynammonium salts were made via isomerization (Scheme 56).[875] In collaboration with Prof. Anders the chemistry of N-(1-haloalkyl)pyridinium salts have been exploited.[1059]

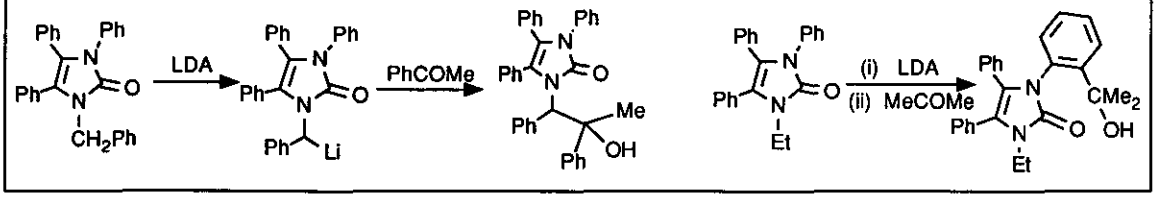
Scheme 56. Preparation of N-Ethynyl Cations



J. N-Substituents in Azoles

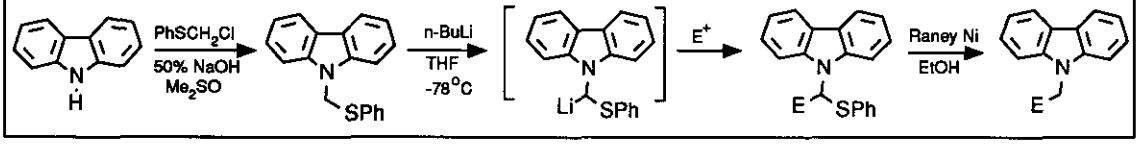
Again, the majority of our work on N-substituted azoles is considered under the preparative aspects section IV.2. We consider here some aspects of the C-lithiation of N-substituents, and of their isomerization.

Scheme 57. Lithiation of Imidazolones



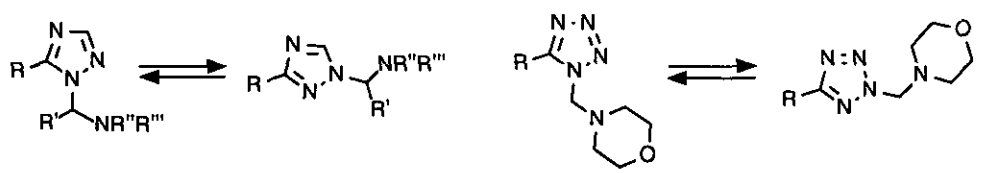
We found the 1-benzyl-3-substituted imidazolones could be C-lithiated in the CH_2 group, whereas the 1-ethyl analogs underwent reaction in a N-phenyl ring (cf Scheme 57).[748] N-Phenylthiomethyl-carbazole,[876] -pyrazole,[1028] and -benzimidazole[936] are easily lithiated at the CH_2 group, and in each case the reactions can be exploited for the synthesis of N-substituted derivatives by subsequent removal of the S-phenyl group, as illustrated for carbazole in Scheme 58. In N-alkylpyrazoles, lithiation was shown to be favored kinetically at the N-substituent, but thermodynamically on the ring[811] (see also document in section II-5).

Scheme 58. Preparation of 9-Substituted Carbazoles



Isomerizations of N-(α-aminoalkyl)-1,2,4-triazoles and -tetrazoles (Scheme 59) have been studied by nmr, and equilibrium constants and activation parameters measured.[1170]

Scheme 59. Isomerizations of N-(α-Aminoalkyl)-1,2,4-triazoles and -tetrazoles

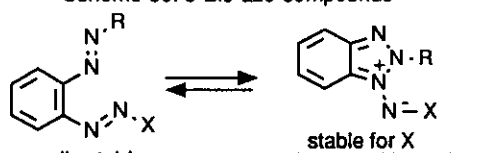


Much of this literature work has been reviewed along with our other work on lithiation of heterocycles (for references see Section IIE).

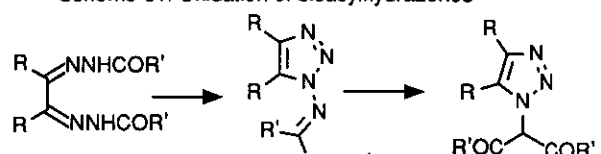
K. Substituent Induced Rearrangements and Ring Chain Tautomerism

Our demonstration that benzofuroxans exist (see Scheme 29 of Section II-7) as rapidly equilibrating forms, led us to investigate aza-analogs. Most o-bisazobenzenes were confirmed to exist in the open chain form, but if a sufficiently electron withdrawing N:NX group is present, then spontaneous ring closure occurs, cf Scheme 60.[134] α-Bisacylhydrazones oxidize to cyclic products (Scheme 61), the structures of which was elucidated.[331,382]

Scheme 60. o-Bis-azo-compounds

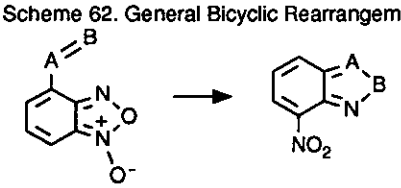


Scheme 61. Oxidation of bisacylhydrazones

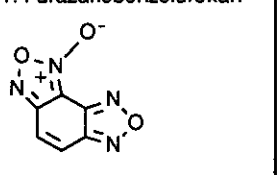


Benzofuroxans with a suitable 4-substituent undergo[127] thermal rearrangements (Scheme 62) as demonstrated for nitro,[93,96] for arylazo and nitroso,[189] for aryl and iminoalkyl,[190] and for nitroso[263] derivatives (Scheme 64).

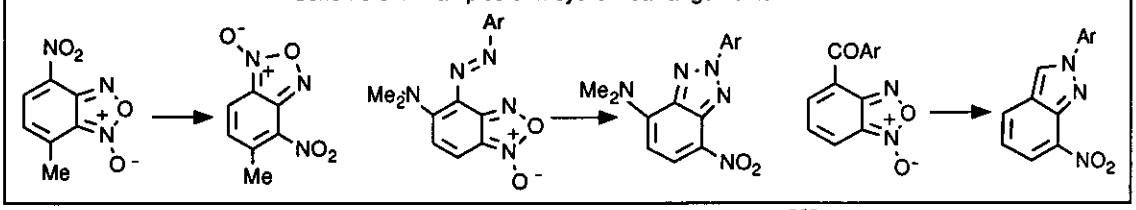
Scheme 62. General Bicyclic Rearrangement



Scheme 61. Furazanobenzofuroxan

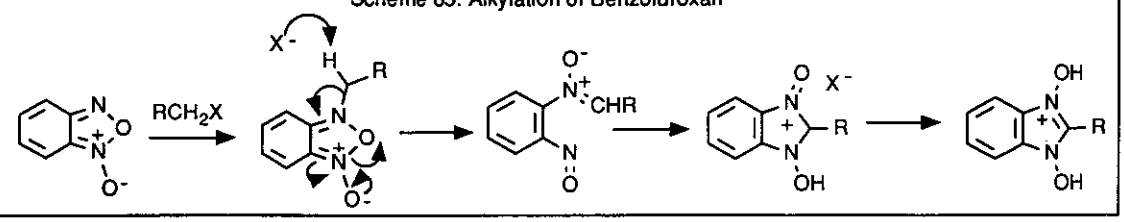


Scheme 64. Examples of Bicyclic Rearrangements



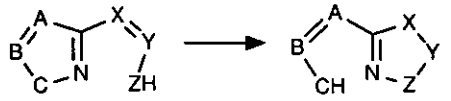
The generality of this bicyclic rearrangment has been demonstrated[355] by its applicability outside benzofuroxans. However the oxygen does not jump in furazanobenzofuroxan (Scheme 63).[166,217]

Scheme 65. Alkylation of Benzofuroxan



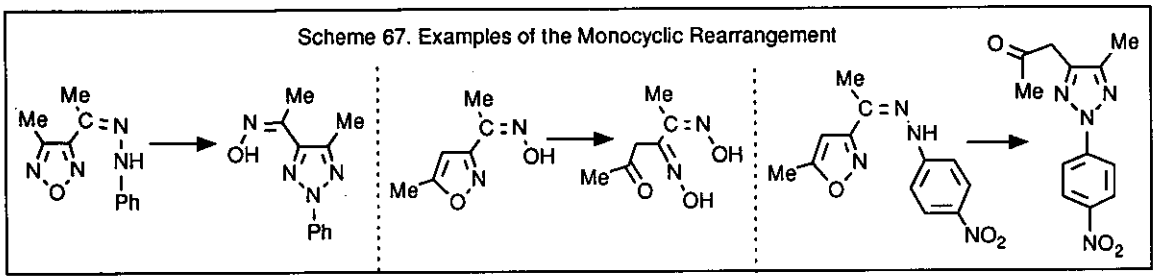
Benzofuroxans are alkylated on nitrogen and the cations thus formed rearrange to 1-hydroxybenzoimidazole-3-oxides (Scheme 65).[195,218]

Scheme 66. Generalized Monocyclic Rearrangement



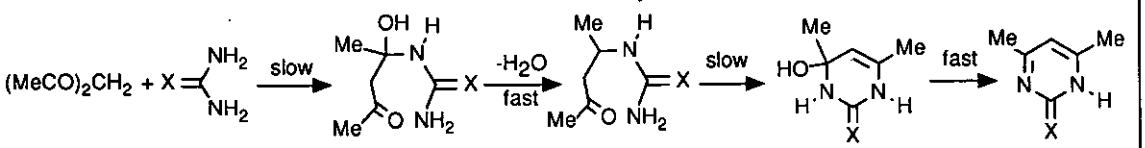
Discovery of an isoxazole to triazole conversion[73] led us to deliniate[232] the general monocyclic rearrangement (Scheme 66) corresponding to the bicyclic rearrangement mentioned above and investigate its limitations[536] (Scheme 67).

Scheme 67. Examples of the Monocyclic Rearrangement



The bicyclic rearrangements have been reviewed.[613,1283]

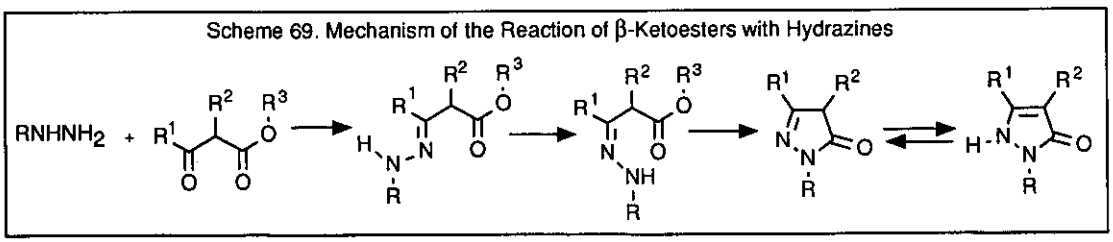
Scheme 68. Mechanism of Reaction of Acetylacetone with Urea and Thiourea



L. *Mechanisms of Ring Closures*

Using nmr techniques we have studied the intermediates formed in the ring closure reactions involved in the formation of some of the common heterocyclic rings. In this work, we have elucidated the mechanisms of the Knorr synthesis of pyrroles,[914] of the synthesis of pyrimidines[890] from 1,3-dicarbonyl compounds with amidines and ureas (Scheme 68), of the Hantzsch pyridine synthesis,[917] and of the reactions of β-keto esters with hydroxylamine[76,906] and with substituted hydrazines[946] (Scheme 69). This work has been reviewed.[965]

Scheme 69. Mechanism of the Reaction of β-Ketoesters with Hydrazines



III. Five- and Six-Membered Non-Aromatic Heterocycles

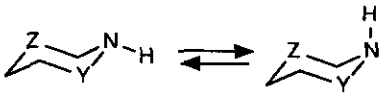
A. Five-Membered Non-Aromatic Azoles

Our studies of azolenine chemistry have been carried out in conjunction with the research group of Professor M. V. Sammes. 2H-Pyrrole-2,2-dicarboxylic esters readily rearrange to isomeric 1H-pyrroles,[862] and Paal-Knorr reactions of blocked 1,4-diketones also lead to rearrangement.[834,984] 2H-Azirines and enamines give dihydropyrroles which are converted by acid into pyrrole-2-carboxylic acids.[835] We have also studied reactions of 4H-pyrazole,[837] and 2H-imidazoles[788] quaternary salts. The chemistry of these classes of compounds have been reviewed in five chapters in *Advances in Heterocyclic Chemistry* comprising the 2H- and 3H-pyrroles,[742] the 3H-pyrazoles,[775] the 4H-pyrazoles,[776] the 2H-imidazoles[815] and the 4H-imidazoles.[816]

B. Six-Membered Conformational Analysis

The conformations of six-membered saturated and partially saturated heterocyclic rings have been studied by a variety of physical and chemical methods, particularly with respect to the relative energies of the conformations and the energies of activation for passage between those conformations. Many of the ring systems mentioned were prepared for the first time by our group. The major topics studied have been (i) the conformation equilibrium of cyclic NH groups, (ii) the conformational behavior of N-alkyl groups leading to (iii) studies on the quaternization kinetics of N-alkyl compounds and the conformations and configurations of the resulting quaternary salts.

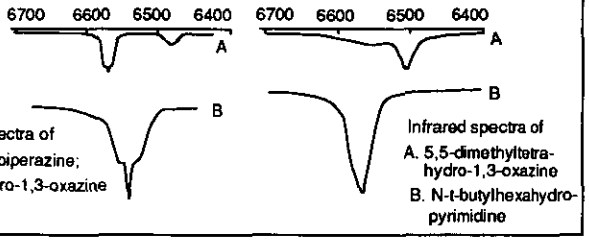
Scheme 70. Orientation of NH Groups in Saturated Heterocycles



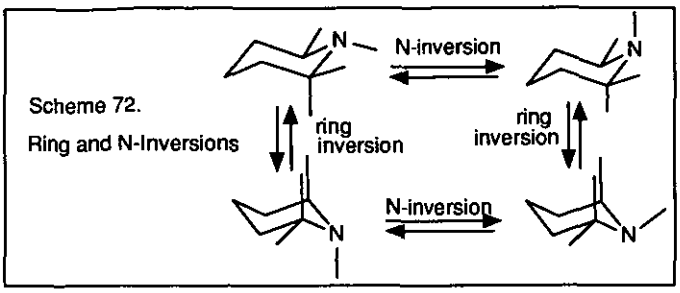
favored for:
$Z = Y = CH_2$
$Z = S, Y = CH_2$
$Z = CH_2, Y = O$

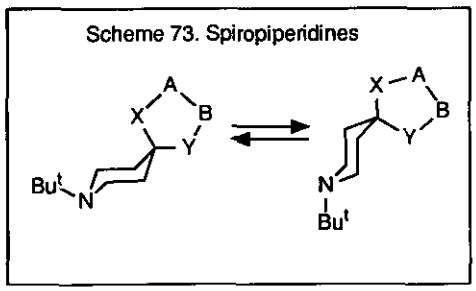
favored for:
$Z = O, Y = CH_2$
$Z = NBu^t, Y = CH_2$

Scheme 71. Infrared Spectra of Gaseous Piperidine at 90°C in the NH-First Overtone Region

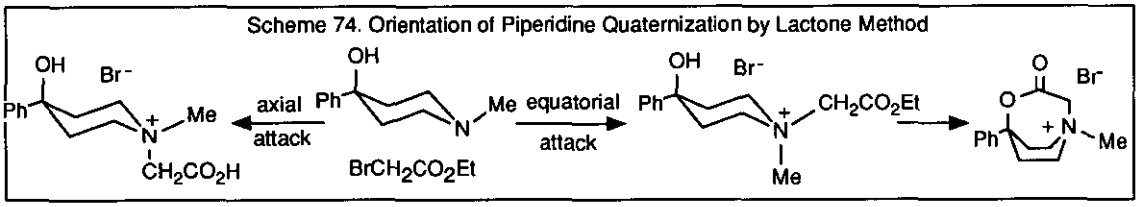


A major method for determining the orientation of NH group from the overtones for the N-H in the infrared spectrum was applied first to piperidines and morpholines,[260,270] and later to piperazines, hexahydropyrimidines, tetrahydro-1,2- and 1,3-oxazine, and tetrahydro-1,3-thiazine.[376] Conclusions regarding the equilibria from IR-band shapes of some of the systems studied are shown in Scheme 70 and an illustration of the contours given in Scheme 71.[410]

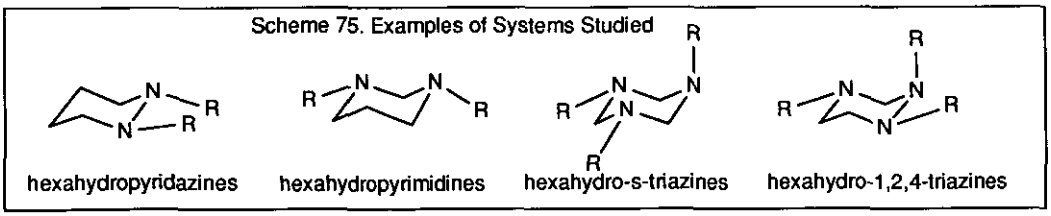




N-Alkylpiperidines (cf Scheme 72) have been studied by dipole moments,[140,213,309,310] by variable temperature nmr spectroscopy,[531] and by differential proton shifts.[341] Other compounds studied containing a single nitrogen include quinolizidines[75] (IR[88] and rates of quaternization[168] studies), tropanes,[191] azadecalines,[141,212] N-alkyl-[194,257] and N-arylpiperidones,[325] and N-alkylpiperidine N-oxides.[344] Spiropiperidines have afforded information regarding the steric requirements of alternative groups in systems of the type shown in Scheme 73.[338,339,340,381,412,455]

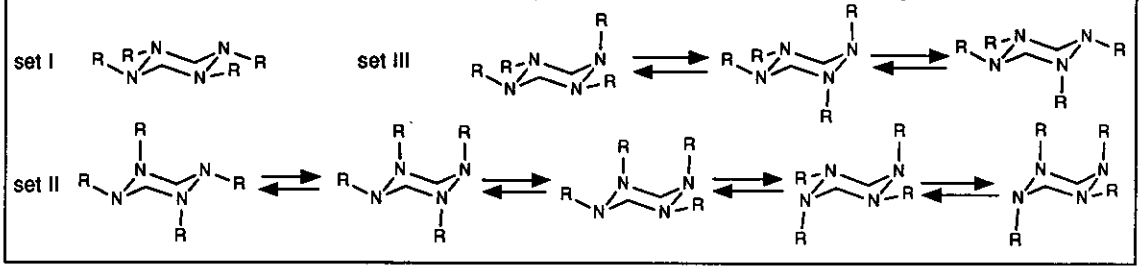


The *kinetics and orientation of quaternization of piperidines*,[183,316,417,467,469] X-ray analysis of the corresponding quaternary salts,[274,375] the additivity of molecular interactions[258] and the orientation of lactone formation[215] (Scheme 74) have received attention.



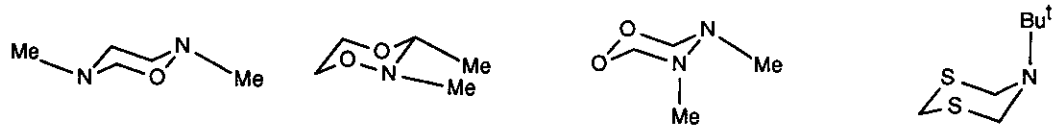
Further studies have been carried out on the following systems with several nitrogen atoms hexahydropyridazines,[358,380] hexahydropyrimidines,[311,580,692] piperazines,[214,563] hexahydro-1,3,5-triazines,[312,419,646] and hexahydro-1,2,4-triazines,[587,649] as well as hexahydrotetrazines (Scheme 76)[283,432,456,459,528,648,690,1029] and decahydroquinazolines[481] perhydropyrazinopyrazines[549] 2-oxa-9,10-diazodecaline[570] 1,4,5,8-tetradecalines.[736]

Scheme 76. The Three Sets of Rapidly Equilibrating Conformers for Tetraalkyltetrazines



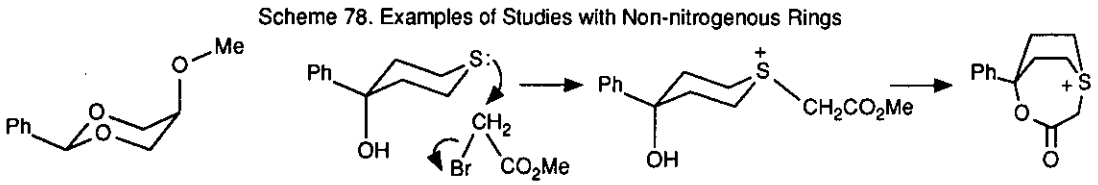
Similar work has presented a rather complete picture of the conformational equilibria in six-membered rings containing nitrogen and oxygen or nitrogen and sulfur: 1,2-[466,471] and 1,3-tetrahydroxazines,[337,490,691] dihydro-1,3-oxazines dihydrobenzoxazines,[1298,1312] 1,2,4-,[658] 1,2,5-[594,650] and 1,3,4-oxadiazines[663,551], 1,3,5-oxadiazine and 1,3,5-dioxazine,[600] 1,4,2-dioxazines,[406,468] 1,2,4,5-dioxadiazines,[651] and 1,4,2,5-dioxadiazines,[602] perhydro-1,3-thiazines,[526,692] perhydro-1,3,5-thiadiazines,[367,385] and -1,3,4-thiodiazines,[587,689] dihydro-1,3,5-dithiazines,[360] and various bicycles.[546] The conformational equilibria can be very different from the carbocyclic analogs. Thus, e.g., in 5-t-butyl-dihydro-1,3,5-dithiazine, the t-Bu is preferentially axial (Scheme 77).[360]

Scheme 77. Examples of Dominant Conformations in Six-membered N,O- and N,S-Containing Rings

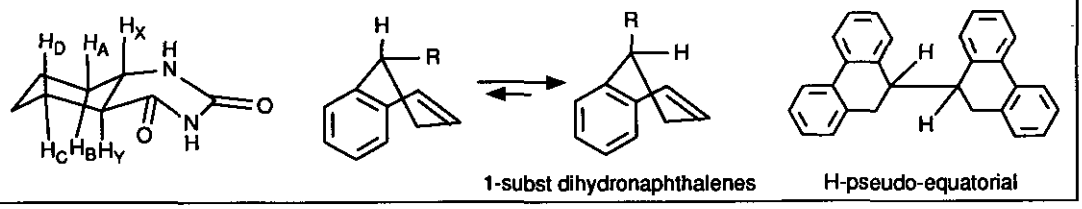


We have also investigated the conformations of six-membered rings not containing nitrogen. Among oxygen compounds we have studied tetrahydro-4-pyranones[350] 1,4-dioxans and benzo-1,4-dioxans,[170,315] 1,3-dioxans.[317] Among sulphur derivatives we have studied the quaternization of thiacyclohexanes,[259] hydrogen exchange orientation in thiacyclohexone sulfoxides[277] and sulfones[364] 1,3-dithians,[431] and among phosphorus compounds phosphorinane-1,4-diones.[461]

Scheme 78. Examples of Studies with Non-nitrogenous Rings



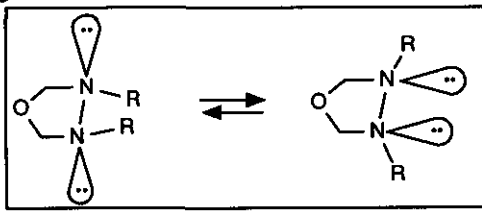
Scheme 79. Examples of Partially Unsaturated Six-membered Rings Studied



Dihydroheteroaromatics studied included 3,4-dihydroquinolines,[342] dihydrouracils,[291] cyclic thiophosphates,[313] together with some partially unsaturated benzenoid systems 1,2-dihydronaphthalenes,[281] tetrahydrobiphenanthryls,[230] bicycloctadienes.[422]

N-SO_2CH_3 groups in piperazines are mainly equatorial.[478] Conformations of N-OMe groups have been studied.[568] It was shown that the nmr shift reagents can give false conclusions because of differential complexing.[433] Related systems studied in the course of this work include acyclic hydrazines and 1,3,4-oxadiazolidines;[436] N-inversion energies for the latter (Scheme 80) demonstrate the importance of strain in N-inversion of hydrazines.[376,498] Photoelectron spectra helped to confirm many conformational assignments.[688]

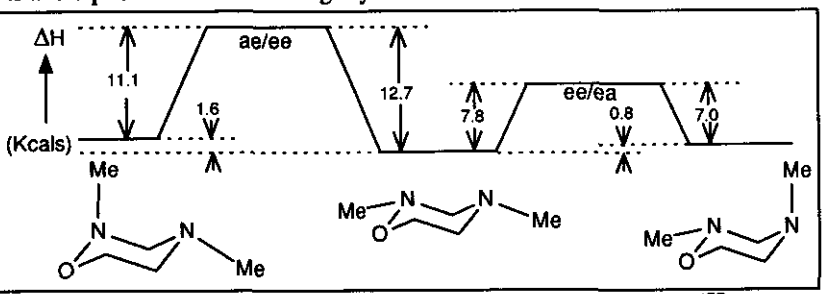
Scheme 80. Related Work on 1,3,4-Oxadiazolidines



R =	Me/Me	Me/iPr	iPr/iPr	CH_2Ph/CH_2Ph
$\Delta G^{\neq}$	10.6	14.6	19.4	12.0 Kcals

Quantitative approaches to intramolecular interactions were proposed[208,411] and applied to determine rotamer populations of axial cyclohexylamine.[343] Two types of N-inversions must be considered[357]: those where one substituent passes another and those where it does not. N-Alkyl inversion barriers must be considered in terms of the two half barriers ax ⇄ ts and eq ⇄ ts to avoid ambiguity.[626]

Scheme 81. N-Inversion in Terms of Half Barriers as Exemplified by 2,4-Dimethyl-1-oxa-2,4-diazacyclohexane



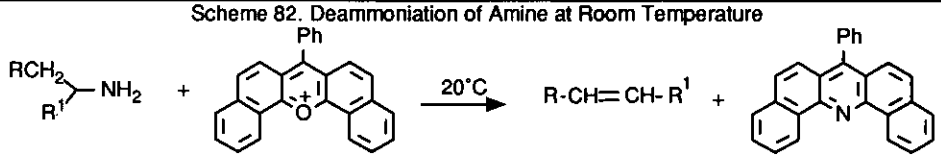
Reviews of this work[208,267,294,510] include NH equilibria in six-membered saturated rings,[477] N-methyl inversion barriers in six-membered rings[705] and the whole area of conformational equilibria in saturated six-membered rings.[817]

IV. The Role of Heterocycles in Organic Synthesis

A. Pyrylium and Pyridinium Cations

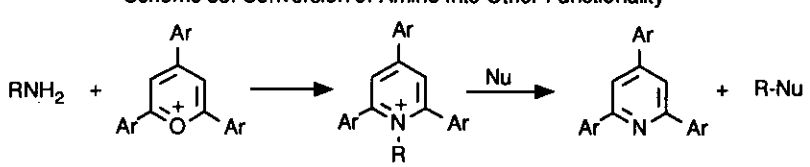
In analogy with the well-known concept of dehydration, we have used pyrylium cations as "deammoniating" agents to remove the elements of ammonia from a compound. The deammoniation of primary alkyl primary amines to olefin[712,766,777] requires a temperature of 150°C, but secondary alkyl primary amines are converted directly at 20°C into olefins at high yields (Scheme 82).[757] Pyrylium salts can also be used to deammoniate with simultaneous rearrangement, hydrazides into isocyanates,[560,636] and amidrazones into carbodimides.[584,641,747]

Scheme 82. Deammoniation of Amine at Room Temperature



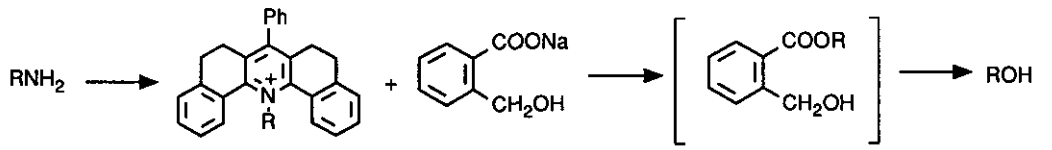
Many transformations of primary amines through pyridinium salts into compounds in which the original amino group has been replaced by a nucleophile have been developed as viable synthetic methods (see Scheme 83). Thus, using the appropriate nucleophile (given in brackets) compounds of the following types have been prepared: phthalimides[672] (potassium phthalimide), sulfonimides[672] (sulfonimide sodium salts), tertiary amines[630] (secondary amines), ammonium salts[630,687] (tertiary amines), nitro compounds[820] (nitrates), azides[672] (sodium azide), phosphonium salts (trialkylphosphines). Using oxygen nucleophiles, the following have been prepared: alcohols[717] (sodium o-hydroxymethylbenzoate) carboxylic esters[573,632] (carboxylate salts), nitrates[693] (sodium nitrate), ethers (sodium alkoxides) aldehydes[643] (sodium N-hydroxypyridone). Using sulfur nucleophiles we have made sulfones (sodium sulfinites), thioethers (sodium mercaptides), dithiocarbonates[598,639] (sodium alkyldithiocarbonates), xanthates (sodium dithiocarbamates), thiocyanates[598,639] (potassium thiocyanate), and other S-functionality,[666] also selenocyanates (sodium selenocyanate). The following halides have been made using the appropriate halide ions: fluorides,[686,619] chlorides,[634,657] bromides,[634,679] and iodides.[585,633]

Scheme 83. Conversion of Amino into Other Functionality



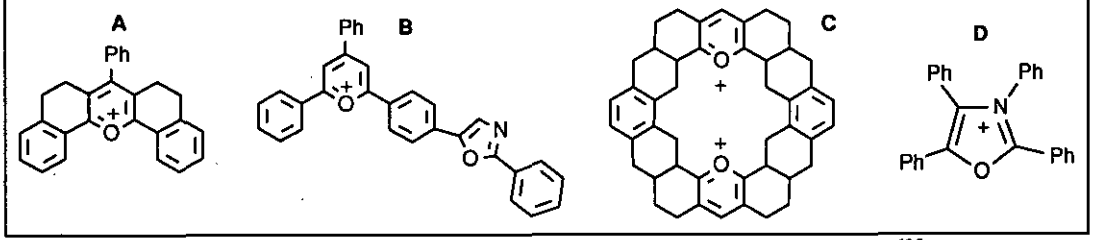
Intramolecular displacements have also succeeded,[733] as for example, in the preparation of alcohols (Scheme 84).[717] All of these reactions proceed by S_N2 displacements and the stereoelectronic restrictions have been explored in the intramolecular mode.[758]

Scheme 84. Preparation of Alcohols by Intramolecular Displacement



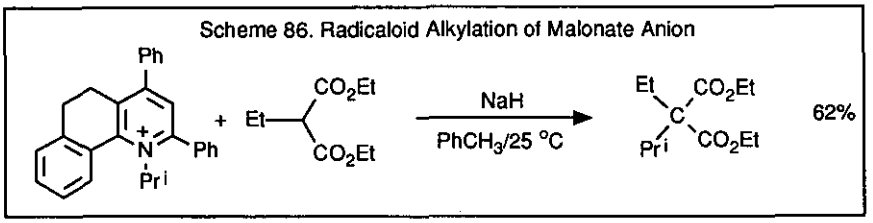
Although the conditions required in our initial recipes utilizing triphenylpyridine as a leaving group often involved quite high temperatures, the introduction of other, especially the pentacyclic, leaving groups and the use of appropriate counter ions and phase transfer catalysts[717] have provided much milder recipes. This required the synthesis of a variety of sterically strained pyrylium cations such as A in Scheme 85[680,714] pyryliums with polycarbocyclic,[785,902] heteroaryl[667,751], and 4-ethoxycarbonyl substituents.[778] We also synthesized colored and fluorescent pyryliums (eg B of Scheme 85) as markers for amino group[848] and the dioxoniakerkulene derivative C (Scheme 85).[782] Methods were developed for pyrylium counterion interchange.[665] We have also studied similar reactions of five-membered heteroaromatic oxonium cations (eg D).[752]

Scheme 85. Specially Prepared Pyryliums

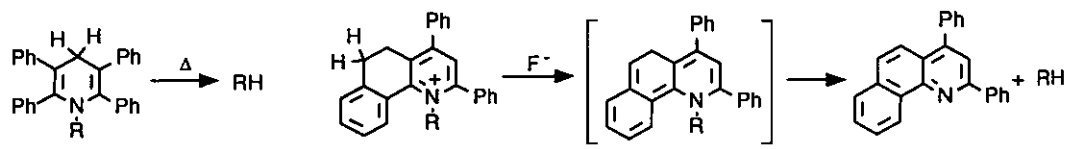


However, when the sodium derivative of a nitroalkane is used, C-alkylation takes place,[625] by what has been shown to be a non-chain radicaloid reaction,[698,913] in a useful preparative method.[732,854] Radicaloid migration of N-substituents was found to occur on thermolysis of pyridinium anhydro bases.[769] Other C-nucleophiles to which N-alkyl substituents can be transformed in preparatively good yield include malonate, acetoacetate, etc.[714] This technique enabled the preparation of hindered malonates under mild conditions (see Scheme 86).[962]

Scheme 86. Radicaloid Alkylation of Malonate Anion

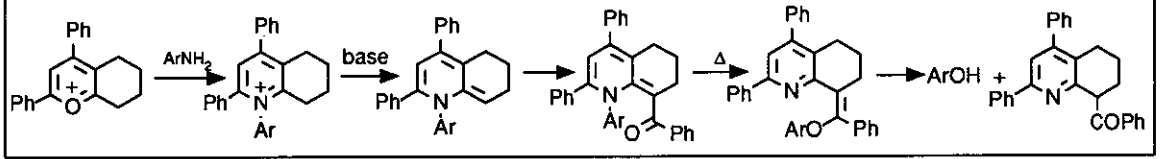


Scheme 87. Deamination Techniques

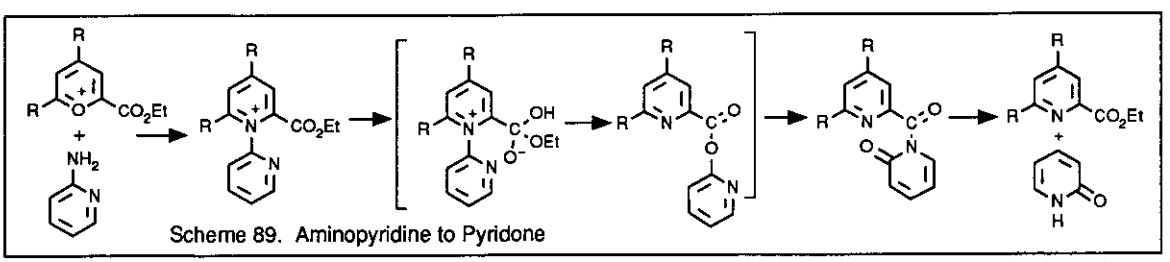


Various techniques have been elaborated for the replacement of NH_2 by H. Allyl- and benzyl-amines are deaminated by conversion into 2,4,6-triphenylpyridinium salts, reduction to the 1,2-dihydro derivatives and then thermolysis.[559,635] For unactivated alkylamines, 2,3,5,6-tetraphenylpyridiniums are reduced to 1,4-dihydro derivatives, which thermolyze to RH in good yield (Scheme 87A).[621,683] We found that aryl- and heteroaryl-amines can be deaminated using the tricyclic pyrylium fluoride: the mechanism of Scheme 87B is postulated.[734] The pentacyclic pyrylium also allows smooth deamination.[838]

Scheme 88. Transformation of Anilines into Phenols

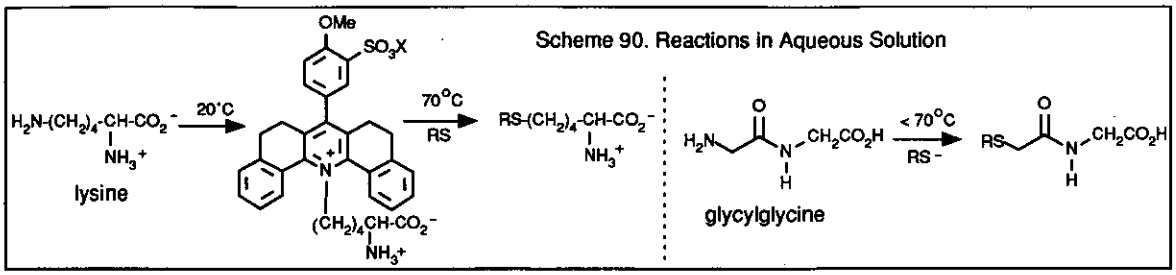


N-Arylpyridinium salts normally do not undergo nucleophilic displacement reactions, with the exception of the pyrolyses of aryl iodides[633] and of aryl thiocyanates[618,673] at temperatures above 160°C. This is because the stereoelectronic requirements are not favored. However, intramolecular reaction can be much easier. The first example we found was a photochemical rearrangement of an N-aryl group to 2-benzimidazolyl substituent.[770] N-Phenyl groups can be transferred onto adjacent acyl substituents, allowing the transformation of anilines into phenols[789] (Scheme 88); onto thiocarbonyl, transforming anilines into thiophenols;[790] onto amide, producing diarylamines;[791] or onto oximino groups.[864] The ease of transformation is greatly increased for N-heteroaryl groups[792] enabling a very smooth conversion of, for example, 2-aminopyridine into 2-pyridone (Scheme 89).[793]

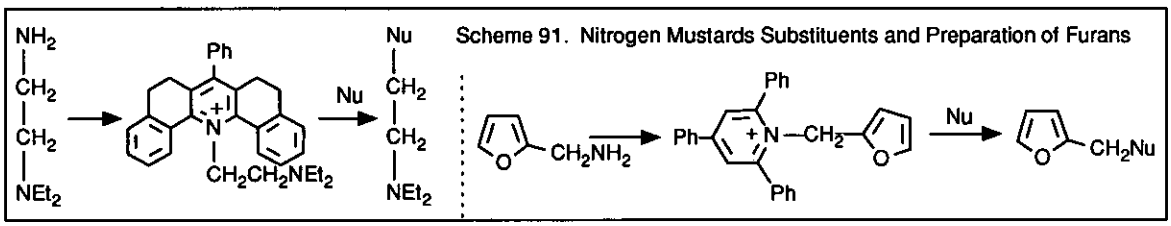


Scheme 89. Aminopyridine to Pyridone

Other intramolecular reactions with participation of the N-alkyl substituents of pyridinium salts have been developed. These include simple cyclizations [see Sections II-F and II-I], also the use of an ortho-nitrophenyl substituent to oxidize a benzyl-type N-substituent to carboxylic acid,[753] and the conversion of amines into aldehydes using pyridinium-2-carbonyl azides.[759]



We have prepared suitably water soluble pyrylium salts[840] and studied the kinetics of their reaction with amines[843] and thus enabled the pyridinium ring formation[841,842] to be effected in aqueous solution. Studies of the kinetics of displacement[869,870] reactions of N-alkyl substituents from the water-soluble pyridinium salts allowed the development of the optimized conditions for the ϖ-amino group of lysine to be replaced by PhS and by $PhCH_2S$ groups by two-step reactions in aqueous solutions at temperatures below 75°C, as could the terminal amino group in glycyl-glycine (Scheme 90).[846] Proteins undergo[844] reactions of this type, and kanomycins A and B react exclusively at the 6-amino group.[845] In collaboration with Professor Dill, such water soluble pyridiniums have been used to block amino groups in complex natural products,[895,982,1005] and in collaboration with Professor Stevens to modify membrane proteins.[1027] In high polarity media, α-amino acids react with pyrylium cations with spontaneous decarboxylation to the corresponding N-alkylpyridinium cations.[786]

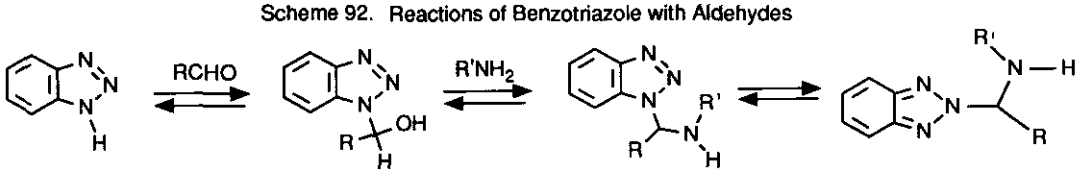


The work described above has made it possible to carry out some transformations that were previously difficult or impossible such as the C-alkylation of nitroalkane anions and the easy preparation of benzyl fluorides. It enables naturally occurring amino compounds to be used, and for amino groups to be converted selectively in multifunctional compounds. It opens up the possibility of transformations of aryl amines without using nitrous acid. The methodology is particularly useful for systems when the amines are available and the corresponding halides or tosylates are unstable - e.g. furfuryl systems,[631] ϖ-substituted picolines,[656] and substitutes for nitrogen mustards[763] (see Scheme 91). Pyrylium mediated transformations of neopentylamine yield the unrearranged products in good yield.[780] The conversion of primary amino groups into other functionality mediated by pyrylium cations has been reviewed.[696,818]

B. Benzotriazole Chemistry

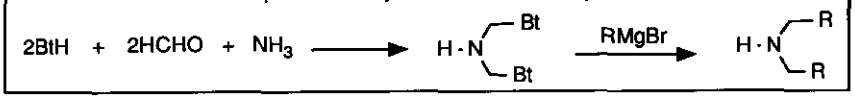
1. Condensation Products with Aldehydes and Amine Benzotriazole reacts with aliphatic and aromatic aldehydes to yield adducts[938] which are converted by $SOCl_2$ into chloroalkylbenzotriazoles[941] and which condense with amines,[939] advantageously in aqueous solution[1072] (Scheme 92). Dynamic equilibria (shown by the cross-over method to be intermolecular[944]) exist between the 1-substituted and the 2-substituted derivatives for both the aldehyde adducts[1135] and the amine products for which ΔG depends on stabilization of the cation intermediates[1040,1150] and which have been calculated by M.O.;[1148] ionization equilibria were measured conductometrically.[1316]

Scheme 92. Reactions of Benzotriazole with Aldehydes



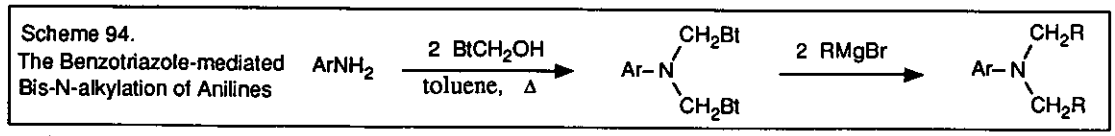
Such intermediates allow rapid synthesis of symmetrical secondary amines using $(BtCH_2)_2NH$ (Scheme 93),[1044] conversion of primary and secondary aliphatic amines into unsymmetrical tertiary amines,[1044] and primary aromatic amine into either secondary,[940,1074,1156] or tertiary amines[1093,1094] (Scheme 94). Thus, 2-aminopyridine is alkylated regiospecifically at the amino group.[940] Some ketones also give adducts which are converted to tertiary amines.[1077]

Scheme 93. Preparation of Symmetrical Secondary Amines



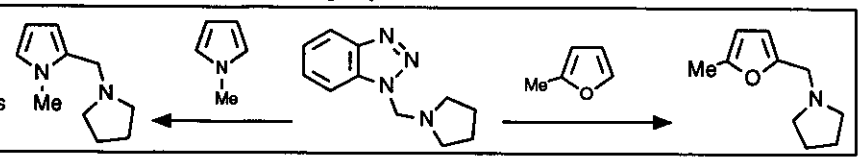
Primary amines with BtH and CH_2O form useful 1:1:1, 2:2:1, and 2:3:2 adducts.[1127] We have successfully prepared secondary aliphatic amines,[1096] 1,2,6-trisubstituted piperidines,[1145] vicinal secondary and tertiary diamines,[1146] and N,N-disubstituted hydroxylamines,[1044] converted mono- into 1,1-disubstituted hydrazines,[1147] and accessed polyfluoroalkyl secondary and tertiary amines,[1198] α-aminoesters,[1078] α-aminoaldehydes,[1166] β-aminoesters,[1175,1079] imines,[1226] α-(arylidineamino)alkylamines,[1181] N,N-disubstituted thioureas and carbodiimides,[1195] propargylamines,[1076] 2-substituted N-alkyl-iminodiacetic acids,[1165] N-t-butylated amines[1145] and bridged iso-indoles.[1051] N-Alkylation of α-aminoacetonitriles provides a route to unsym-secondary amines.[1128] The Bi^{III}-Al promoted alkylation of Bt-derived immonium cations occurs in aqueous media.[1234,1269] The effect of chiral catalysts on aminoalkylation of organometallics was studied.[1278]

Scheme 94.
The Benzotriazole-mediated Bis-N-alkylation of Anilines



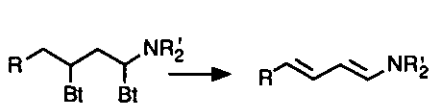
N-(α-Aminoalkyl)benzotriazoles mediate generalized Mannich reactions with nitroalkanes[1118] and with aldehydes and ketones.[1171] Aminoalkylbenzotriazoles aminoalkylate electron rich heterocycles[1276] (Scheme 95) and alcohols and thiols;[1309] they add to enamines and vinyl ethers in novel routes to 1,3-diamines and 1,3-aminoalcohols.[1290] Derived immonium cations undergo cycloadditions with olefins and dienes.[1295]

Scheme 95.
Aminoalkylation of Reactive Heterocycles

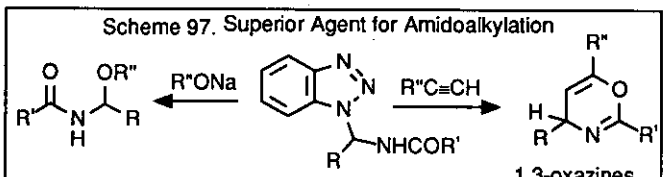


In related eliminations, Bt-assisted synthesis of enamines and dienamines[1173,1233] (Scheme 96) have been realized. Conversely BtH adds to enamines.[1275] Oxidation of BtCH(Bt)NHAr with H_2O_2-SeO_2 allows t-butylation of aromatic amines.[1045]

Scheme 96. Preparation of Dienamines

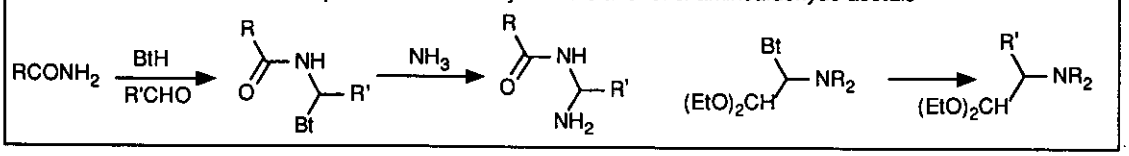


Scheme 97. Superior Agent for Amidoalkylation



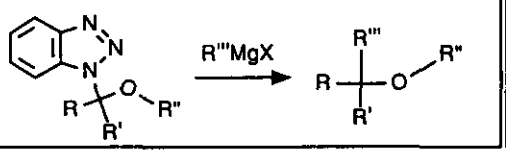
2. *Amidoalkylation* Bt-mediated alkylation of amides occurs specifically at the N-atom and in high yield,[987,1002] secondary amides also react.[1293] Thioamides can also be alkylated at the nitrogen atom using this technique[1002,1020] as can sulfonamides.[1032] Amidoalkylations are advantageously accomplished by Bt-methodology (cf Scheme 97), as applied to CH-acids,[1206] aromatic compounds,[1228] hemithioaminals,[1229] N-(α-alkoxyalkyl)amides,[1257] 4H-1,3-oxazines[1262] and mono-acyl-α-aminoglycines.[1042] Intramolecular amidoalkylation leads to dihydro-3-isoquinolones.[1288] $BtCH_2NHCHO$ enables convenient synthesis of α-substituted isocyanides,[1308] unsymmetrical formamidines,[1130] α-hydroxyaldehydes and oxazoles.[1083] Benzotriazole assisted synthesis of acylaminonitriles has led to novel peptide elongation[1131] and advantageous synthesis of monoacylaminals (Scheme 98) and related peptides.[1144] Hydroxamic acids yield N-(α-hydroxybenzyl)benzamides.[1163]

Scheme 98. Preparation of monoacylaminals and of α-aminoaldehyde acetals

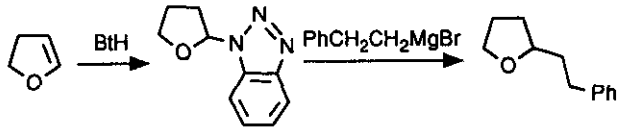


3. Preparation of Ethers and Sulfides Applications of Bt to the synthesis of oxygen compounds include a general ether synthesis[1060,1196,1224] (Scheme 99) and a route to enol ethers.[1225] Conversely, benzotriazole adds readily to vinyl ethers to give products which afford substituted ethers[1129] (Scheme 100).

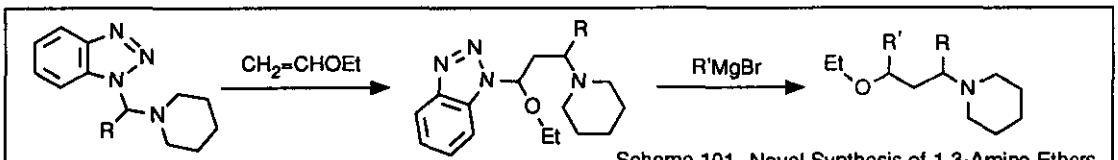
Scheme 99. Synthesis of Ethers: Grignard Reactions on α-Benzotriazolyl-alkyl and -aryl Ethers



Scheme 100. Conversion of Unsaturated into Saturated Ethers



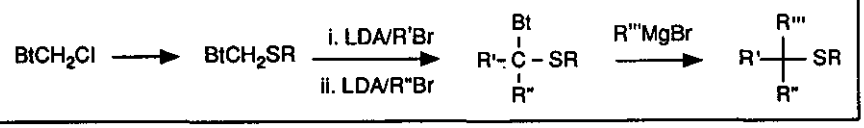
Novel routes to 1,3-diethers[1259] and to 1,3-amino ethers[1260] are provided by additions to enol ethers of 1-(α-alkoxyalkyl)- and 1-(α-aminoalkyl)-benzotriazoles, respectively (Scheme 101).



Scheme 101. Novel Synthesis of 1,3-Amino Ethers

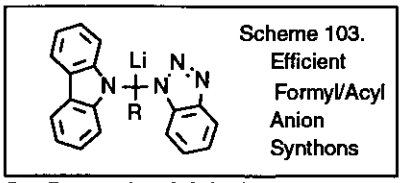
In sulfur chemistry, new synthons were reported for *t*-alkyl sulfides[1189] (Scheme 102) and for vinyl sulfides.[1190] The isomerization of N-(α-arylthioalkyl)benzotriazoles was studied[1191] and these compounds used for intermolecular thioalkylation,[1307] and for aromatic annulation.[1285]

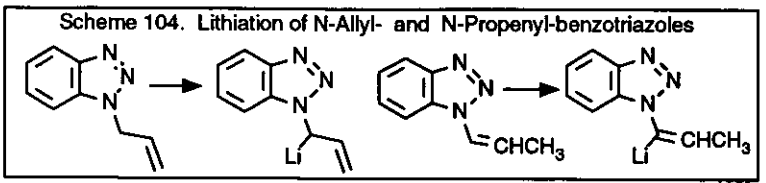
Scheme 102. Novel Synthesis of t-Alkyl Sulfides



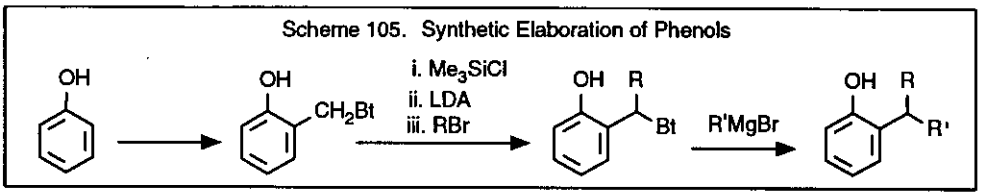
4. Benzotriazole Stabilized Carbanions Benzotriazolylmethyl-N-heterocycles undergo deprotonation and subsequent reaction with electrophiles.[1053] 1-(Carbazol-9-ylmethyl)benzotriazole (Scheme 103) is the basis of efficient formyl[1204] and acyl anion synthons,[1210] including β-aminoacylanions.[1291] $ArCH(Bt)_2$ allows synthesis of aryl ketones.[942] Bt_3CH is a useful synthon for $^{-}CO_2H$,[1164] and $BtCH(OMe)^{-}$ is a methylal anion equivalent.[1321]

N-Vinyl-, N-allyl- and N-propenyl-benzotriazoles and their lithium derivatives[1264] (Scheme 104) and 1-(trimethylsilylmethyl)benzotriazole[1119] have been studied. N-Propagylbenzotriazole opens up new routes to furans[1294] and pyrroles.[1332] Deprotonation of Bt-mediated imine intermediates has led to novel synthesis of enaminones and dienaminones[1310] (cf. also [1337]). Cyclopropanations of 1,1-diarylethylenes are achieved with α-Bt-carbanions.[1303] 2-Methylbenzotriazole anion opens the door to Bt-radical chemistry.[1329]

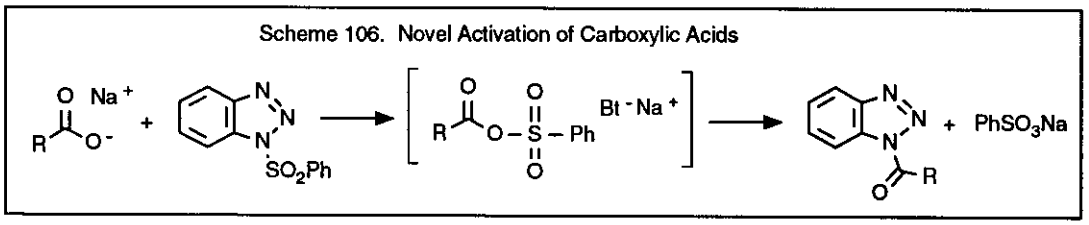




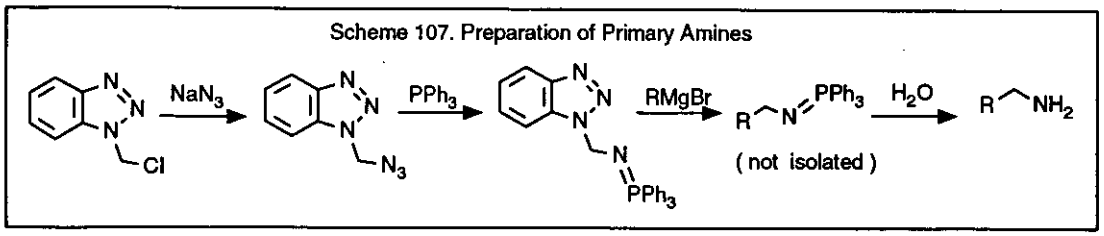
5. Benzotriazolylalkylation Benzotriazole mediated transformations allow the elaboration of phenols[1183] (Scheme 105), of phenol ethers,[1184] and of anilines,[1320] and also the preparations of symmetrical and unsymmetrical 1,1-bis(heteroalkyl)alkanes.[1296] o-(α-Benzotriazolylalkyl)phenols shown to be effective precursors for o-quinone methides.[1273] 1-(Arylmethyl)benzotriazoles[1252] allow a novel diarylacetylene synthesis.[1253] Methylenebisanilines[1160] and other diarylmethanes and heterocyclic analogues[1205] are accessible using Bt-methodology as are N-substituted heteroaromatics.[1311]



6. Applications of Sulfonylbenzotriazoles These form convenient sulforylation reagents.[1323] Reaction of sodium carboxylates with benzensulfonylbenzotriazole gives the corresponding N-acylbenzotriazoles[1277] (Scheme 106). 1,1'-Carbonyl- and 1,1'-sulfonyl-dibenzotriazole are versatile reagents for dehydration[1300] and the latter allows new alkylations of benzotriazole.[1284] 1-Alkoxycarbonylbenzotriazoles undergo decarboxylative rearrangement.[1326]



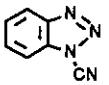
7. Phosphorus Benzotriazole Chemistry The readily available benzotriazolylphosphinamine $BtCH_2N{:}PPh_3$ affords a general route to primary amines (Scheme 107),[1082] and new routes to carbodiimides, imines, and isothiocyanates,[1162] and to 1,4,5-trisubstituted imidazoles.[1121] It has been converted into convenient 1,2- and 1,3-monoazabisylid equivalents,[1292] and used to prepare functionalized N,S-acetals.[1331] Other Bt-P compounds have been studied.[1282]



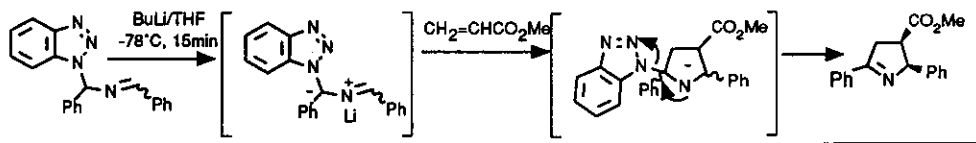
8. Miscellaneous New N-alkylations of benzotriazole and of 1,2,4-triazole have been reported.[1220,1330] The rates and mechanisms of the interconversion of 1- and 2-arylmethylbenzotriazoles have been studied.[1139] Substitution reactions of 1-chloromethylbenzotriazole give benzotriazol-1-ylmethylammonium salts,[937,1056] undergo other substitutions,[1280] and easily form Wittig reagents.[1015] α-Hydroxyalkylbenzotriazoles yield the fluoro derivatives with DAST.[1302] 1-Hydroxymethylbenzotriazole converts nitriles into N-(benzotriazolylmethyl)amides by the Ritter reaction.[1268] Amines and benzotriazole add to unsaturated aldehydes to give 1,3-bis(benzotriazolyl)propylamines,[1270] intermediates for the preparation of propenylidenimiun cations.[1271]

The addition of organolithium reagents to O-(1-benzotriazolylalkyl)oximes[1254] is the key step in a convenient non-oxidative conversion of aldehydes into acids. The phenylhydrazones of benzotriazolylmethyl ketones react with Grignards to replace the Bt group in a reaction equivalent to $R^- + R'COCH_2^+ \longrightarrow R'COCH_2R$.[1092] 1-Cyanobenzotriazole (Scheme 108) is a safe and convenient cyanide cation equivalent.[1222] We have also studied the chemistry of Bt-derivatives of glyoxal.[1141]

Scheme 108. Convenient Source of ^+CN



Scheme 109. Dihydropyrrole by 1,3-Dipolar Cyclization



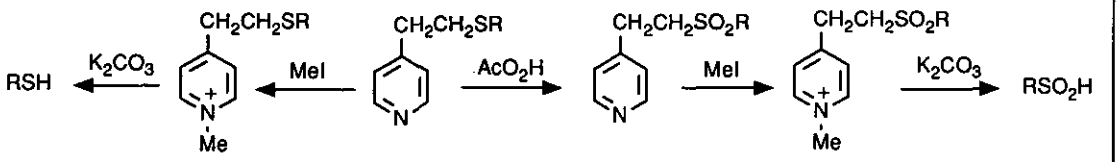
$(BtCH_2)_2NOH$ is a 1,3-dipole synthon;[1132] other Bt-derived 1,3-dipoles yield pyrroles and dihydropyrroles (Scheme 109).[1227] Diazidobis(benzotriazolyl)methane provides a novel route to 2H-imidazoles.[1125] A benzotetrazolotriazepine was prepared.[1203]

Early work examined Graebe-Ulmann reactions of 1-phenylbenzotriazoles.[1,4] Flash vacuum pyrolysis of N-vinylbenzotriazoles gives N-phenylketimines.[986] Ring fragmentations of benzotriazolyl carbanions were explored.[1182] Exceptionally, scission of the azole ring can occur in organometallic reactions of N-substituted benzotriazoles.[1097] Novel Dimroth rearrangements in the benzotriazole system were elucidated by ^1H and ^{13}C NMR.[1256] Benzotriazole containing lubricants show improved oxidation stability;[1178] benzotriazole methodology was used in the synthesis of an amino acid based sweetener.[1266] Benzotriazoles with fused heterocyclic rings have made.[1255]

9. Overviews Our work on benzotriazole was first briefly reviewed in 1988.[981] A comprehensive survey of progress up to 1991 is available,[1232] and also a short survey of some of the more recent progress.[1241]

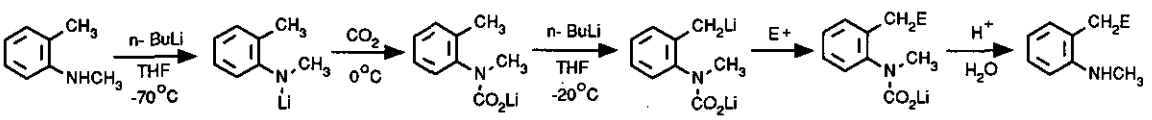
C. Protective Methods and Lithiation

Scheme 110. 4-Pyridylethyl Group Protection for S-Functionality



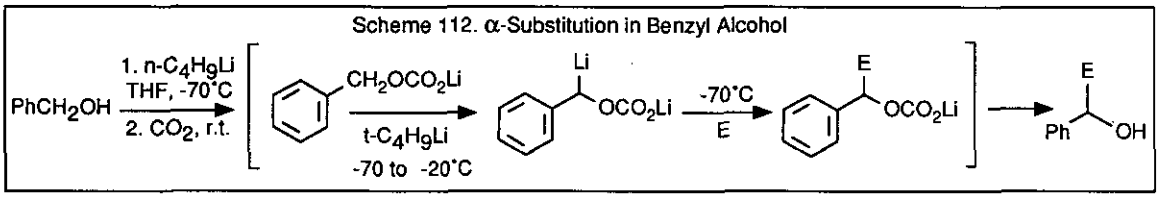
The 4-pyridylethyl group has been introduced[855] as a new group for the protection of active hydrogen compounds with release effected by successive quaternization and very mild base treatment. It has been used successfully for carboxylic acids,[855] heterocyclic NH groups,[951] and sulfur functionality (Scheme 110).[907] The 2,2-pyridylpropane-1,3-diol similarly provides[966,1021] novel protection for carbonyl groups. 1,2,3-Triazoles and aziridines have been prepared using 2,4-pyridylethyl azide and then removing the 4-pyridylethyl group.[978]

Scheme 111. Use of CO_2 Method for Substitution in o-Alkyl Group in Anilines



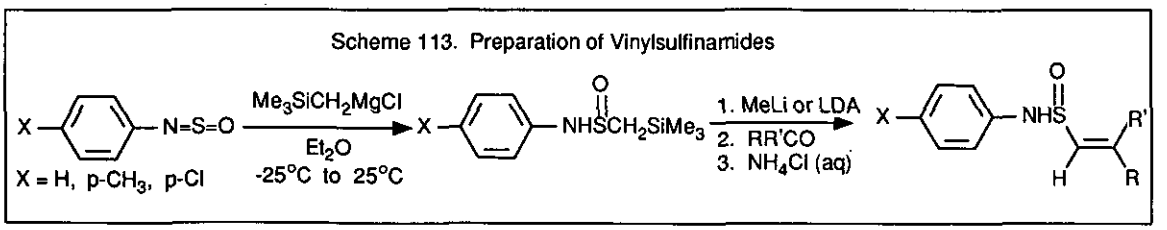
The method of CO_2 protection and activation in lithiation chemistry (see Section IV-3) has proved very useful in the ortho-lithiation of N-alkylanilines,[916,1026] and benzanilide.[960] It has been extended to naphthylamines and enables the activation of the C-methyl group in o,N-dimethylaniline (Scheme 111).[1208,1120] The same strategy allows substitution in the CH_2 group of benzyl alcohol (Scheme 112) and benzylamine.[963] α-Lithio(trimethylsilylmethyl)lithium carbonate is a methanol dianione synthon.[967]

Scheme 112. α-Substitution in Benzyl Alcohol



Vinylsulfinamides are available from trimethylsilylmethanesulfinamides via a Peterson reaction (Scheme 113).[1188] β-Lithiation of carboxamides was studied.[1318]

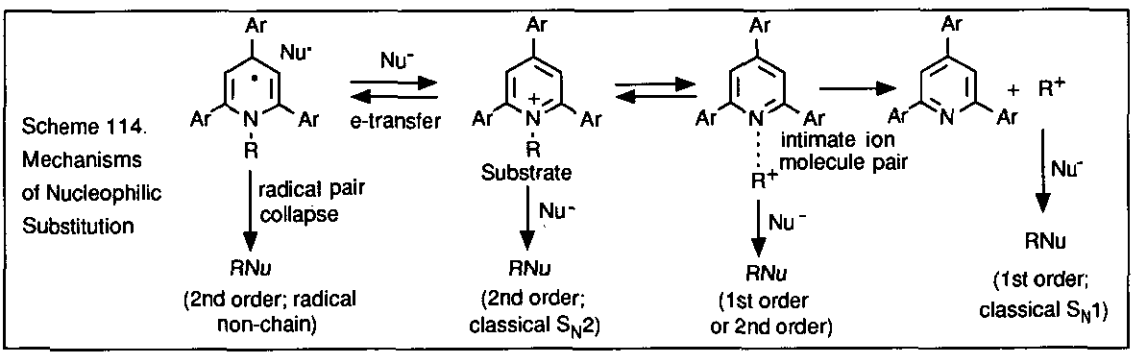
Scheme 113. Preparation of Vinylsulfinamides



V. The Role of Heterocycles in Attempts to Understand Mechanisms

A. *Nucleophilic Substitution at sp^3 Carbon*

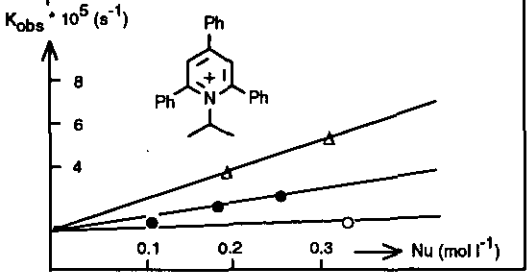
The kinetics and mechanisms of nucleophilic displacements of N-substituted pyridinium cations have been intensively studied in work that has varied the leaving group, the N-substituent, studied the effect of substitution in N-benzyl substituents[725,762] and considered the effect of the nucleophile and of the solvent.[761,798,839] It has been shown that increase in the strain of the starting compound and in particular constraining α-phenyl groups to near planarity[700,800] results in marked steric acceleration. Solvolysis rates of N-α-methylallyl and N-α-phenylethyl derivatives have been studied.[799] The influence of the nature of the N-substituent,[743,796] electronic effects in the leaving group,[760] kinetic effects of α-heteroaryl substituents,[801] steric effects in the leaving group,[724] ionic strength[723], pressure,[831] substrate concentration or aggregation,[872] traces of water,[945] and nature of the gegenion[945] have been examined. Crystallographic evidence has been obtained for steric crowding in the substrates and correlated with rate acceleration.[947] Rates obtained spectrophotometrically have been checked conductometrically.[795] Products from reactions with solvent in the absence of nucleophile have been identified.[901]



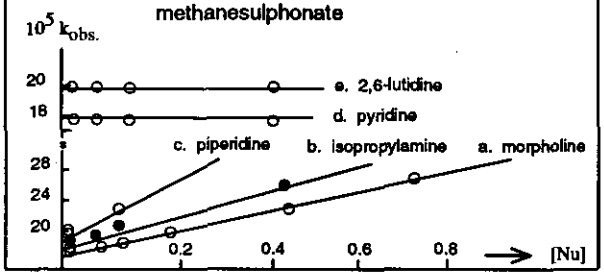
The above work has been interpreted in terms of the diagram of Scheme 114 and the following conclusions have been drawn. t-Alkylpyridinium cations solvolize exclusively[900] by an S_N1 type mechanism. The solvolysis of N-secondary alkylpyridinium cations[797,881] can occur by both S_N2 and S_N1, cf Scheme 115. In non-nucleophilic and weakly nucleophilic solvents, the S_N1 can dominate even in the presence of sufficiently small concentrations of good nucleophiles. However, in the presence of nucleophiles the bimolecular S_N2 mechanism competes effectively with the S_N1 mechanism. N-(Primary-alkyl)pyridinium cations can react[832] either by an S_N1 or and S_N2 mechanism depending on the circumstances.[866] In particular, there is evidence for a clean mechanistic change-over with S_N1 to S_N2 with no merging of these mechanisms.[699]

Further, S_N1 type reactio. : can occur by two distinct mechanisms involving intimate ion molecule pairs or involving free carbonium ions. There is no indication of any merging of these mechanisms[798,889] (cf Scheme 116). Reactions via intimate ion molecule pairs can be either second order when rate determining attack by nucleophile occurs, or first order when rate determining formation of an ion molecular pair, with no evidence of any merging between them. Bimolecular S_N2 reactions can proceed by rate determining attack of a nucleophile either on the substrate or ion molecule pair formed in a fast pre-equilibrium.[831] There is no evidence of merging of these mechanisms.[889]

Scheme 115. Nucleophilic Substitutions by Simultaneous S_N1 and S_N2 Reactions:

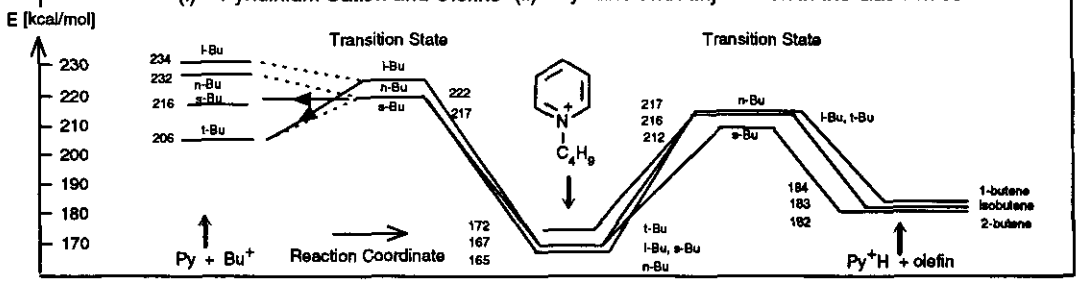


Scheme 116. Rate Constants for Solvolyses of 1-(2-Pentyl)-5,6-diphenylbenzo[h]quinolinium Trifluoromethanesulphonate



Solvolysis of N-n-octyl acridinium cations in phenol gave the unrearranged phenyloctyl ethers and all the isomeric straight chain o- and p-octylphenols: the results point to primary carbonium ion intermediates.[767] Studies of the transfer of alkyl groups from N-alkylpyridinium iodides to pyridines showed that alkyl iodides could be intermediates.[647] The formation of σ, π, and charge-transfer complexes between pyridinium cations and various anions has been studied[905] together with subsequent reactions with N-substituent transfer is not favored.[903]

Scheme 117. Collisionally Activated Dissociation of N-Alkylpyridinium Cations to (i) Pyridinium Cation and Olefins (ii) Pyridine and Alkyl Cation in the Gas Phase



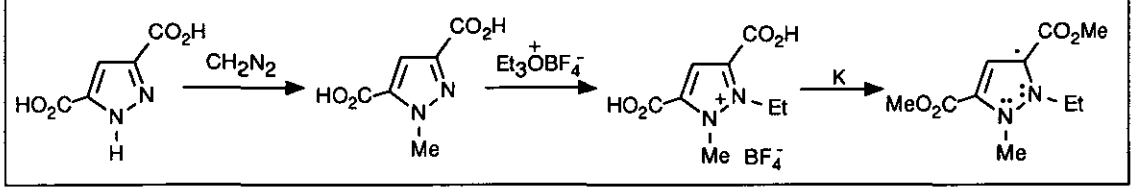
In addition to the regular S_N1 and S_N2 mechanisms, we have shown that certain carbanions, especially nitroalkane anions, react with N-alkylpyridiniums to transfer the N-alkyl group by a non-chain radical mechanism[781] (see also section IV-1). The effect of pyridinium ring substitution on rates has been investigated.[783] In collaboration with Professor Moreno-Manas, we showed that β-diketone anions procure a radical chain reaction.[1172] This work on radical mechanisms has been reviewed.[911]

Collisionally activated dissociation[975] of N-alkylpyridinium to allyl cations and pyridines[1123] and to olefins and pyridinium cations[1124] in the gas phase (in collaboration with Professor Eyler) strongly supports these conclusions. In our gas phase work we also elucidated other fragmentations[1070] especially for 1-benzyloxypyridinium.[1136] We also studied N-(diarylmethyl)pyridiniums,[1212] considered substituent effects on appearance potentials,[1243] and elucidated ion-molecule reactions. [1338] p-Methylbenzylpyridiniums can dissociate to give the quinodimethane.[1265] The stability of ion-molecule complexes as possible reaction intermediates has been investigated[1207] in collaboration with Professor Anders. Our work in this area has been reviewed[822,859,881,1003,1099] and the rate variations treated chemometrically.[871]

B. Stabilization of Free Radicals

In 1972 we conceived[404] the principle of merostabilization: when an electron donor and an electron acceptor group are simultaneously substituted at the same carbon atom, such a carbon atom centered radical RC·AD is stabilized more than the mean stabilization of the two radicals $RC{\cdot}A_2$ and $RC{\cdot}D_2$. This principle was demonstrated by the preparation of various stable indole, pyrazole[439] (Scheme 118) and pyridinyl[440] radicals. More recently we have carried out calculations to assess quantitatively the merostabilization energy of carbon-centered radicals[899] and examined solvent effects[1122] on such stabilization energies.[1202] Stable radicals from 1-hydroxybenzimidazole-3-oxide were investigated by esr.[1202]

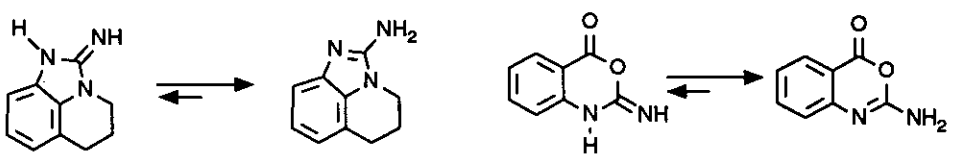
Scheme 118. Merostabilized Pyrazole Radicals



C. *Infrared Measures of Intramolecular Interactions*

Our studies in infrared spectroscopy commenced with a systematic investigation of classes of substituted heterocycles which identified series of bands characteristic of variously substituted rings: 2-,[24] 3-[25] and 4-[23] substituted pyridines, 2-,[22] 3-[40] and 4-substituted[21] pyridine 1-oxides, substituted pyridinium-boron trichloride complexes,[32] pyridinium anhydrobases.[197] For comparison we studied mono-[28] and ortho-,[38] meta-,[34] and para-[33] di-substituted benzenes. We noticed that the marked variations found in the apparent extinction coefficients of the ring stretching bands could be rationalized by considering the effects of the substituent (s) on the charge distribution in the ring.[29] These qualitative results, which were extended to pyridones[56] and pyrones,[77] encouraged the more quantitative approach (see below). Five-membered rings examined on a semi-quantitative basis include 2-substituted furans,[30] 2-[37] and 3-[117] substituted thiophenes, and isoxazoles.[78] Among polycyclics we examined monosubstituted quinolines,[55] substituted quinoxalines,[116] and quinoxaline-2,3-diones,[74] and quinazolines.[145] This work has been reviewed.[43]

Scheme 119. Use of IR to determine Dominant Tautomeric Form for Amines



Concurrently with these studies of the effects of the orientation and nature of substituents on characteristic ring vibrations, we investigated the influence of the various rings on characteristic substituent vibrations for the following groups: alkoxy,[35] acylamino,[36] amino and alkylamino,[39] carbamoyl,[48] halogens,[53] sulfonamido,[59] nitro.[63] The orientation of methoxy and nitro groups in bicyclic systems can be deduced from their spectra.[144] We introduced a partial deuteration technique which allows the unambigous proof of the presence of an NH_2 group in a molecule because the remaining NH-stretch in NHD occurs between the sym and asym modes of NH_2: this was applied to various heterocyclic amino compounds[164,187] (Scheme 119) and to distinguish NN- and NN'-disubstituted ureas.[290] Vibrational spectroscopy allowed the structure of hexanitrosobenzene to be settled as benzotrisfuroxan.[238] Band assignments were made in halobenzenes,[374] we identified the C=O in benzotropones,[70] and recorded regularities of the spectra of esters[64,65] and ketones.[79]

Scheme 120. Equations Relating 1600 cm Band Intensity to σ_R^o in Substituted Benzenes

Monosubstituted Benzenes : $A = 17600\,(\sigma_R^o)^2 + 100$

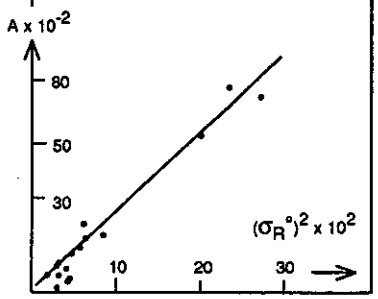
Monosubstituted Durene : $A_{durene} = 11300\,(\sigma_R^o)^2 - 30$

meta-Disubstituted Benzenes : $A_{meta} = 18230\,[(\sigma_R^o1)^2 + (\sigma_R^o2)^2 + \sigma_R^o1\sigma_R^o2] + 500$

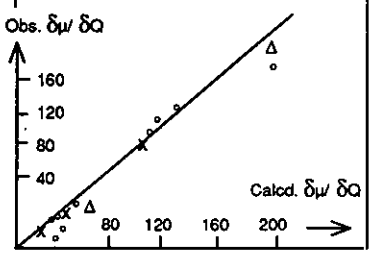
para-Disubstituted Benzenes : $A_{para} = 15000\,[\sigma_R^o1 - \sigma_R^o2 + \lambda] + 170$

Encouraged to make more quantitative measurements, we discovered[157] that the square root of the integrated intensity of the two ring stretching bands near 1600 cm^{-1} in monosubstituted benzenes[180] is proportional to σ_R^o (cf Scheme 120). A similar relationship holds for meta-disubstituted benzenes.[275] For para-disubstituted benzenes[248] the interaction between the substituents can be deduced[442] from the corresponding deviation. Similarly in durenes[247] the angle of twist can be correlated with the decrease in intensity and the effective σ value. We have also considered the ring stretch near 1500 cm^{-1}.[284] This work has been extended to substituted pyridines and pyridine N-oxides[276] and also to furans and thiophenes,[396] and selenophens.[508]

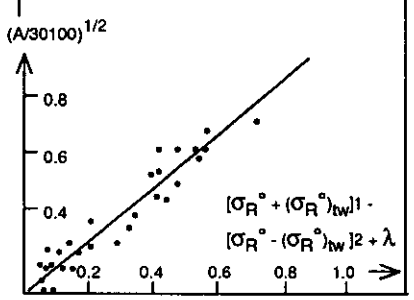
Scheme 121. Integrated Intensity of the IR C=C Stretching Vibration for Monosubstituted Ethylenes



Scheme 122. Comparison of Observed and Calculated Values of $\delta\mu/\delta Q$ (esu) for Mono- (•), 1,1-di- (∘), Trans-1,2-di- (Δ), and Cis-1,2-disubstituted (x) Ethylenes



Scheme 123. Plot of $(A/30100)^{1/2}$ for Disubstituted Acetylenes Against $[\sigma_R^\circ1 + (\sigma_R^\circ1)_{tw} - \sigma_R^\circ2 - (\sigma_R^\circ2)_{tw} + \lambda]$



Considerable insight has also been obtained in the nature of interactions between substituents and the ethylene system. For monosubstituted ethylenes[278,306] the equation $A_{eth} = 27{,}100\,(\sigma_R^\circ)^2 + 80$ holds (cf Scheme 121); this is of similar form to that found ealier for monosubstituted benzenes. Infrared intensities for $\nu_{C=C}$ of 1,1-disubstituted ethylenes are proportional to the sum of the aquares of σ_R^o for the substituents.[470] In *cis*- and *trans*-1,2-disubstituted ethylenes, substituent interactions are qualitatively similar and quantitatively *ca* 1.5 times those in the corresponding *para*-disubstituted benzenes (cf Scheme 122).[499] Similar relationships hold for mono-[448] and disubstituted[449] acetylenes (Scheme 123).

This work has given much insight into substituent groups and σ_R° values for many common substituents have been listed. Hyperconjugation was investigated for alkyl groups.[303,443] Ethynyl is a weak donor but highly polarizable.[447] Conjugative possibilities and conformations have been studied for ether and thioalkoxy groups,[397] and for acyl groups,[398] in ethylenes and benzenes. Among S-substituents, resonance donation varies SMe > SH >> SBu^t;[445] SO_2Me is an acceptor, but SOMe a resonance donor.[446] We have shown that charged ammonio substituents are resonance electron donors while the charged diazo substituent is a strong acceptor.[391] Trivalent phosphorus substituents are generally weak in resonance interaction,[479,480] other metalloids show more interaction.[279] Isocyanate, isothiocyanate and azide are all moderate electron donors, but can each accept electrons from stronger donors,[305] NSO is similar.[444] $SiMe_3$ is a weak and CH_2SiMe_3 a strong donor[392] as is CH_2SnMe_3.[473] Nitrile C≡N stretches intensities relate precisely to substituent constants unlike frequencies.[423]

Scheme 124. Energy Terms for Rotational Barriers in Monosubstituted Benzenes

$E = 33\,[\,|\,\sigma^\circ_R\,| - |\,(\sigma^\circ_R)_{tw}\,|\,] - S$ $\quad R = 33\sigma_R^\circ$ $\quad R_{tw} = 33\,(\sigma_R^\circ)_{tw}$

Group	E	R	R_{tw}	S	Group	E	R	R_{tw}	S
CHO	7.9	7.9	0	0	NHMe	7.4	17.2	4.3	5.5
COMe	6.3	7.2	0	0.9	OMe	2.6	14.2	7.6	4
CO_2Me	5.3	5.3	0	0	OH	3.4	13.9	8.5	2
NMe_2	5.1	17.5	4.3	8.1	NO_2	5.8	5.6	0	ca. 0
NH_2	8.0	15.5	4.3	3.2	$CH{:}CH_2$	0	ca. 1	0	ca. 1

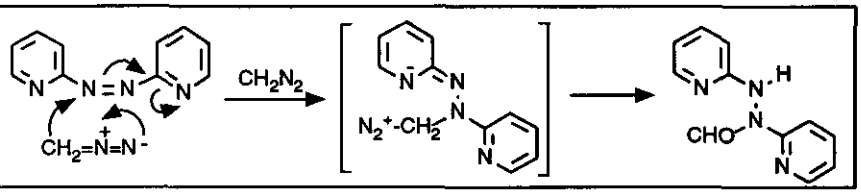
We have related the σ_R° scale to the energy scale by considering rotational barriers around substituent ring bonds, both in monosubstituted benzenes[399,450] and ethylenes (Scheme 124) and in para-disubstituted benzenes[497] and trans-disubstituted ethylenes.[500] We found it possible to calculate the absolute value of the infrared bands by finding the change in dipole moment along the normal coordinate for the vibration for semi-empirical M.O. methods for benzenes,[272,304,421] for ethylenes,[407] for furan,[472] for isoxazoles.[552] Most of this infrared intensity work was done in collaboration with Professor R. D. Topson.

In reviews, we covered early work,[209] considered the role of distortions of the π-electron system of benzenes,[297] clarified the role of σ- and π-inductive effects[332], overviewed substituent effects in olefinic systems[593] and summarized our whole approach of the application of infrared intensities to study intramolecular interactions in organic chemistry.[565,771]

D. Applications of NMR Spectroscopy

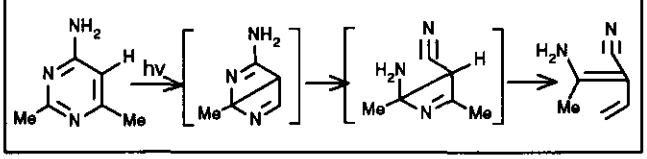
Nmr has been used extensively throughout most of our work. The present section references only those papers not mentioned elsewhere in this overview. Reviews of our nmr work include.[94,125,139] Much of the work reported below was carried out in collaboration with other groups - often they provided the samples and we the answers.

Scheme 125.
Product from Azopyridine and Diazomethane

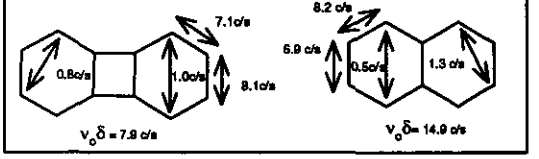


The interaction between pyridines and Lewis acids was investigated by ^{1}H-nmr.[181] Hydroxymethyl derivative of five-membered heterocycles were studied[1010] as a background to investigation of the reaction of pyrrole with formaldehyde.[1009] The mechanism of the Wallach rearrangement of chloral to dichloracetic acid was elucidated[69] and the identity established of the products from CH_2N_2 and azopyridine[192] and of the alkaloids Wisathomnine[199] and Chakranine.[52] Structural problems were solved in the benzofuran field,[91] for pyrrolones[90], dihydropyridazines,[122] disulfonyl derivatives of 2-aminopyridine[142] and 2-aminothiazole.[159] We elucidated pyrimidine photchemistry (Scheme 126),[111,129] degradation products from elastin,[120] structures of boroxazolidines,[146] bond fixation in biphenylene (Scheme 127),[143] cyclohexanethione dimers[165] pyrrolinium salts,[156] dibenzobicyclooctadenes,[132] cyanopyrrolines,[163] t-butylated pyrylium cations,[236] orientation of nitroimidazoles,[231] autoxidation of alkylpyrroles,[237] tetrahydropyrimidines,[289] mechanism of nitropyridine reduction (Scheme 128),[318] vinylogous pyrones,[89] silsequioxanes,[169] conformations of aryloxyalkylaminoquanidines,[234] aminoguanidines,[171] azabicylcooctenones.[654]

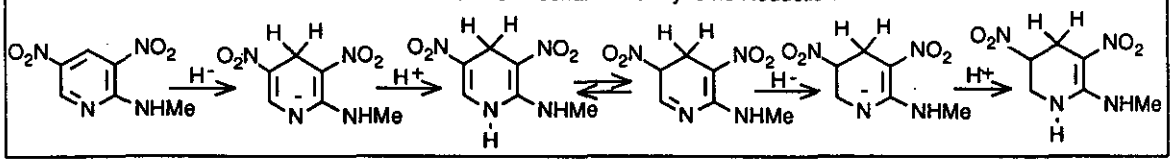
Scheme 126. Pyrimidine Photochemistry



Scheme 127. Bond Fixation Biphenylene/Naphthalene

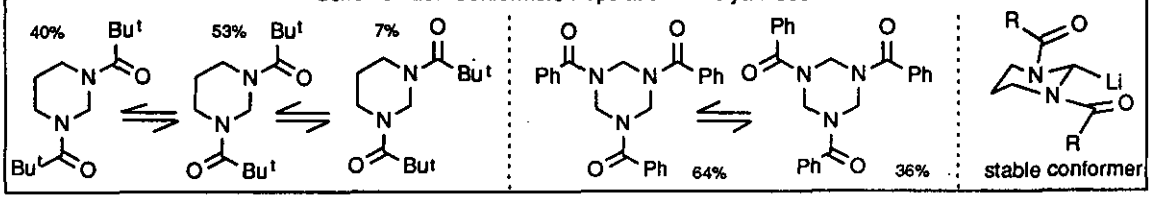


Scheme 128. Mechanism of Pyridine Reduction



Conformer populations around the amide bonds have been deduced for N-acylindolines[323] and for 1,3-diacylimidazolines, 1,3-diacylhexahydropyrimidines, 1,3,5-triacylperhydrotriazines and their lithiated derivatives (Scheme 129)[948] and their interconversions studied,[949] and compared with X-ray results.[1239] Hindered rotations were investigated in 2-dimethylaminopyridines.[286]

Scheme 129. Conformers Population in Polyamides

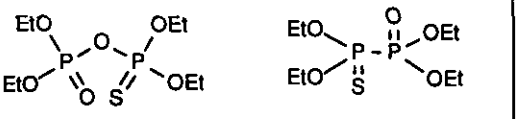


We have studied extensively the proton spectra of various series of heterocycles, particularly bicycles: quinazolines,[182] quinoxalines,[228] cinnolones,[229] quinolones,[727] chromones and thiachromones,[265] benzoxazoles and benzothiazoles.[321] Chemical shifts for these bicycles were correlated with substituent effects.[320,387] Pyrylium cations[136] have been studied and particularly rotational equilibria in crowded derivatives.[805] Other systems investigated include pyrrole-2-carboxylic acids,[910] carbazoles,[1011] pyridinium cations,[1068] dibenzothiophene,[1154] dinaphthothiophenes.[1158]

Scheme 130. Substituent Constants for Aza- and Modified Aza-Substituents

substituent	sigma-constant α	β	γ
>N	1.0	0.6	0.8
>N⁺-O⁻	[1.5]†	0.7	0.4
>NH⁺	2.2	1.9	1.3

Scheme 131. Studies on Phosphorus NMR

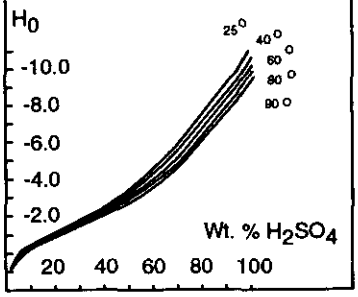


We proposed standards for nmr in aqueous solution,[87] compared C-13 shifts in C=O and C=S compounds,[1012] and studied the nmr spectra of vinyl substituted aromatics,[1214] correlated substituent effects and clarified shifts and coupling constants[201] determined σ-constants for heterocycles (Scheme 130) [167] and demonstrated the lack of aromaticity in benzo-1,4-dioxins.[207] In P-31 nmr work, we pointed to the correlation of shifts with degree of ionization of phosphates,[61] elucidated the structure of monothiophosphates (Scheme 131),[42] studied cyclic phosphorus derivatives,[58] hypophosphates,[211] selenophosphites,[288] reinvestigated oxidation of dialkyl phosphoroselenothioates[694] and reviewed the extent of P=31 nmr studies in 1962.[83]

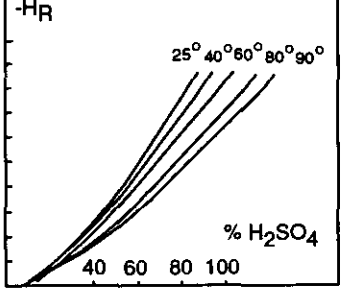
E. Acidity Functions

Our work with the electrophilic substitution of heterocycles led us to examine the behavior of various substrates in strong acid. We found that amides required[124] a new acidity function[130] which we named H_A. The protonation behavior of substituted pyridines and pyridine oxides has been elucidated[172] as has the second protonation of certain diacid bases[226] such as aminopyridines[384] and their N-oxides.[227] It was necessary to measure the temperature variation of the H_O (Scheme 132),[280] the H_R (Scheme 133) [488] and of the H_A acidity functions (Scheme 134).[460] We showed that acidities determined by the indicator overlap method were consistent with LFE correlations.[301]

Scheme 132. T-Variation of H_o



Scheme 133. T-Variation of H_A



Scheme 134. T-Variation of H_A

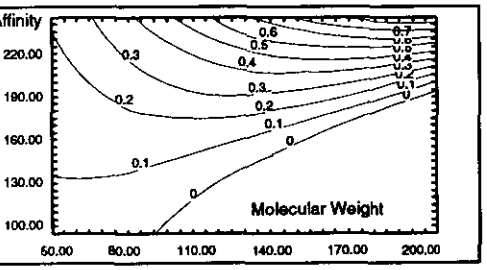
% H_2SO_4	H_A 25°	60°	90°
2	0.626	0.609	0.610
10	-0.264	-1.190	-0.239
16	-0.632	-0.543	-0.543
24	-1.099	-0.965	-0.851
32	-1.457	-1.347	-1.231
40	-1.907	-1.771	-1.499
48	-2.332	-2.123	-1.817
56	-2.762	-2.485	-2.246
64	-3.177	-2.868	-2.534
72	-4.272	-3.779	-3.426
80	-5.259	-4.678	-4.200

We have also looked at some methods for the definition of basicity in absolute methanol[512] and compared methods for pK determinations in strongly basic systems.[519] The solution[861] and gas phase[794] basicities have been determined for pyridines with bulky α-substituents. σ-Constants for the pyrryl group were measured from basicities of pyrrylpyridines.[523]

Scheme 135.

Contour Plot of Predicted Poisoning Values Using

$$y = 0.075 + 0.7351\,(\overline{MW^2})\,(\overline{PA^2}) - 0.4067\,(\overline{MW^3})$$



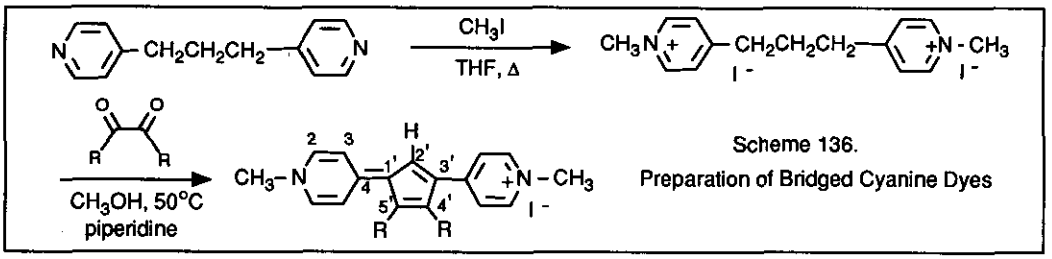
F. Quantitative Structure Activity Relationships

Our use of statistical methods in the clarification of heteroaromaticity led to a new QSAR program[1327] and applications in other areas.[1328] In collaboration with Professor G. Musumarra we predicted GC-response factors by PLS [1084] and have used the classical and magnetic aromaticity as new descriptors[1217,1315] for biological activity.[1218,1219] The MOLGEO program assists in geometry optimization.[1286] In collaboration with Dr. T. C. Ho we have studied the effect of nitrogen compounds on cracking catalysts.[1250] Much further work is in hand and this area has been reviewed.[1185]

VI. Applications of Heterocycles in Society

A. Dyestuffs

We have elucidated the structure of oligomeric blue dyes[897] from 9-alkylcarbazoles and studied various aza[904] and other analogues[991,1052] of indoxyl dyestuffs. In the field of cyanine dyes we have prepared a variety of cycopenta-1,4-dienes with various substituents,[992,993,994] and cyanines from imidazoloquinoline.[298] Naphthaquinone[990] and naphthalene azo[1287] dyes have also been examined as well as conjugated systems derived from piperazine-2,5-dione,[988] dyestuffs containing the dicyanomethylide group,[1055] reactive dyes from triazines,[892] novel chromophores based on maleimide,[1054] soluble versions of Eriochrome Red B,[1325] thiopyrylium sensitizers,[772] precursors of alizarin violet-N,[1304] and nondiffusing bis(thiazolinethione) photographic additives.[920]

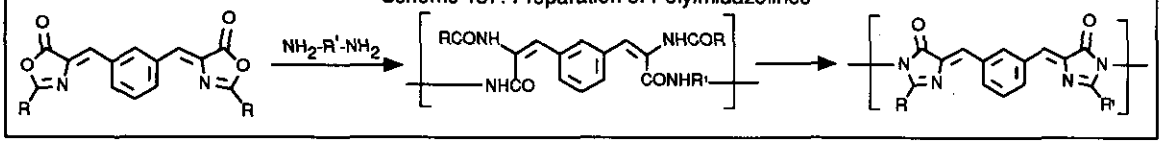


Scheme 136.
Preparation of Bridged Cyanine Dyes

B. Polymers

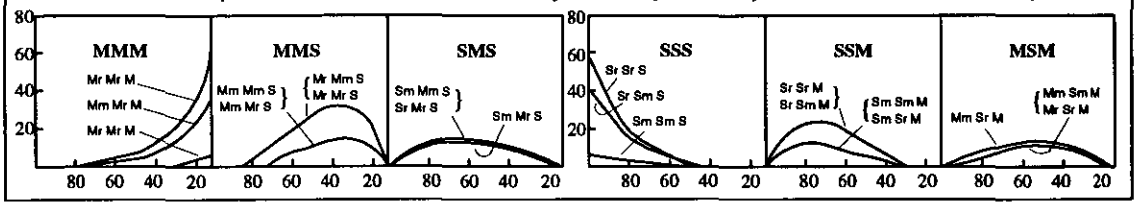
Most of our work in polymer chemistry has been mainly in two areas: (i) the preparation of heterocyclic polymers carried out in collaboration with our friends at the 3M Company, and (ii) C^{13} nmr elucidation of polymer structures.

Scheme 137. Preparation of Polyimidazolines



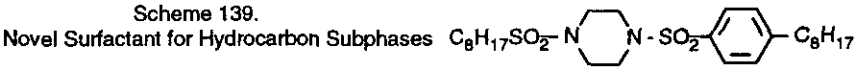
We have studied a wide range of condensation methods for the preparation of heterocyclic polymers in which two difunctional compounds were reacted with each other to form links consisting of heterocyclic rings. In this way, we have made poly-2-imidazolin-5-ones (Scheme 137),[909,980] poly-triazolinethiones,[957] poly-thiazole-2-thiones,[958] poly-benzimidazoles,[1062] and pyridines. We have also studied various polymers based on azlactone chemistry,[1063] looked at the polymerization of pyrylium monomers,[1004] and prepared and studied fluorescent properties of poly(1-vinylpyrene)s.[1297] 1-4′-Iodobutyl-4-pyridone polymerizes by self quaternization.[138]

Scheme 138. Population of the Tactic Triads for Stryene-Methyl Methacrylate as a Function of % Composition



With the help of C^{13} nmr, we studied the tacticity and monomer distribution analysis in ethylene-vinyl acetate co-polymers,[463] butadiene-acrylonitrile co-polymers,[464] styrene-methyl methacrylate co-polymers (Scheme 138)[465] and styrene-butadiene co-polymers.[495,496] We have applied[366,434] contact shift reagents to the nmr of polymers.[372] This work has been reviewed.[373,520] The importance of nmr to polymer structure analysis was emphasized.[395] In miscellaneous polymer work, we showed that 3-vinylperylene is a powerful radical trap,[1065] developed a method to formylate pendent aryl groups,[1213] and made perylene condensation polymers.[1261]

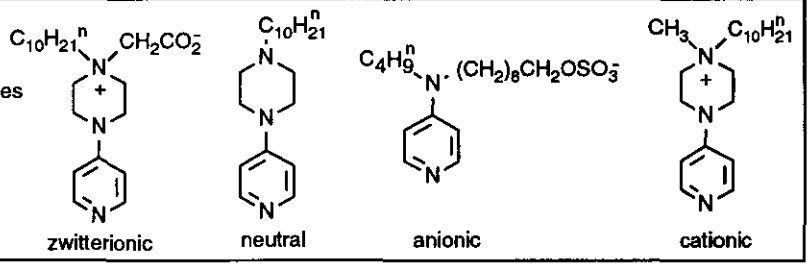
Scheme 139.
Novel Surfactant for Hydrocarbon Subphases



C. *Surfactants and Coatings*

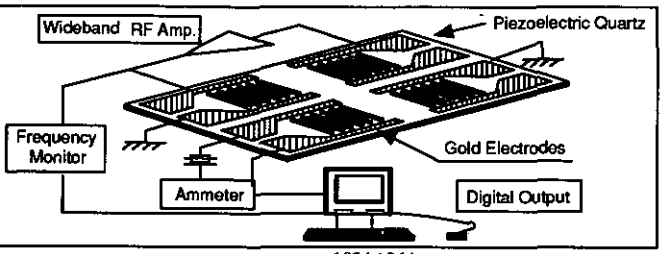
Our work in this area (much of it in collaboration with Dr. H. D. Durst) has been in the following main directions: (i) searching for surfactants with particular ability to hydrolyze fluorophosphinates and other active agents, (ii) the preparation of novel compounds for testing as sensor coatings for the detection of agents, and (iii) the preparation of novel fluorinated surfactants for hydrocarbon subphases (Scheme 139).[1007]

Scheme 140. Surfactant Analogues of 4-Dimethylaminopyridine



In the first area, we have synthesized[997] many substituted o-iodoso- and o-iodoxy-benzoic acids,[968] studied their catalytic activity, and developed convenient large scale preparations.[1073] We have investigated such compounds by nmr and X-ray methods,[1138] considered their acidity relationships[1137] and studied intramolecular interactions by C-13 nmr.[1066,1067] We have looked at varied analogues (cf Scheme 140) of 4-dimethylaminopyridine[959,1008] and its N-oxide as neutral, anionic, cationic, and zwitterionic surfactants, and found unusual activity of such anionic compounds.[1006] Copper chloride cyanopyridine complexes were prepared[1050] as catalysts, and liquid crystal behavior of N-oxide surfactants studied.[1314]

Scheme 131. Dual 52-MHz SAW Device Used for Simultaneous Mass and Conductivity Measurements on Thin Films

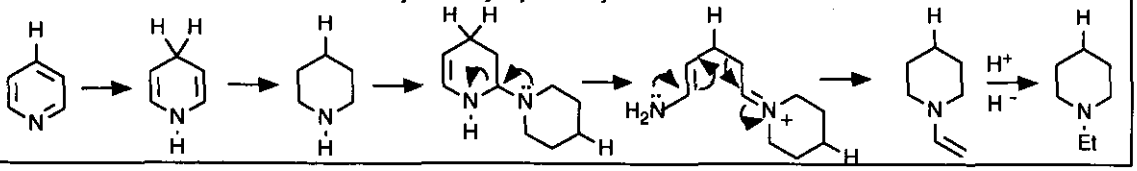


New microsensor coatings studied have included pyridinium salts[1034,1064] acridinium betaines,[1167] arylphosphonic acids,[1168] 2,4,6-trisubstituted-1,3,5-triazines,[1231] 2-phenyl-1-(phenylthiomethyl)-benzimidazoles,[1033] thiadiazoles,[1037] and nicotinamides.[1038] We have also tested these coatings for the detection of organic vapors.[1230] Our work on microsensor coatings has been reviewed.[1039,1157]

D. Aquathermolysis

Our work on aquathermolysis has been carried out incollaboration with Dr. Michael Siskin of the Exxon Company. Aquathermolysis, the study of the behavior of organic compounds in water at temperatures of 250° or above, has been compared with thermolysis.[1100] Among aliphatic compounds cross-linked cyclohexylphenyl derivatives[1101] and various ethers and esters[1102] have been studied. The behavior of various of C-linked substituents in the 2-,[1105] the 3-,[1103] and 4-position[1106] of pyridine have been compared with the behavior of the same substituents attached to a benzene ring.[1104] Mono-substituted benzenes with a 2-carbon atom side chain oxygenated either at the α,[1108] the β,[1107] or both the α and β positions,[1109] have been surveyed. The aquathermolysis of phenols,[1110,1111] phenol ethers,[1112] and arylamines[1113] has been studied in the presence and absence of sodium bisulfite. We have also looked at nitriles and amides,[1114] sulfides and disulfides,[1115] mercaptans and sulfonic acids,[1116] sulfur compounds in the presence of bisulfite[1117] and as H_2S generators.[1187] The aquathermolytic behavior has been studied of thiophenes and benzothiophenes,[1245] pyrroles and benzopyrroles,[1247] and pyridines and benzopyridines.[1246] We have examined the cleavage of diaryl ethers[1319,1186] and find that alkali metal salts show dramatic effects on the behavior of aqueous solutions at high temperatures indicating in some cases considerable hydrolysis of such salts.[1251] Aqueous formic acid ring-cleaves pyridines (Scheme 142).[1322] The geochemical and technological implications of aquathermolysis have been summarized.[1223]

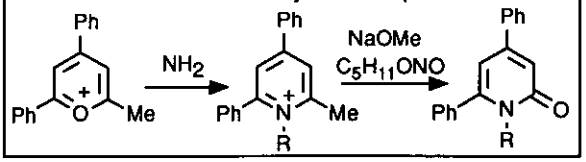
Scheme 142. Hydrous Pyrolysis of Pyridine with Formic Acid



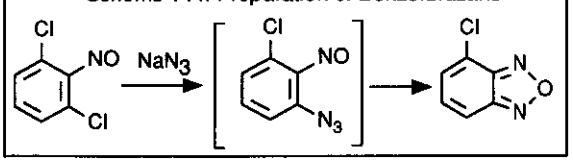
VII. Further Research Areas

A. *New Preparative Methods*

Scheme 143. Pyridone Preparation

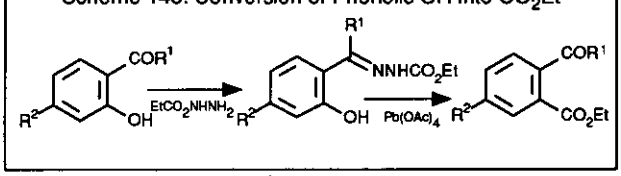


Scheme 144. Preparation of Benzofurazans

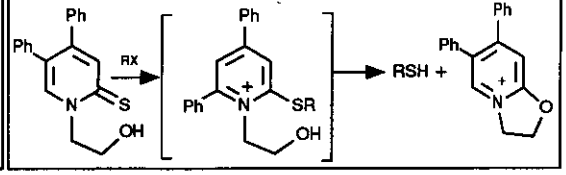


Novel preparative methods developed include the direct amination of nitrobenzenes by vicarious nucleophilic substitution,[908,998] a general route to meta-substituted benzenes via the directed metallation of benzenesulfinamides,[1143] a new method for the preparation of pyridones (Scheme 143) [624] in which the 2-cyanopyridinium cation is an intermediate,[678] novel cyclizations to prepare 1,3-benzoxazapines,[830] and a conversion of o-nitrosophenyl azides by thermolysis to benzofurazans (Scheme 144).[202] The oxidation of o-hydroxyphenyl(ethoxycarbonyl)hydrazones allows the conversion of the phenolic OH into an ethoxycarbonyl group (Scheme 145),[1176] the mechanism of this and similar conversions was clarified by cross-over and o-labelling experiments.[1209] We have described the synthesis of benzothiazoles from azlactones[1016] and a one-pot procedure for the conversion of alkyl halides into phosphonic acids.[1155]

Scheme 145. Conversion of Phenolic OH into CO_2Et



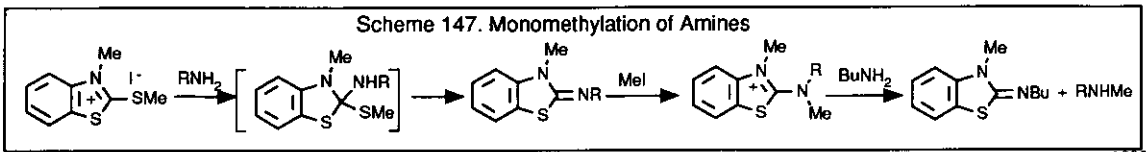
Scheme 146. Halide to Thiol Conversion



B. *Novel Reagents*

The sequence of Scheme 146 converts alkyl halides into thiols in one-pot reactions under mild conditions.[883] Lithiated 2-methylthiobenzothiazole is a synthon for mercaptomethylation[935] and (2-benzothiazolylthio)(trimethylsilyl)methane was developed as a general reagent for α-mercaptoalkylation.[953] 3-Methyl-2-methylthiobenzothiazole allowes the monomethylation of primary amines *via* the sequence of Scheme 147.[943]

Scheme 147. Monomethylation of Amines

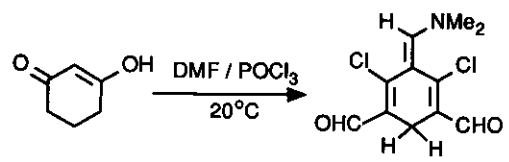


The Radizewski conversion of RCN into $RCONH_2$ by H_2O_2 is facilitated by use of DMSO as solvent.[1080] 2,2'-Iminodibenzoyl chloride allows the reversible dearomatization of benzimidazoles;[530,575] the product undergoes reversible oxidation as proved by X-rays.[858]

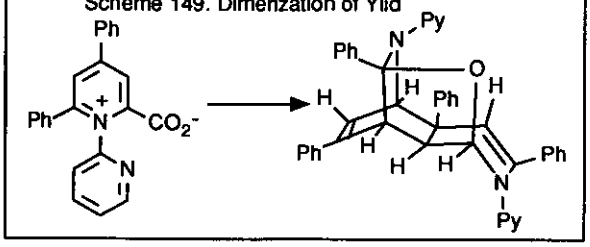
C. Vilsmeyer and Pyridinium 2-Betaine Chemistry

Cyclohexane-1,3-dione is converted[884] by the Vilsmeyer reagent into a stable nonaromatic isomer of a benzenoid compound (Scheme 148); the product has been investigated by X-ray and theory.[1019] We have studied further the reactions of cyclohexanones[954] and their alkyl derivatives[955] with Vilsmeyer reagents and elucidated structures of products[977] and intermediates.[1091] Vilsmeyer reactions of unactivated olefins have been achieved.[1242]

Scheme 148. Formation of Nonaromatic Benzenoid

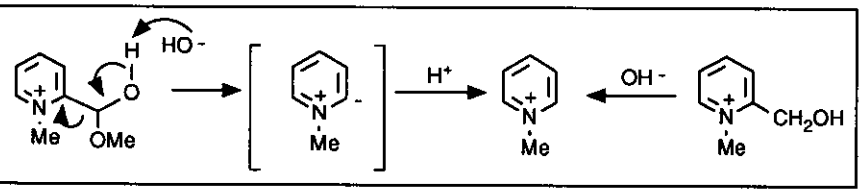


Scheme 149. Dimerization of Ylid



Pyridinium-2-carboxylate betaines decarboxylate to ylides which can be captured by a variety of electrophiles[865] or form cage-dimers (Scheme 149).[893] Heating with S_8 allows a synthesis of pyridine-2-thiones[809] and acid chlorides form 2-acylpyridinium salts.[865] The same ylides are formed by the alkali-catalyzed clevage of 2-hydroxymethyl- and 2-formyl-pyridinium cations (Scheme 150).[153] The chemistry of bicyclic pyridinium anhydro bases has been explored.[756]

Scheme 150.
Formation of Pyridinium Ylids



D. Other Preparative Chemistry

We have also prepared the following compounds and compound classes: α-aminosulfides,[1031] 3-styrylpyridine,[44] pyridine acid hydrazides,[2] 1-hydroxy-7-phenoxynaphthalene,[1317] dihydroimidazoylazoles,[1161] arylazo derivatives of pyridoxine,[196] substituted 1,4-benzodioxins;[198] pyrrylpyridines,[524] benzimidazodiazocines[535] N,S-acetals;[912] branched long chain primary[1071] and symmetrical sec-alkyl bromides;[923] pyrazinylalkane nitriles;[933] methazolamide analogs;[956] phenylglycollic acids;[1335] thiadiazolopyrimididinesulfanamides;[952] alkylsalicylic acids;[1305] alkylbenzocarbazoles;[989] vanadyl phosphonates;[1098] 1,3,4-thiadiazole thiones;[1140,1201] bis-(N,N-dialkylamino)trisulfides;[1159] tetradecyl-substituted benzacridines;[1199] nitroindoles;[1215] hindered tertiary aromatic amines;[1216] 1,4-diazabicyclo octanes;[1200] 6-, 7-, and 8-membered sultones;[1267] 4,7-disubstituted phenanthrolines.[1274]

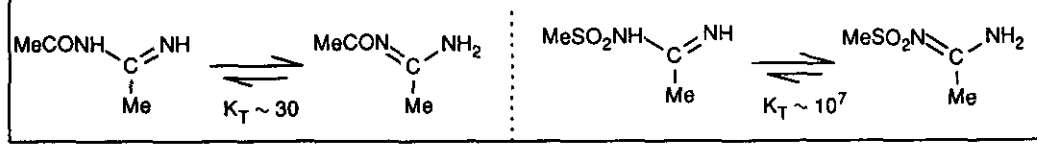
Phthaloacylation of amino-heterocycles,[534] the reactions of 4-dimethylaminopyridine with electrophiles,[821] of alkoxycarbonylisocyanates with nucleophiles,[1299] thiol-olefin co-oxidation,[1340] and the structure of oxidation products of semicarbazones and thiosemicarbazones[819] have been studied, and isonitrosoflavanones converted to imidazoles and pyrazoles.[562,670] 3-s-Triazolylpyridines undergo cycloaddition to form tricycles.[891]

E. Other Physical Organic Investigations

The correct nomenclature of meso ionic compounds as heteroaromatic betaines was pointed out.[3] Dipolar resonance structures were shown to be important in determining ground state charge distribution; particularly in polar media[1174] whereas geometries are much less affected by solvation.[896] Interactions in p-disubstituted benzenes was studied by UV spectra[68] and the influence of lone pair interactions on bond lengths discussed.[1126] X-ray and MO investigation of α-naphthyloxymethylbenzazoles clarified geometries:[1095] X-ray structures were determined for dihydropyrroles.[1240]

Already in 1971, a multiparameter approach to solvent effects was suggested.[336] Conformations of 2-pyridylmethylene-indanones[249] and -coumaranones[250] were discussed in terms of the steric requirements of lone pairs. *cis-trans-Equilibria about the single* bonds in meta-chlorophenyl aldehydes, ethers, and ketones were studied by dipole-moments,[345] and iminium isomerism by nmr.[878] Conformational effects in the alkali metal reductions of diaryl sulfides and dibenzothiophenes were investigated by GC/MS of the products[995] and evidence found for episulfide intermediates.[1000] Oxadiazole fluors[1035] and polysiloxane-base scintillators were examined.[1036] H-Bonding in dichloroacetic acid complexes was studied by Cl-35 and IR spectra.[1149] Thermal O to N rearrangements of 4-alkoxypyridines were shown to be intermolecular by *D*-labelling.[979] We studied detection of phthalic acid and related compounds by CI-ms,[1069] and measured gas-phase bonding of metal ions by crown ethers[1272] and intramolecular charge-transfer properties of dicyanovinyl-substituted aromatics.[1211]

Scheme 151. Tautomerism of Acyl- and Sulphonyl-amidines



In the area of aliphatic tautomerism we have studied substituent effects in acyl- and sulphonyl-[458] (Scheme 151) and phenyl-amidines,[533] and considered amine-imine tautomerism.[518]

VIII. Edited Works, Reviews, Monographs, Texts, etc

A. Edited Works

Volume 1 of Advances in Heterocyclic Chemistry was published in 1963. Now, thirty years later, the series is well and truly established[888] and Volume 58 will shortly appear. Physical Methods in Heterocyclic Chemistry also had Volumes 1[100] and 2 [101] appear in 1963, Volume 3 [328] and 4 [329] in 1971, Volume 5 [369] in 1972 and Volume 6 [424] in 1974.

Comprehensive Heterocyclic Chemistry[853] (Co-Editor-in-Chief Charles Rees) was published in eight volumes in 1984. The "Handbook of Heterocyclic Chemistry",[880] authored in collaboration with the Editors of CHEC, formed a ninth volume. Work is in progress on the first supplement to CHEC, which will be entitled "Comprehensive Heterocyclic Chemistry, Second Edition" (Co-Editors-in-Chief Eric Scriven and Charles Rees), and will consist of ten volumes as an essentially new work, due to appear in 1996.

Organic Functional Group Transfermations (Co-Editors-in-Chief Otto Meth-Cohn and Charles Rees) is a new Comprehensive work due to appear in 8 volumes in 1995.

Scheme 152. Best Synthetic Methods

Free-Radical Chain Reactions in Organic Synthesis, (W. B. Motherwell, D. Crich)
Electroorganic Synthesis, (Tatsuya Shono)
Palladium Reagents in Organic Synthesis, (R. F. Heck)
Organolithium Methods, (B. J. Wakefield)
Hydrogenation Methods, (P. N. Rylander)
Biotransformations in Preparative Organic Chemistry, (H. G. Davies and R. H. Green, D. R. Kelly, Cardiff, S. M. Roberts)
Photochemical Synthesis, (I. Ninomiya and T. Naito)
Borane Reagents, (A. Pelter and K. Smith, H. C. Brown)
Silicon Reagents in Organic Synthesis, (E. W. Colvin)
Methods for the Oxidation of Organic Compounds, (A. H. Haines)

The series "Best Synthetic Methods" (co-edited with Otto Meth-Cohn and Charles Rees) now comprises some fifteen volumes on various topics in organic chemistry (Scheme 152). A new venture "Organic Functional Group Transformations" (Co-Editors-in-Chief Otto Meth-Cohn and Charles Rees) is presently being written and should appear in seven volumes in 1995. The monograph series "Topics in Applied Chemistry" (co-edited with Gabi Sabongi) now comprises six volumes.

B. Reviews and Contributions to Encyclopaedias

Reviews dealing mainly with our own work have already been mentioned in the appropriate research sections and will not be referred to again. The present section lists reviews of wider scope: a general survey of heterocyclic chemistry;[299] the structures of protonated amides[66]; heterocyclic N-carboxylic acids[929] and N-dithiocarboxylic acids;[930] applications of nmr to organic chemistry in the early 60's;[107,108] the infrared spectra of heterocycles;[82,121,363] linear free energy relationships and optical spectroscopy.[371] Contributions on heterocyclic chemistry were written for Encyclopaedia Brittanica,[430,1333] Encyclopedia della Chimica,[525] and Encyclopedia of Physical Science and Technology.[925,1244]

C. Texts and Monographs

The textbook on heterocyclic chemistry entitled "Heterocyclic Chemistry" and co-authored with Jeanne Lagowski was published in 1960.[46] Translations of this book appeared in the dates indicated in the following languages French,[240] German,[242] Spanish,[241] Italian,[243] Polish,[176] Russian,[98] Japanese.[239] A revised version, also co-authored with Jeanne Lagowski, was published in 1967 under the title "Principles of Heterocyclic Chemistry".[204] The "Handbook of Heterocyclic Chemistry"[880] can be considered a sequel to these two texts. Philosophy on the teaching of heterocyclic chemistry has been formulated.[158,285] Monographs on N-oxide chemistry,[327] electrophilic substitution[1086] and tautomerism[514] have already been mentioned.

Chapters written for Comprehensive Heterocyclic Chemistry include: Introduction,[823] Review Literature of Heterocycles,[824] and "The Structure[825] and Reactivity[826] of Five-Membered Rings with Two or More Heteroatoms". Two further chapters were written on the literature of heterocycles.[179,612]

D. Miscellaneous Publications

The introduction[877] for the "Chemistry Today" Encyclopedia was provided. Available methods for ascertaining the availability of chemical starting materials were reviewed,[924] and an illustration of the refereeing system provided.[1180] The work of the Chemical Education and Training Board was summarized[403] and the university systems in UK and USA compared.[879]

The scope, timeliness and quality of chemical abstracts from VINITI and CAS have been compared.[1289]

IX. Service

A light-hearted overview of my life under the title: "The Ups and Downs of Fifty Years of Heterocyclic Chemistry" will appear in *J. Het. Chem.*[1336]

A. University of East Anglia

As Foundation Professor (1963-1980) and as first Dean of the School of Chemical Sciences (1963-1970 and again 1976-1980) I was responsible for the organization and development of chemistry at the new University of East Anglia. In particular the appointment of the academic and technical staff, the formulation of the curriculum content, the design of the buildings, the marshalling of the resources and the leadership of the new school were my responsibility. Our plans, as outlined in an early paper[109] were largely achieved. Original ideas, novel at the time, were applied to teaching.[123,133] After four years at UF, I looked back to the university system in the UK in an article in *Nature*.[879]

B. Interaction with Industry

A major emphasis was placed at the University of East Anglia on interactions with industry at the start[322] and these were later reemphasized.[521,522,591,606] A research review emphasizes the academic-industrial connection.[1263]

In 1970, a series of annual short courses in organic chemistry were started for industrial chemists (and it is a source of great satisfaction that these are still running). In 1976, annual long courses were commenced at East Anglia to offer a further in-depth training to industrial chemists. These were later turned into industrially based Masters and PhD degrees under which system the research could be carried out at the industrial location under joint supervision and the course work at the university. At the University of Florida, several short courses have been held on campus and on the road with the participation of colleagues. Industrial academic contacts in UK and USA have been compared.[744]

Over the years consultancy has been provided to organizations and companies including the following: Bristol-Meyers-Squibb, Exxon, International Synthetic Rubber Company, Merck, Minnesota Mining and Manufacturing, Monsanto Ag Company, Monsanto Rubber Company, NutraSweet, Pharmatec, Pharmos, Pfizer, Reilly Industries.

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