

HETEROCYCLIC *N*-OXIDES AND *N*-IMIDES

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Abstract - Heterocyclic *N*-oxides and *N*-imides show a variety of fascinating reactions. This review exemplifies their preparation, discusses their structures, and considers some of their reactions.

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*Dedication: This review is dedicated with admiration and affection to Professor Masatomo Hamana on his 75th birthday. Professor Hamana has made many seminal contributions to *N*-oxide chemistry as a worthy successor to the great Professor E. Ochiai.*

1. Introduction

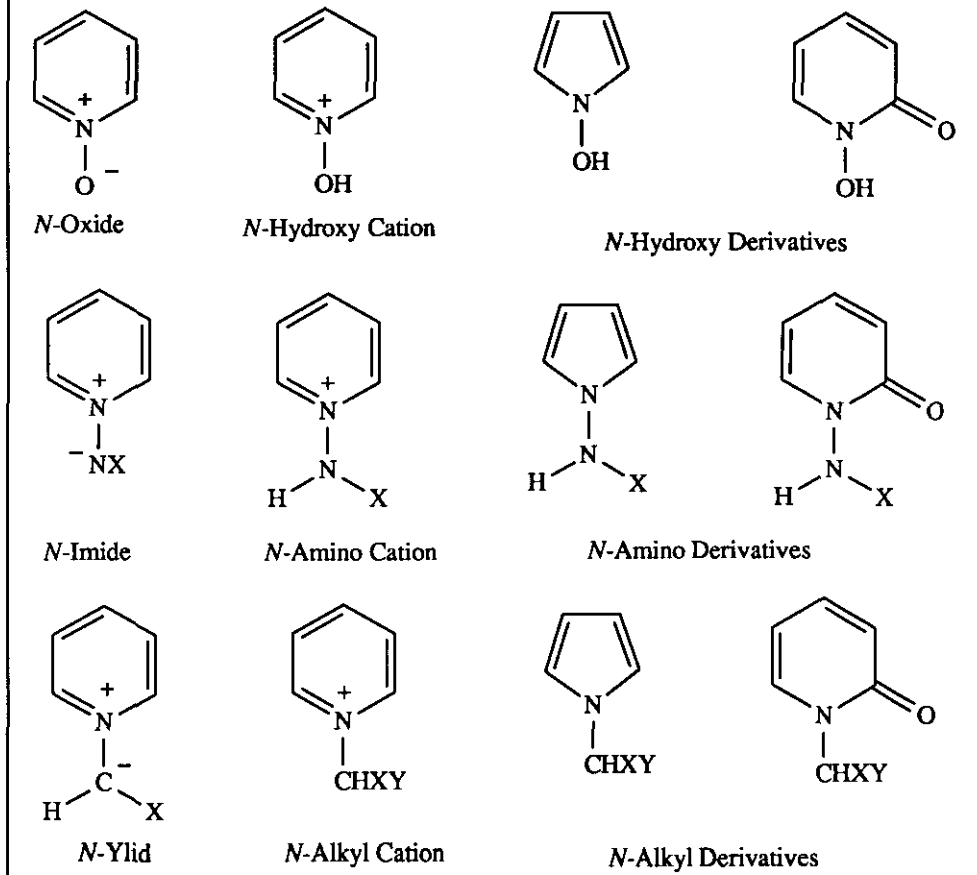
Two chemical texts^{1,2} and a recent monograph³ are devoted to *N*-oxide chemistry. Several reviews exist for *N*-imide chemistry.⁴⁻⁸ The purpose of the present review is to highlight some of the new interesting aspects with emphasis on work from the senior author's group.

2. Overview and Preparative Methods

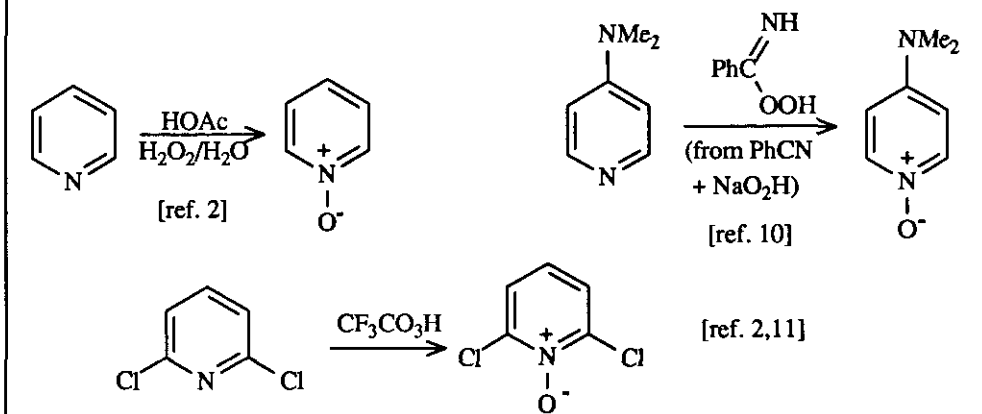
Scheme 1 gives a general overview of the types of compounds that are considered in this review. An oxygen atom attached to a neutral pyridine-like ring nitrogen atom affords an *N*-oxide. Such *N*-oxides are basic and can pick up a proton to form an *N*-hydroxy cation. Equally, hydroxy groups can be attached to pyrrole-like nitrogen atoms, either in 5-membered rings as in 1-hydroxypyrrole itself or in a 6-membered ring as in 1-hydroxy-2-pyridone. These four parent compounds are shown in the top row of Scheme 1, with their nitrogen analogs, the neutral *N*-imides, the *N*-amino cations, and the *N*-amino derivatives in the second row. In the *N*-analogs, the exocyclic nitrogen atom can hold a substituent which is denoted in Scheme 1 by X. For comparison, the corresponding carbon analogs are shown in the bottom row of Scheme 1: the *N*-ylids, *N*-alkyl cations, and the *N*-alkyl derivatives.

Preparative methods for *N*-oxides by direct oxidation of the corresponding pyridines are outlined in Scheme 2. Most common is the oxidation of the corresponding *N*-heterocycle with a peracid. The strength of the peracid used depends upon the compound to be oxidized. This is illustrated by the three examples in Scheme 2. For most pyridines, peracetic acid or performic acid suffices, but for the very strongly basic 4-dimethylaminopyridine, it is better to use the peroxyimidic acid which is very much less acidic and, therefore, does not cause so much conversion of the DMAP into unreactive cation. Finally, the non-basic and unreactive 2,6-dichloropyridine requires trifluoroperacetic acid. Pentachloropyridine has also been converted into its *N*-oxide with trifluoroperacetic acid, although in this case, care is needed since prolonged heating causes deoxygenation.⁹

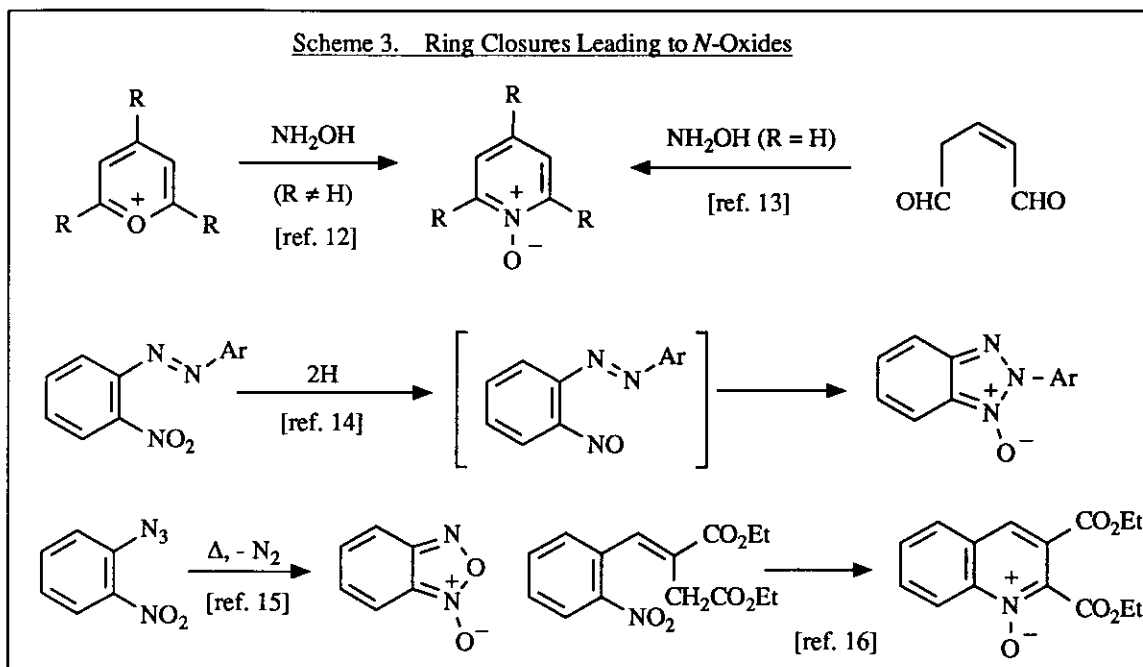
Scheme 1. Substitution at Heterocyclic Nitrogen: Types



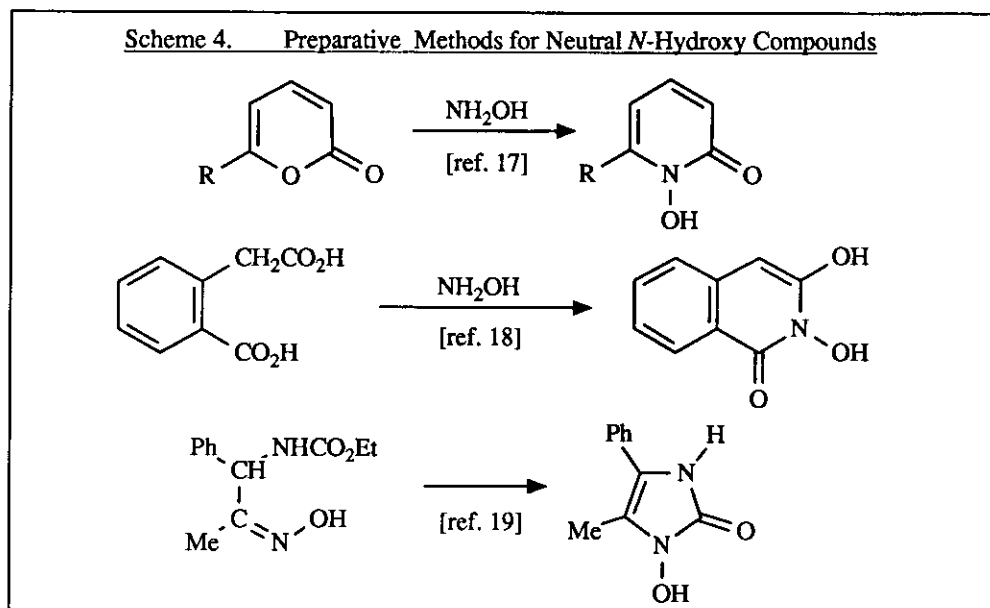
Scheme 2. Preparative Methods for *N*-Oxides



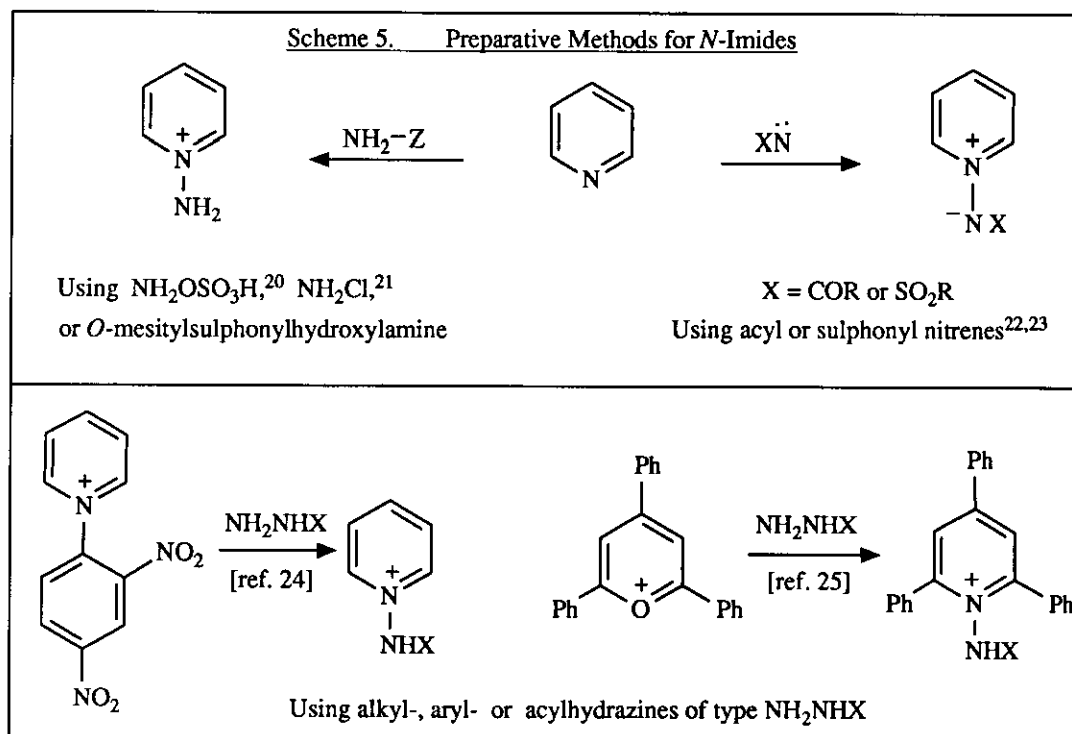
Many ring closure methods are also known for *N*-oxide preparation² and a few are illustrated in Scheme 3. Such ring closures generally involve either hydroxylamines (as in the first two examples) nitroso compounds (as in the 3rd example), but a few appear to be true examples of nucleophilic attack at nitro groups (see last example of Scheme 3).



Scheme 4 illustrates some of the preparative methods for neutral *N*-hydroxy compounds by ring closures. In each case a hydroxylamine is involved.

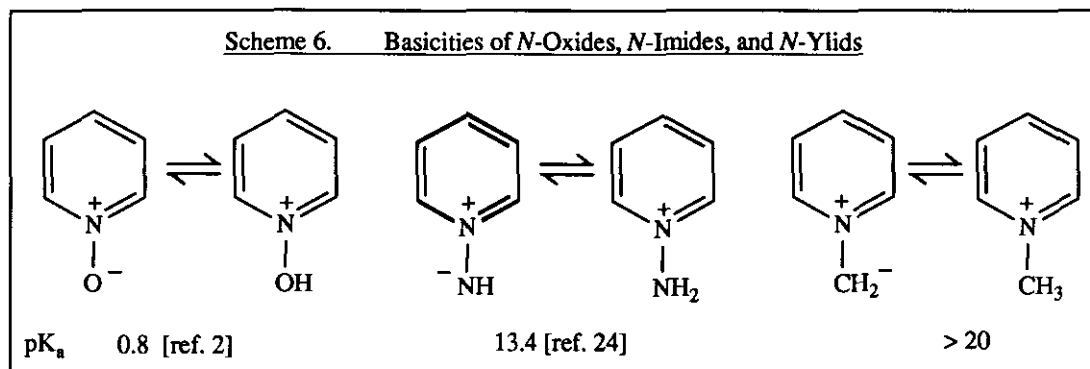


Scheme 5 gives some preparative methods for *N*-imides. In the upper half of the Scheme the conversion of a neutral nitrogen into the *N*-imide or into the *N*-imonium cation is illustrated. At the bottom, two examples of a ring opening/ring closure method are described.

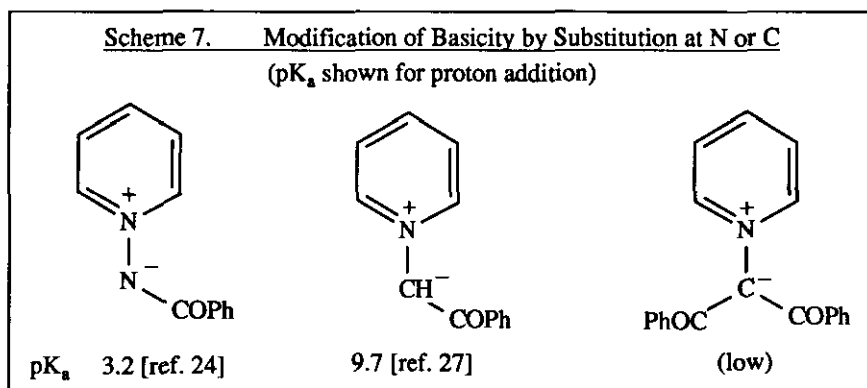


3. Basicity of *N*-Oxides and *N*-Imides.

The tendency for these classes of compounds to exist in the neutral form varies considerably. Thus, as shown in Scheme 6, *N*-oxides are weakly basic, *N*-imides are strongly basic, and for comparison, unsubstituted *N*-ylids are extremely strong bases which cannot normally be isolated. Pyridine *N*-oxides readily undergo hydrogen bonding, and form hemisalts which have been much investigated [see eg ref. 26].



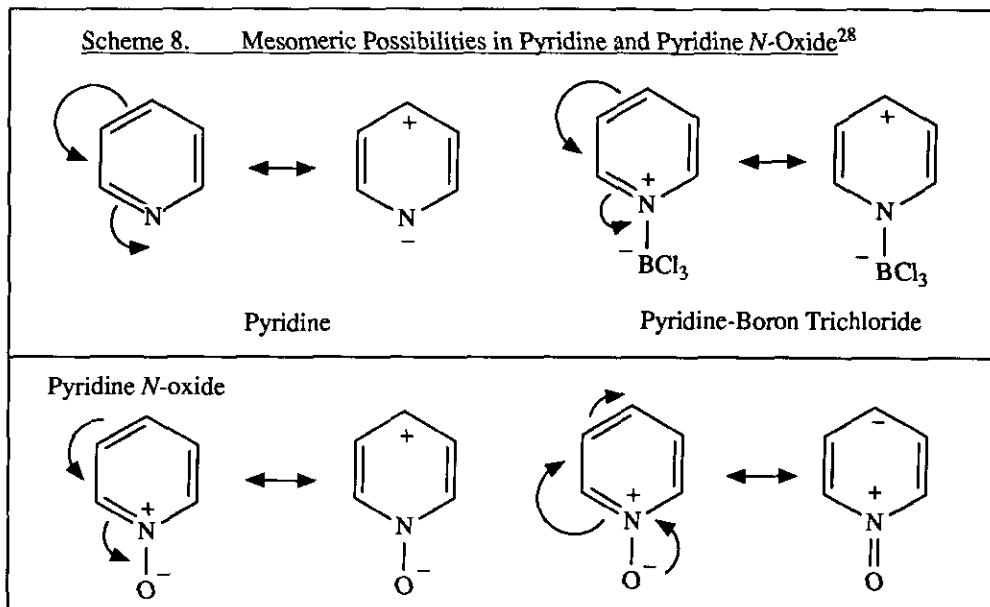
However, as is shown in Scheme 7, the basicity of *N*-imides and *N*-ylids can be considerably affected by substituents attached to the exocyclic nitrogen or carbon atom. Thus, pyridine *N*-benzoylimide is quite a weak base and is quite stable in the neutral form.



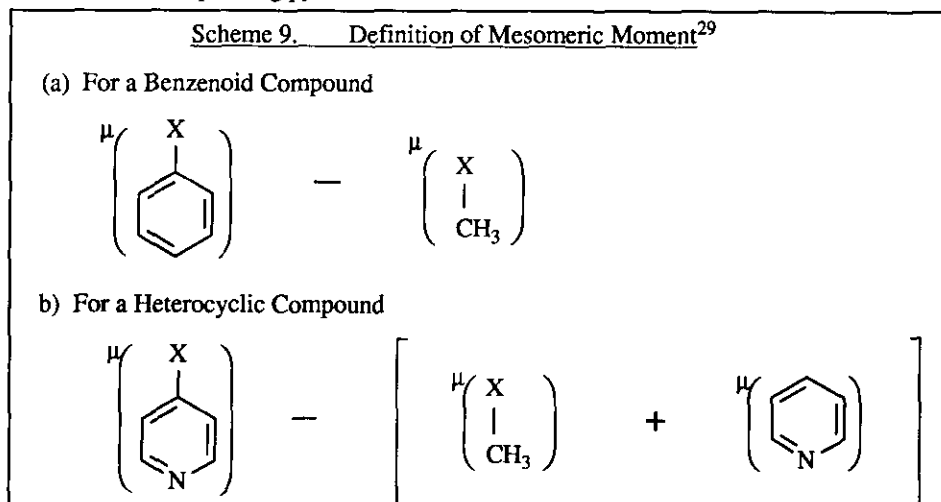
4. Electronic Structure and Back Donation of Electrons in *N*-Oxides and *N*-Imides

Because of the lone pair of electrons on the exocyclic atom attached to the heterocyclic nitrogen, *N*-oxides and *N*-imides can show back donation of electrons. This phenomenon has been examined mostly for *N*-oxides. The mesomeric possibilities in pyridine *N*-oxide are contrasted with those in pyridine and pyridine boron trifluoride in Scheme 8. There is ample experimental evidence for the occurrence in pyridine *N*-oxide not only of the pull of electrons towards the positively charged nitrogen (which is greater than that which is

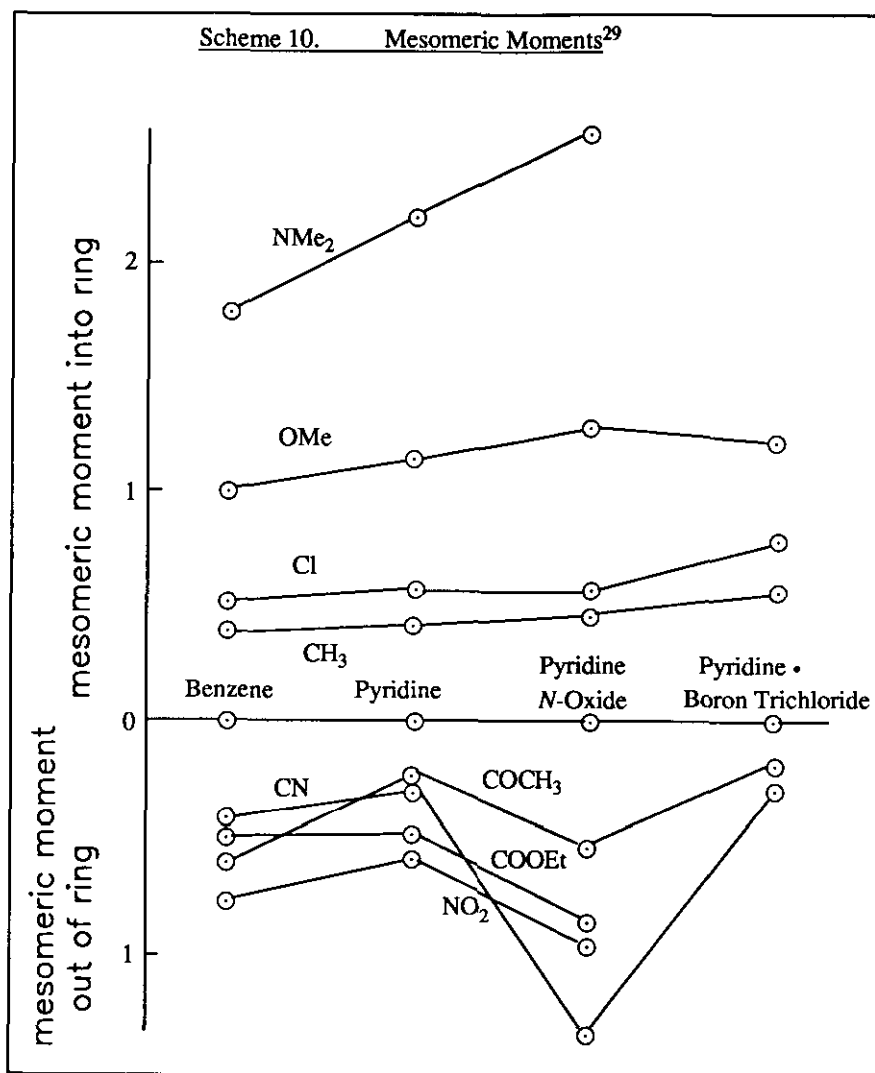
found in neutral pyridine and comparable to that which is found in the Lewis salt pyridine-boron trichloride), but also for those in which electrons are donated from the oxygen into the ring.



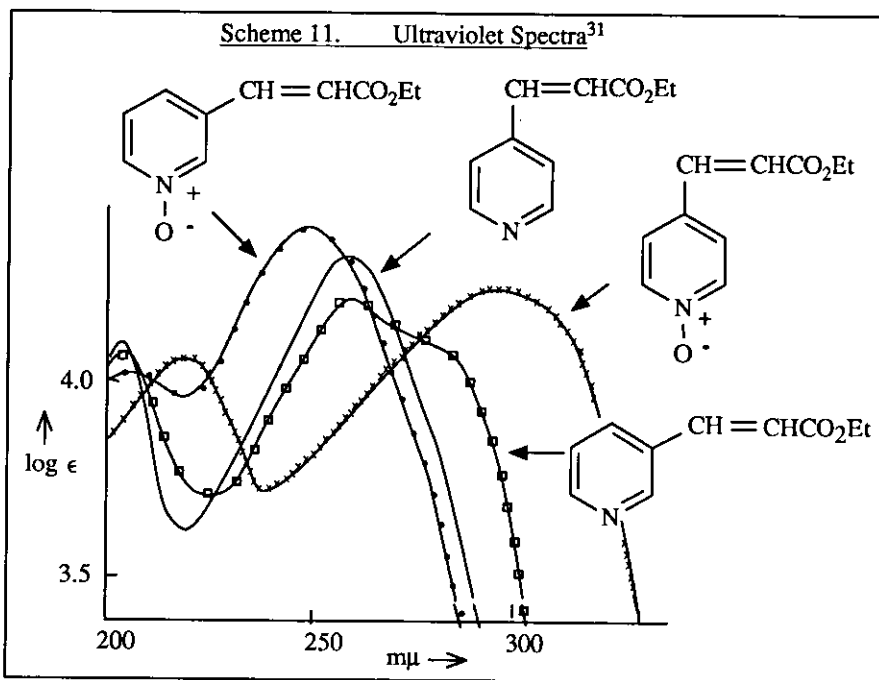
One of the first pieces of evidence for this donation of electrons from the *N*-oxide group into the ring was from dipole moments. In Scheme 9, the concept of mesomeric moment is defined for benzenoid and heterocyclic compounds, and the values of these mesomeric moments for a series of monosubstituted benzenes and 4-substituted pyridines, pyridine *N*-oxides and pyridine boron trichlorides is shown in Scheme 10. The values for pyridine *N*-oxides clearly show greater conjugation with both e-donor and e-acceptor substituents than the corresponding pyridines.



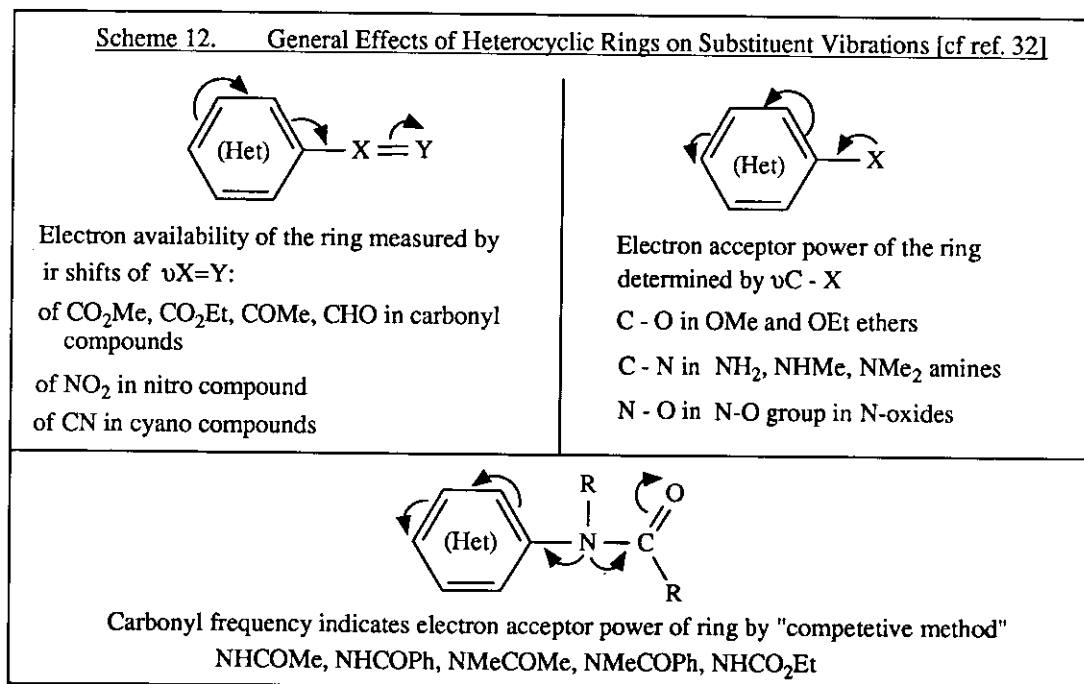
Natural abundance ^{17}O Nmr chemical shifts of the oxygen of pyridine *N*-oxides correlate with σ_1 substituent constants and support interactions with substituents of both classes.³⁰



Much further evidence comes from spectroscopy. Scheme 11 shows some ultraviolet spectra. Comparison of the 4-substituted *N*-oxide with the parent pyridine clearly shows the extension of the conjugation by the pronounced bathochromic shift in the *N*-oxide. However, such extended conjugation is absent in the 3-substituted *N*-oxide, as demonstrated by its hypsochromic shift with respect to the corresponding pyridine.



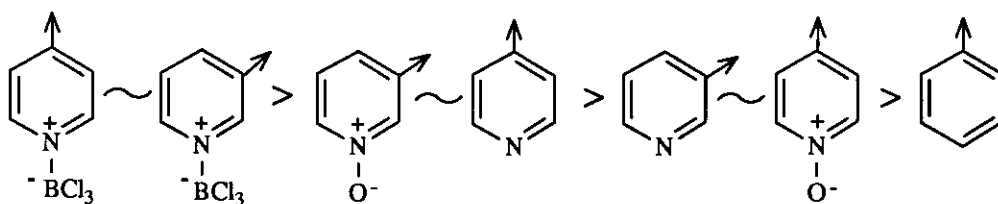
These interactions are also clearly demonstrated by infrared spectroscopy. The general effects of heterocyclic rings on substituent vibrations are shown schematically in Scheme 12.



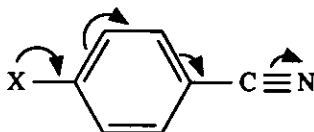
Scheme 13 lists the increments measured for the carbonyl group $\nu_{\text{C=O}}$ for various heterocyclics together with the corresponding benzenoid compound. The largest bathochromic shifts are found in the pyridine boron trichlorides with slightly higher values in the 4- than in the 3-position. The 3-position of pyridine *N*-oxide is also very electron-deficient, whereas the 4- and 3-positions of pyridine are successively less so. The 4-position of pyridine *N*-oxide is least affected. Interpretation for the degree of electron acceptance at the 2-position is complicated by steric effects, however such steric effects are much less in the case of the cyano derivatives.

Scheme 13. Increments for $\nu_{\text{C=O}}$ for Heterocyclic Compared with Benzenoid Compounds³³

	4 PyBCl ₃	3 PyBCl ₃	3 PyO	4Py	3Py	4PyO	Ph
CO ₂ Et	23	21	16	14	8	6	0
CO ₂ Me	21	21	17	11	6	3	0
COCH ₃	—	—	27	20	10	12	0
CHO	—	—	—	25	16	—	0



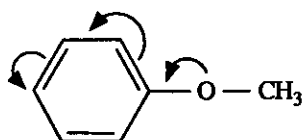
Infrared spectral details for the three isomeric cyanopyridines and the three derived pyridine *N*-oxides are compared with those for benzonitrile in Scheme 14. The intensity is reduced in all the heterocycles, but by very little in the 4-position in pyridine *N*-oxide, next least in the 3-position in pyridine, and very much in the other positions. The same trend is shown in the frequency shifts. This clearly demonstrates the back coordination of electrons to the 4-position of pyridine *N*-oxide, and also shows that any such back donation at the 2-position is swamped by the electron accepting effect of the adjacent positively charged nitrogen atom.

Scheme 14. $\nu_{C\equiv N}$ Frequencies and Integrated Intensities³⁴PhCN $\nu = 2233 \text{ cm}^{-1}$ area = 4300

Position	Pyridine		Pyridine <i>N</i> -oxide	
	$\nu \text{ (cm}^{-1}\text{)}$	A	$\nu \text{ (cm}^{-1}\text{)}$	A
4	2238	1110	2230	3910
3	2235	2480	2243	1190
2	2240	720	2241	760

Electron acceptance can be seen in the way in which the methoxy group interacts with heterocyclic rings. The increment by which the ring oxygen stretching vibration variation is displaced in the different compounds compared with anisole is shown in Scheme 15.

In all the methoxy-heterocycles the increment is positive showing that all positions are electron accepting relative to benzene. For the isomeric pyridines, the increments are higher for the 2- and 4-position than for the 3-position. By contrast, for the isomeric pyridine *N*-oxides, the increment is lowest for the 4-position.

Scheme 15. IR of Heterocyclic Methoxy Derivatives³⁵ $\Delta \nu$ -Values (cm^{-1}) referred to anisole (1244 cm^{-1})

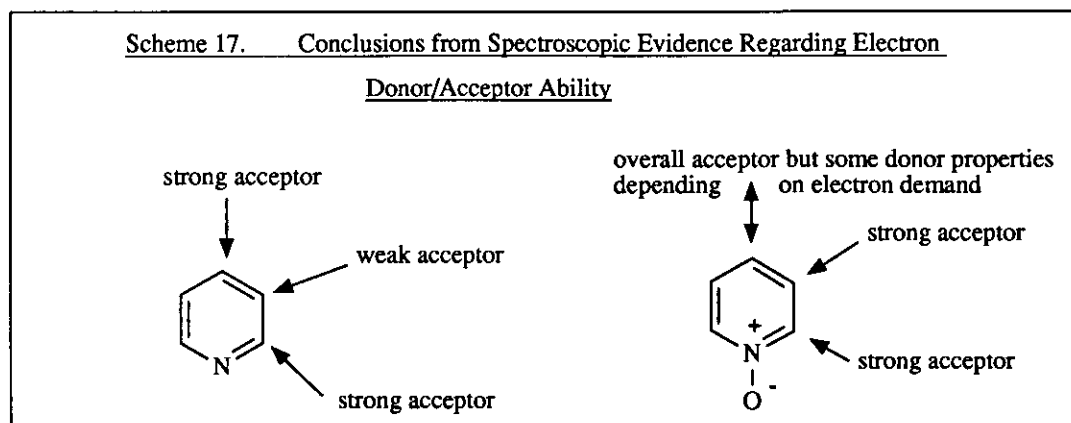
	2-subst.	3-subst.	4-subst.
Pyridine	48	19	44
Pyridine <i>N</i> -Oxide	67	64	48
Pyridine BCl_3	—	—	69

In Scheme 16, the intensities are given for the triple bond stretch in a set of heterocyclic derivatives of phenylacetylene carrying a substituent in the 4-position. In diphenylacetylene, because of symmetry, the vibration is forbidden in the infrared, and the intensity rises with either an electron donor or an electron acceptor substituent. However, for the pyridine series and the pyridine *N*-oxide series, the intensity rises for electron donor substituents, but falls for electron acceptor substituents. This indicates that the 4-position of both pyridine *N*-oxide and pyridine behave as electron acceptors in this rather neutral situation.

Scheme 16. Extinction Coefficients for $\nu_{C\equiv C}^{36}$

X	Z		
	CH	N	N ⁺ -O ⁻
OMe	20	90	--
Me	7	70	70
H	<1	40	40
Cl	4	40	15
NO ₂	80	5	5

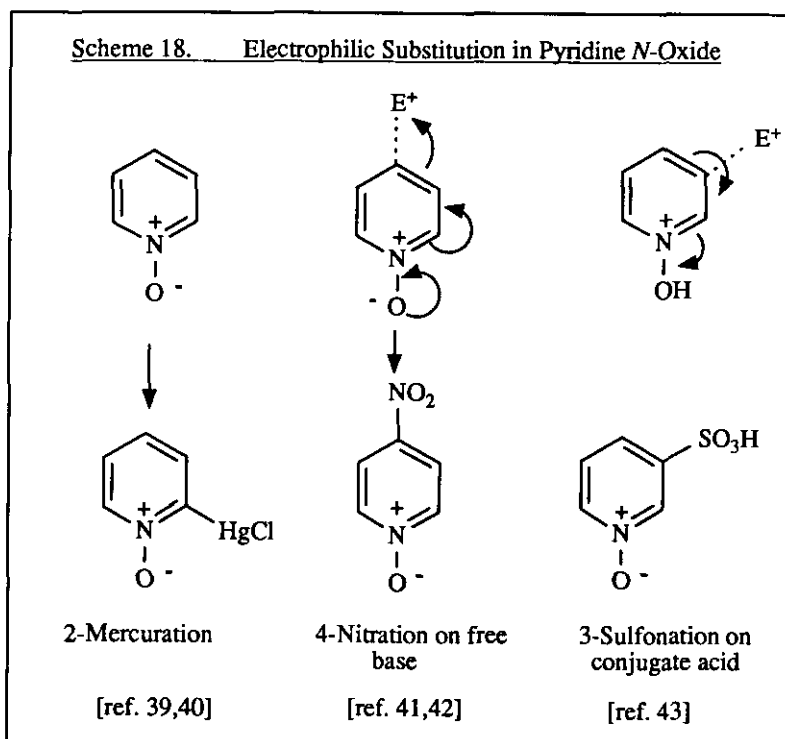
The overall conclusion from the spectroscopic evidence is that the pyridine ring is uniformly an electron acceptor, stronger at the 2- and 4-positions than at the 3-position. The pyridine *N*-oxide ring is a strong acceptor at the 2- and 3-positions whereas at the 4-position it is normally an acceptor, but that it can donate electrons at the 4-position when faced with strong electron demand.



The strongly polar character of *N*-oxides endows them with catalytic activity: thus 4-dimethylaminopyridine *N*-oxide effectively catalyzes the rearrangement $\text{ROCSSR}' \rightarrow \text{RSCOSR}'$ [cf. ref. 37] as well as phosphate ester hydrolysis.³⁸

5. Reactions of *N*-Oxides and *N*-Imides with Electrophiles

All compounds of this type react readily with electrophiles. In *N*-oxides, electrophiles can attack ring carbon atoms and indeed, under different conditions, at the 2-, the 3-, or the 4-positions, as is shown in Scheme 18.



Attack on the 4-position of the pyridine *N*-oxide takes place on the neutral molecule, whereas electrophilic attack at the 3-position occurs on the pyridine *N*-oxide conjugate acid because in the cation the 2- and 4-positions are more electron-deficient. Attack at the 2-position can occur because of anchimeric assistance from the oxygen atom. The conditions for these electrophilic substitution reactions are shown in Scheme 19.

Scheme 19. Electrophilic Attack at Carbon in Pyridine *N*-Oxide

Nitration (Ochiai and den Hertog)^{41,42}

100°C, H₂SO₄-HNO₃ good yields of 4-nitro

Sulphonation (Mosher)⁴³

230°C, H₂SO₄-SO₃-HgSO₄ 3-sulphonic acid (good yield)

Mercuration (van Ammers and den Hertog)⁴⁰

130°C, Hg(OAc)₂-HOAc 2-mercuriacetate (poor yield)

170°C, HgSO₄-H₂SO₄ 3-mercurisulphate (poor yield)

Bromination (den Hertog)

200°C, Br₂-H₂SO₄-AgSO₄ 10% of 2- and 4-bromo
(ca. 1 : 2)⁴⁴

120°C, Br₂-H₂SO₄-SO₃ 3-Bromo⁴⁵

Hydrogen exchange⁴⁶

no exchange at 200°C with 100% H₂SO₄

Pyridine *N*-oxide can also undergo electrophilic attack at oxygen. Shown in Scheme 20 are typical examples of reactions of protons, alkylating agents and Lewis acids. The products of such electrophilic attack are themselves often intermediates for further attack by nucleophiles at the 2- and 4-positions of the ring.

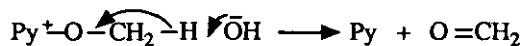
Scheme 20. Electrophilic Attack at Oxygen in Pyridine *N*-Oxide

Proton Acids

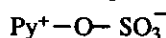
N-oxides are weak bases, pK_a ≅ 1

Quaternary Salt Formation with MeI or TsOMe⁴⁷

Salts produced react with alkali



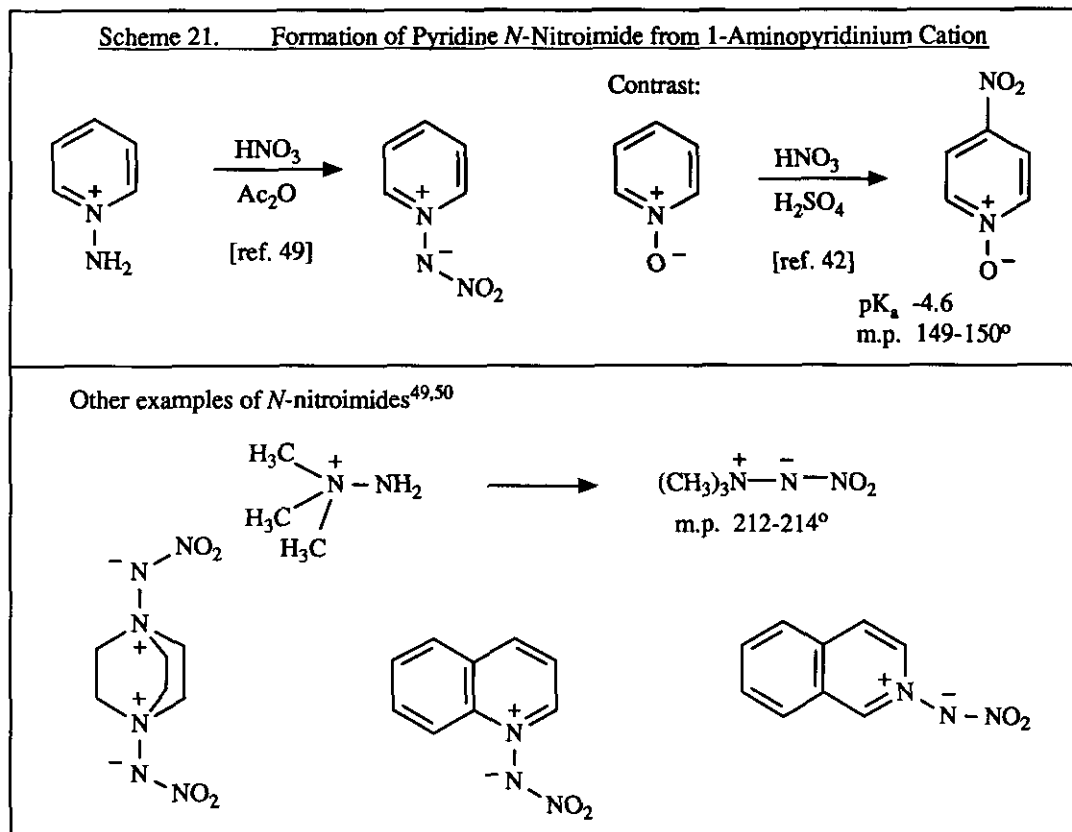
Co-ordination Compounds⁴⁸



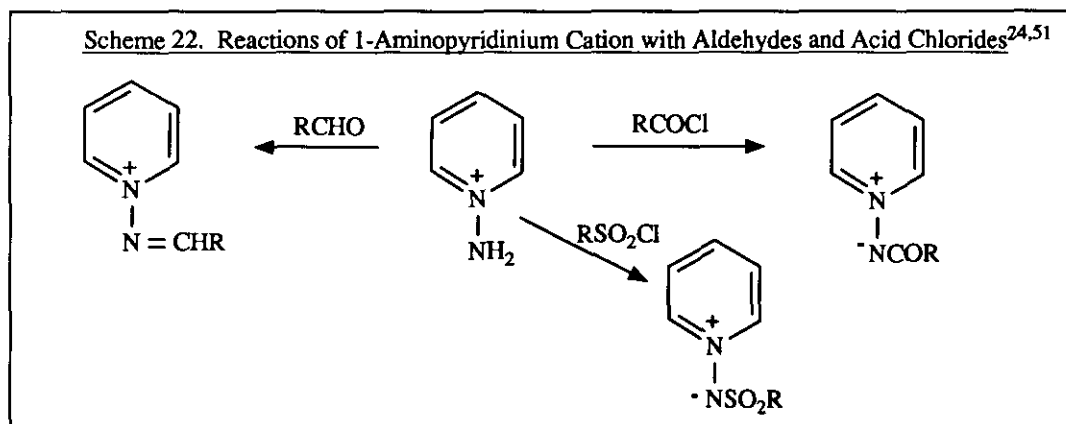
Intermediates for Further Reactions

Py⁺-O-X undergoes very facile attack by nucleophilic agents at carbon - cf later discussion

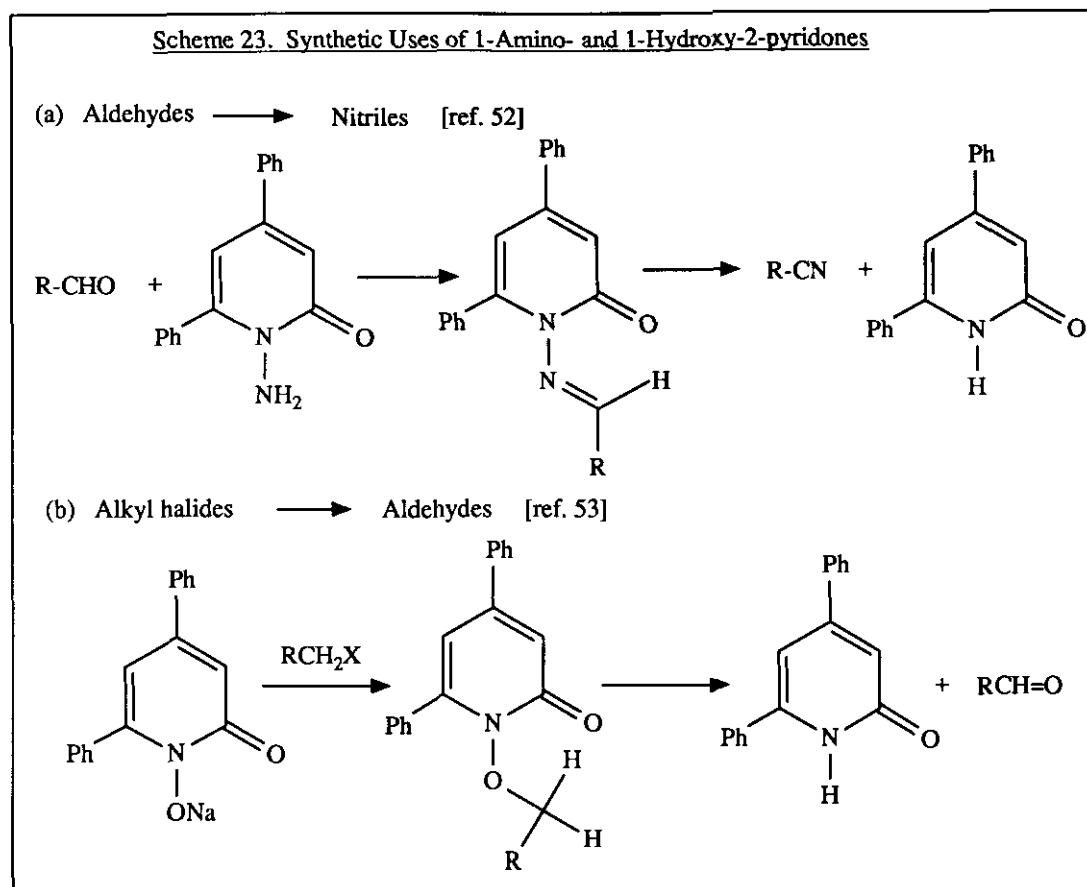
For *N*-imides, electrophiles attack exclusively at the exocyclic *N*-atom. Thus, the 1-aminopyridinium cation is nitrated in the amino group to give a stable *N*-imide and such *N*-imides have been formed from other *N*-amino ammonium ions as is also shown in Scheme 21.



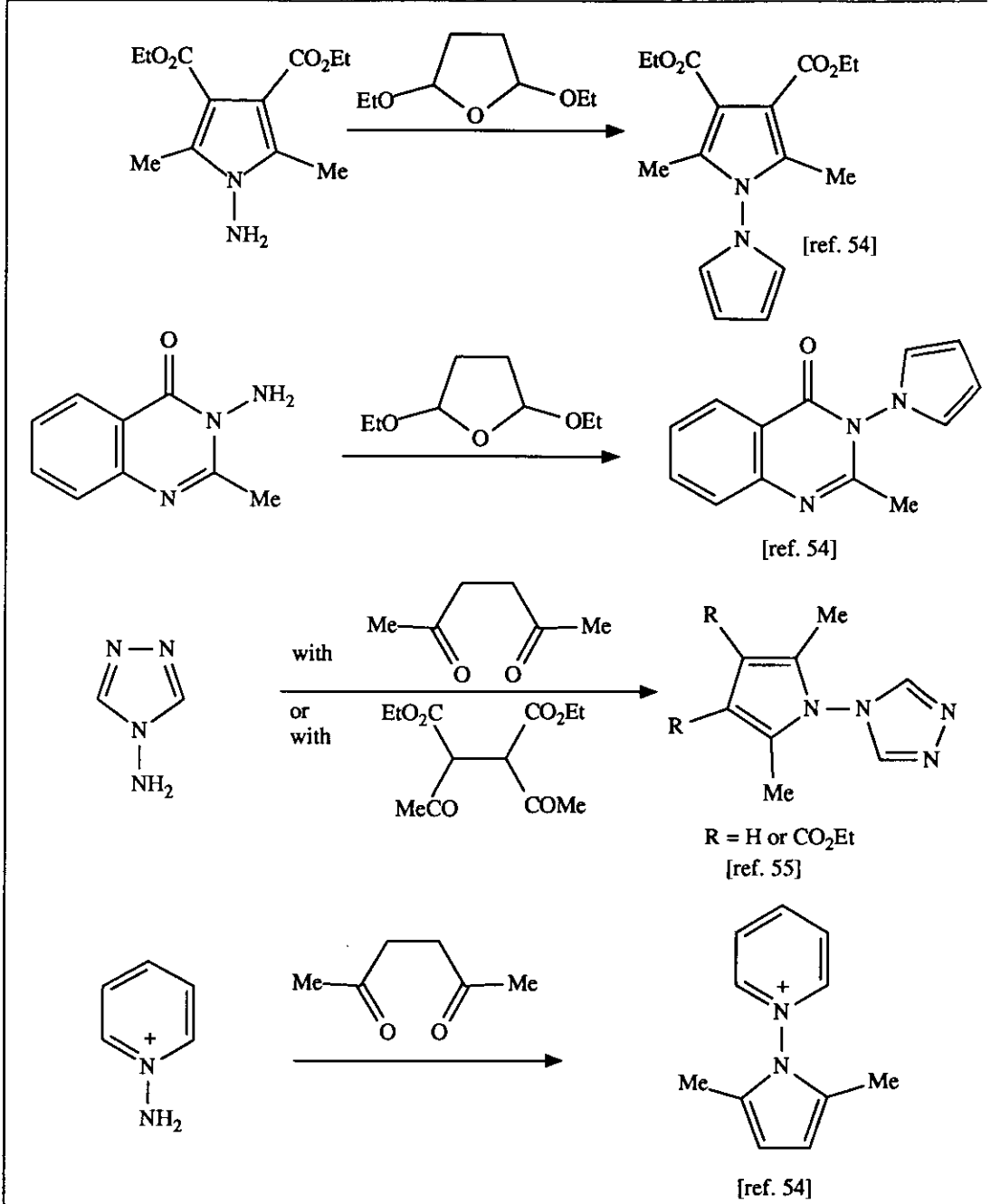
Scheme 22 illustrates further the reactions of 1-aminopyridinium cation with other electrophiles, i.e. with aldehydes, and acyl and sulfonyl chlorides.



Scheme 23 gives details of two synthetic uses of neutral *N*-hydroxy and *N*-amino heterocyclic derivatives.

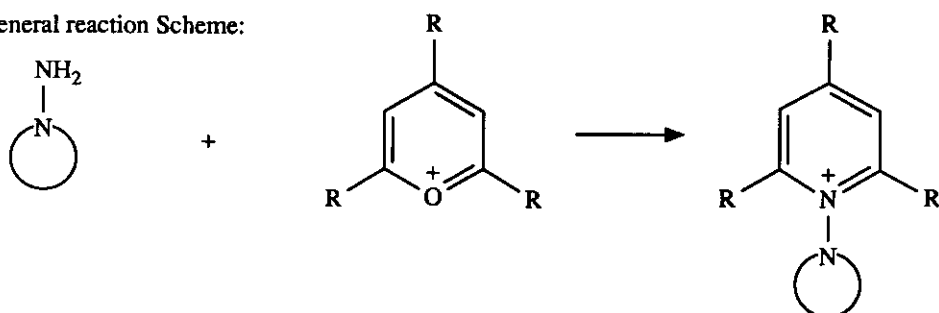


An interesting extension of the above type of reaction is to biselectrophiles. Neutral *N*-aminoheterocycles such as *N*-aminopyridones, *N*-aminopyrroles, and *N*-aminotriazoles, as well as *N*-aminopyridinium ions can react with suitable biselectrophiles to form bis(heterocycles) in which the two heterocyclic rings are linked by an NN bond. Reactions of this type are shown in Scheme 24 for the production of a pyrrole ring as the new heterocycle, and in Scheme 25, for the production of a pyridinium ring as the new heterocycle.

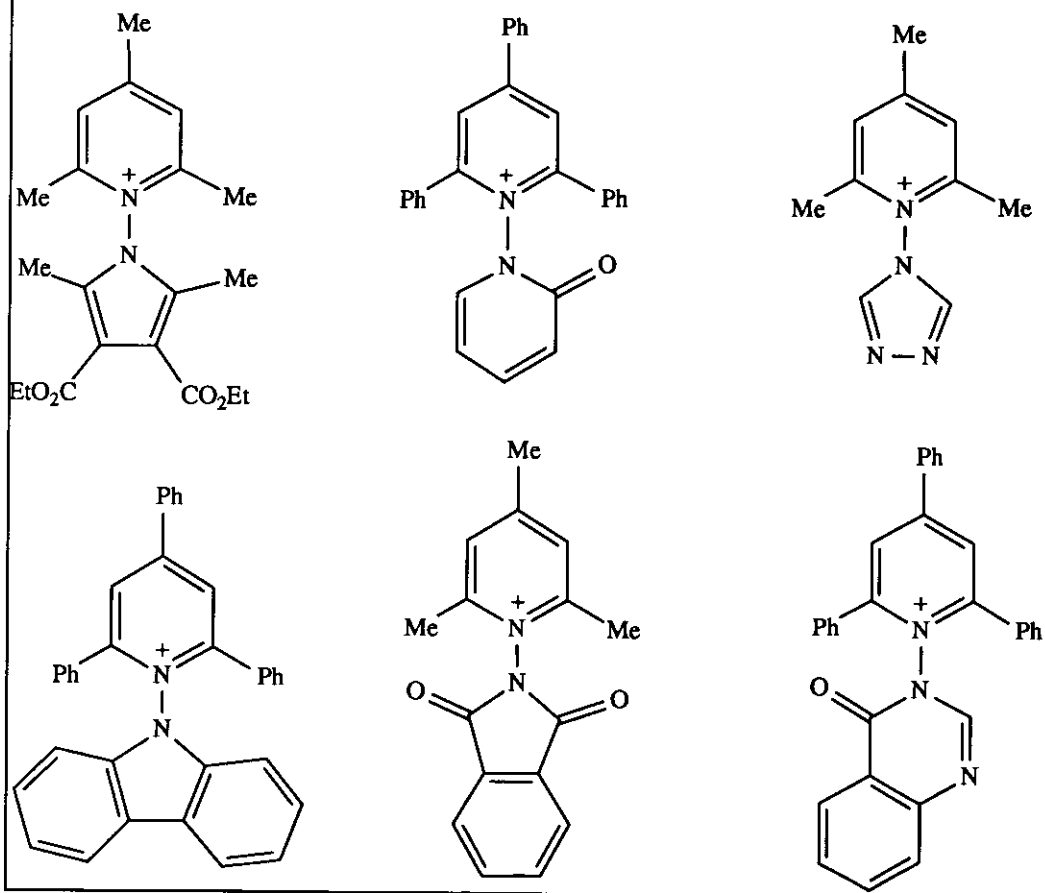
Scheme 24. Reaction of *N*-Aminoheterocycles with 2,5-Diethoxytetrahydrofuran and with 1,4-Diketones

Scheme 25. Reactions of *N*-Aminoheterocycles with Pyrylium Salts

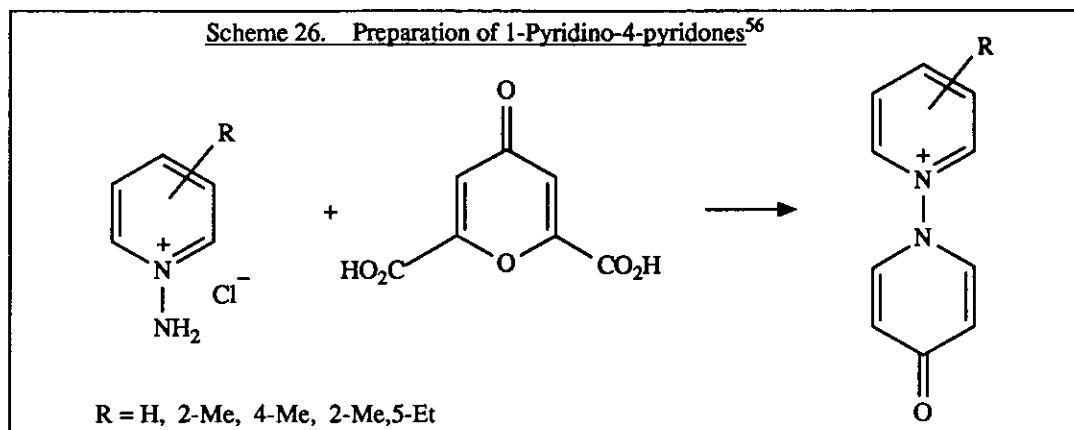
General reaction Scheme:



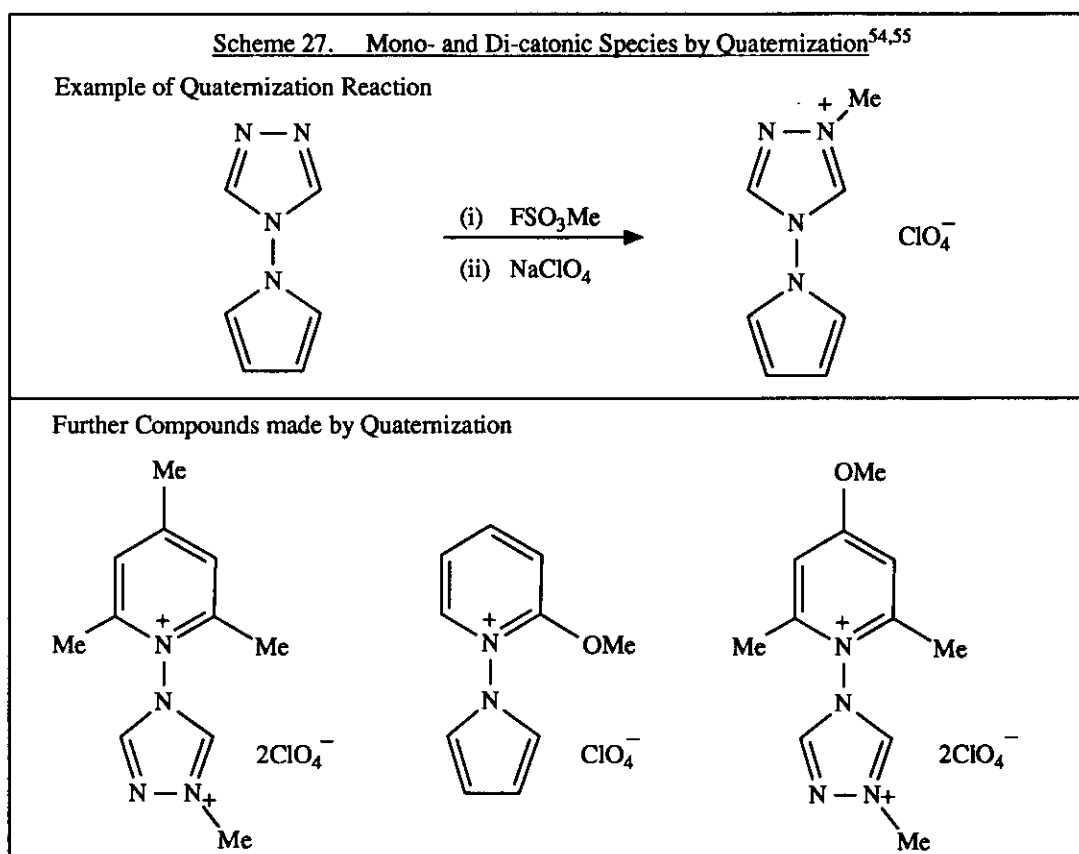
Examples of compounds prepared^{54,55}



The reactions of various 1-aminopyridinium cations with pyrone 2,6-dicarboxylic acid are of interest as they give bis(heterocycles) with simultaneous decarboxylation (Scheme 26).

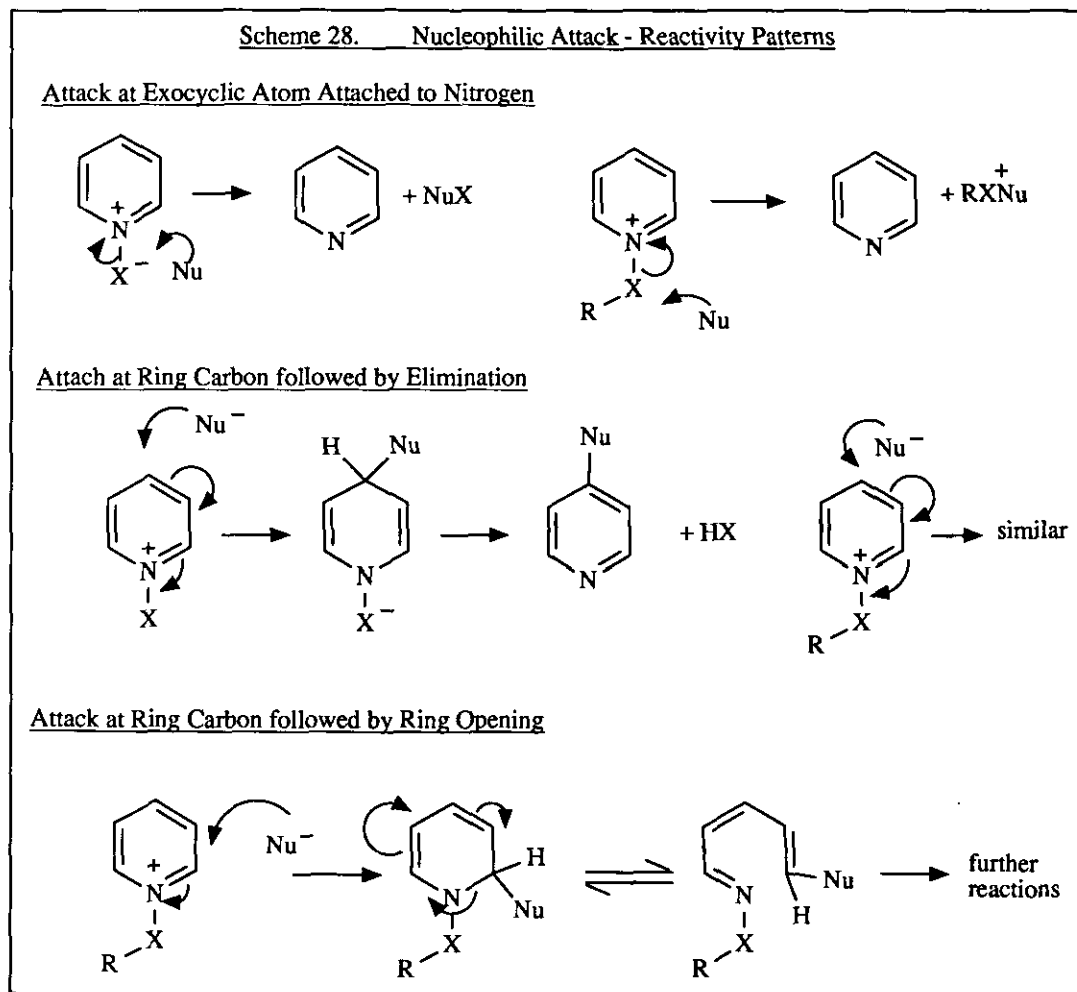


Although it has not been possible to prepare a bis(quaternary) by reaction e.g. of 1-aminopyridinium cation with a pyrylium cation, such bis(cationic) species have been made by quaternizations. Scheme 27 gives examples of the production of both mono- and di-cationic species by quaternization.

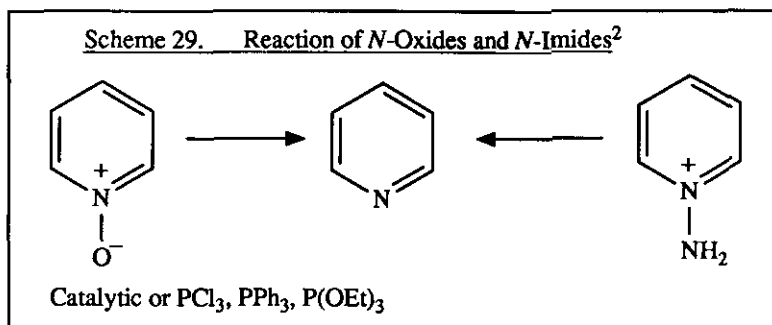


6. Nucleophilic Attack on *N*-Oxides and *N*-Imides and their Conjugate Acids

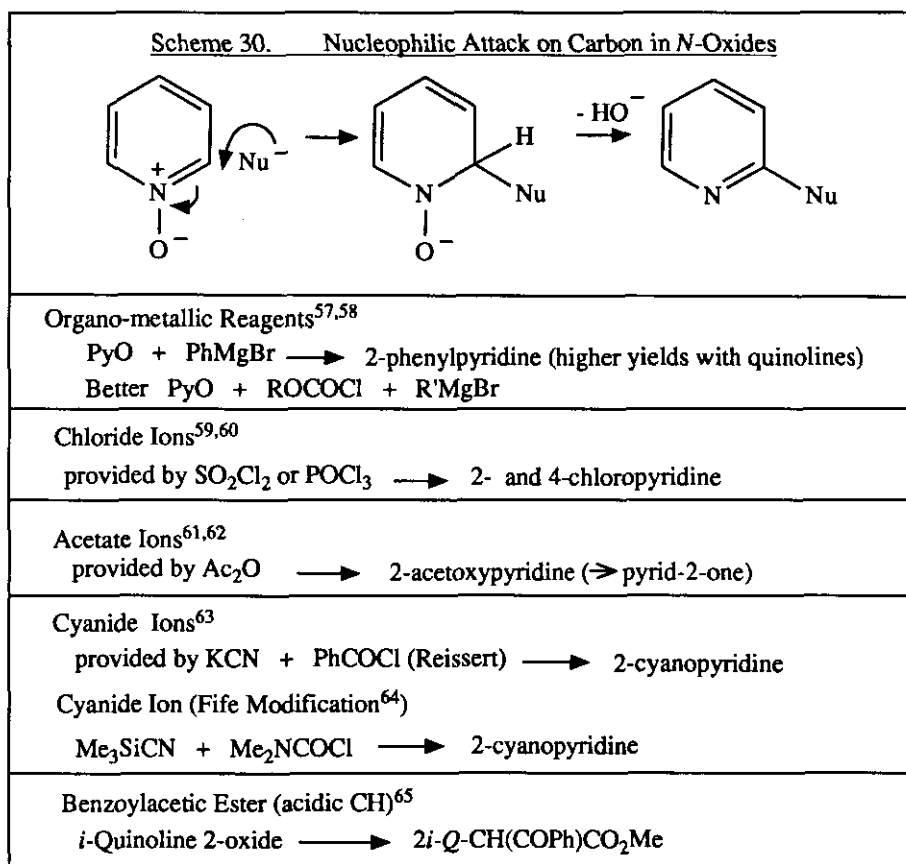
The pattern for nucleophilic attack on these species is shown in Scheme 28. There are three major possibilities. Attack at the exocyclic atom attached to nitrogen results in conversion into the neutral heterocycle, e.g. pyridine. Secondly, there is the possibility of attack at a ring carbon followed by an elimination reaction which can occur in *N*-oxide and *N*-imide derivatives quite easily, but much less readily in cases where X is a carbon atom. Finally, we have the possibility of attack on ring carbon followed by ring opening. The ring opened intermediate can be stable or can undergo numerous other reactions.

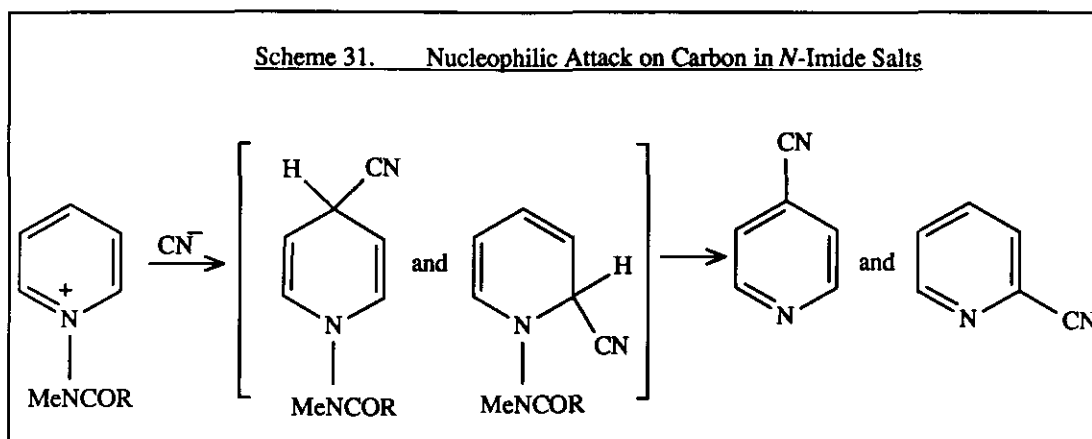


N-Oxides and *N*-imides are readily reduced. Examples of conditions used are illustrated in Scheme 29.

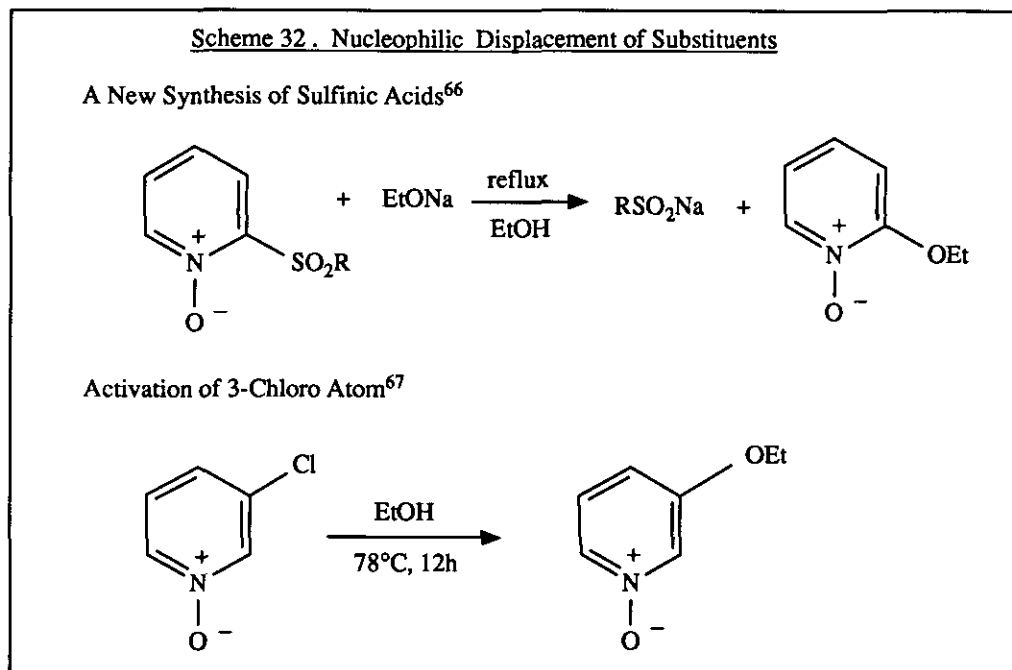


In Scheme 30, we see some examples of nucleophilic attack at the ring carbon atom of *N*-oxides. An example of a corresponding reaction in an *N*-imide derivative is shown in Scheme 31.

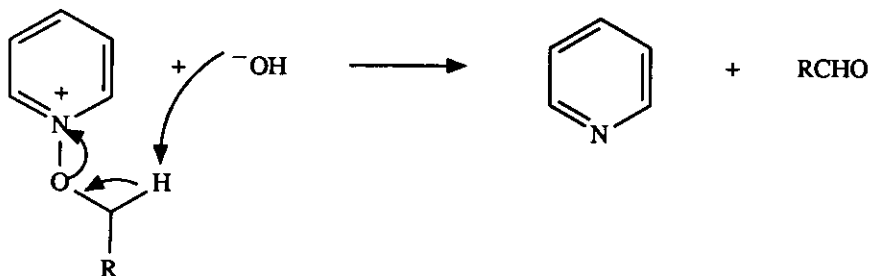
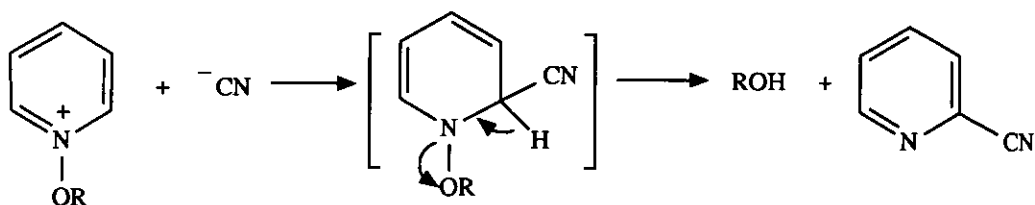
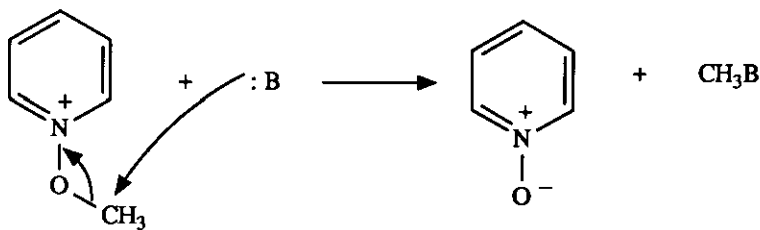




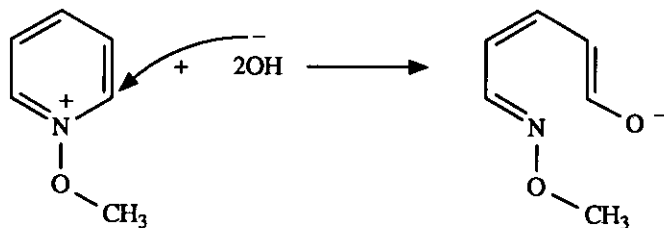
Nucleophilic displacement of leaving groups is easier in *N*-oxides as compared to the corresponding parent heterocycles: two examples are given in Scheme 32.



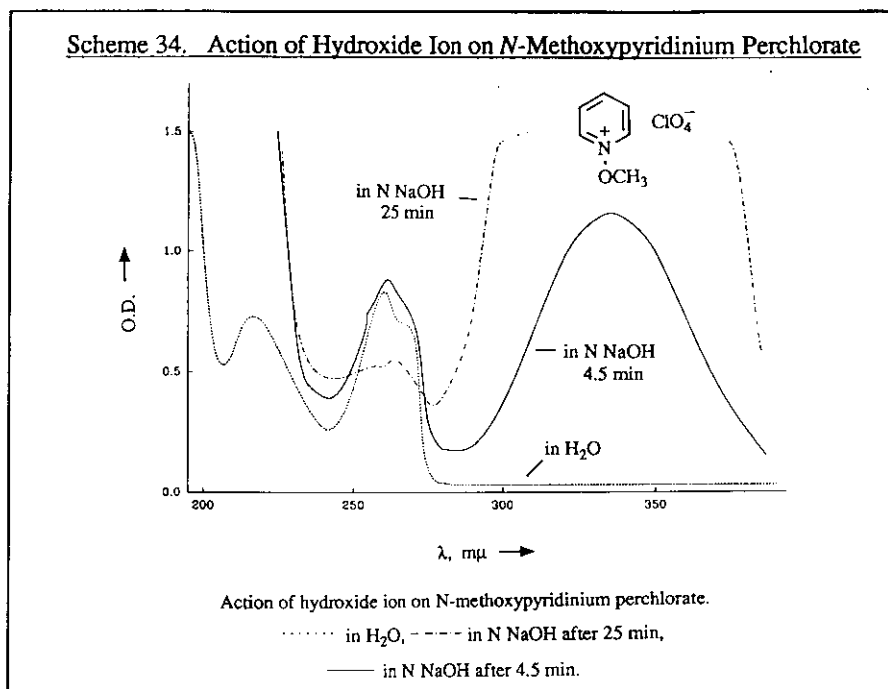
Four modes of reaction for *N*-alkoxy-pyridinium cation with nucleophiles were recognized in 1965 (Scheme 33),⁶⁸ and many further reactions were thus classified.⁶⁹

Scheme 33. Four Modes of Reaction of *N*-Alkoxyppyridinium SaltsPath A: Abstracting a Proton (e.g. by OH⁻, OR⁻):Path B: Nucleophilic Substitution (e.g. by CN⁻ or an organometallic):Path C: Nucleophilic Displacement (e.g. by PhS⁻):

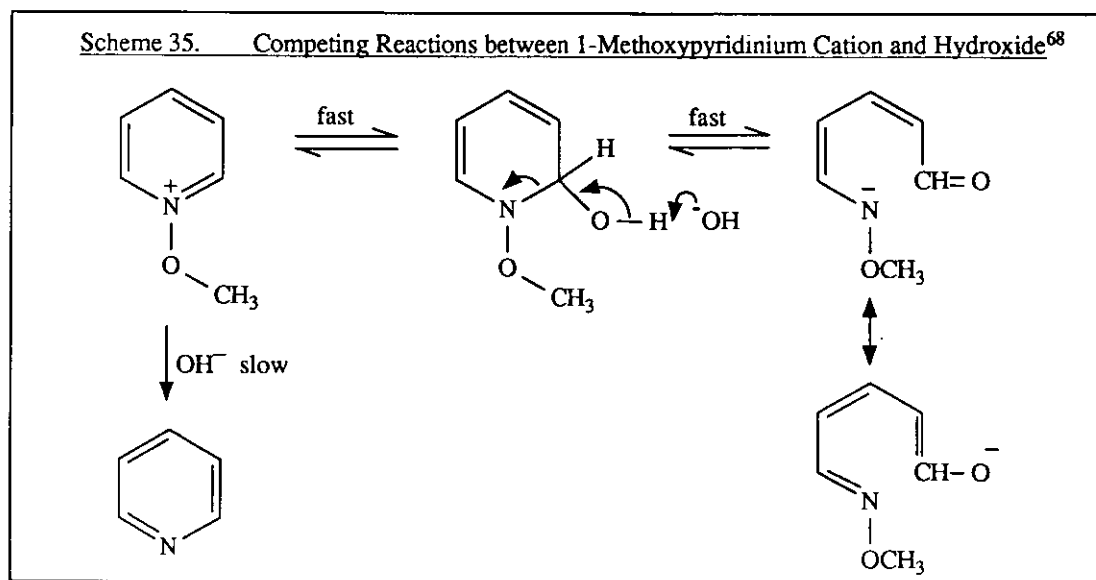
Path D: Nucleophilic Addition, then Ring Opening:



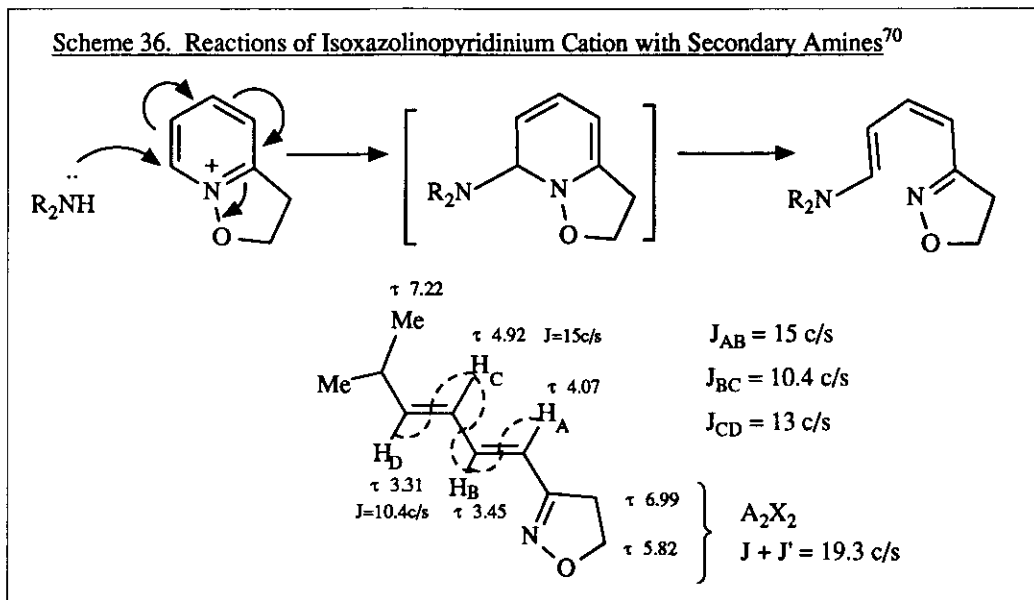
Scheme 34 shows the interesting changes in the ultraviolet spectrum with time which occur when hydroxide ion is added to a solution of 1-methoxypyridinium cation. The overall reaction is simple decomposition to formaldehyde and pyridine, but clearly some other species with a strong absorption near 340 m μ is produced.⁶⁸



The explanation of the uv spectrum of Scheme 34 is a reversible ring opening as shown in Scheme 35.

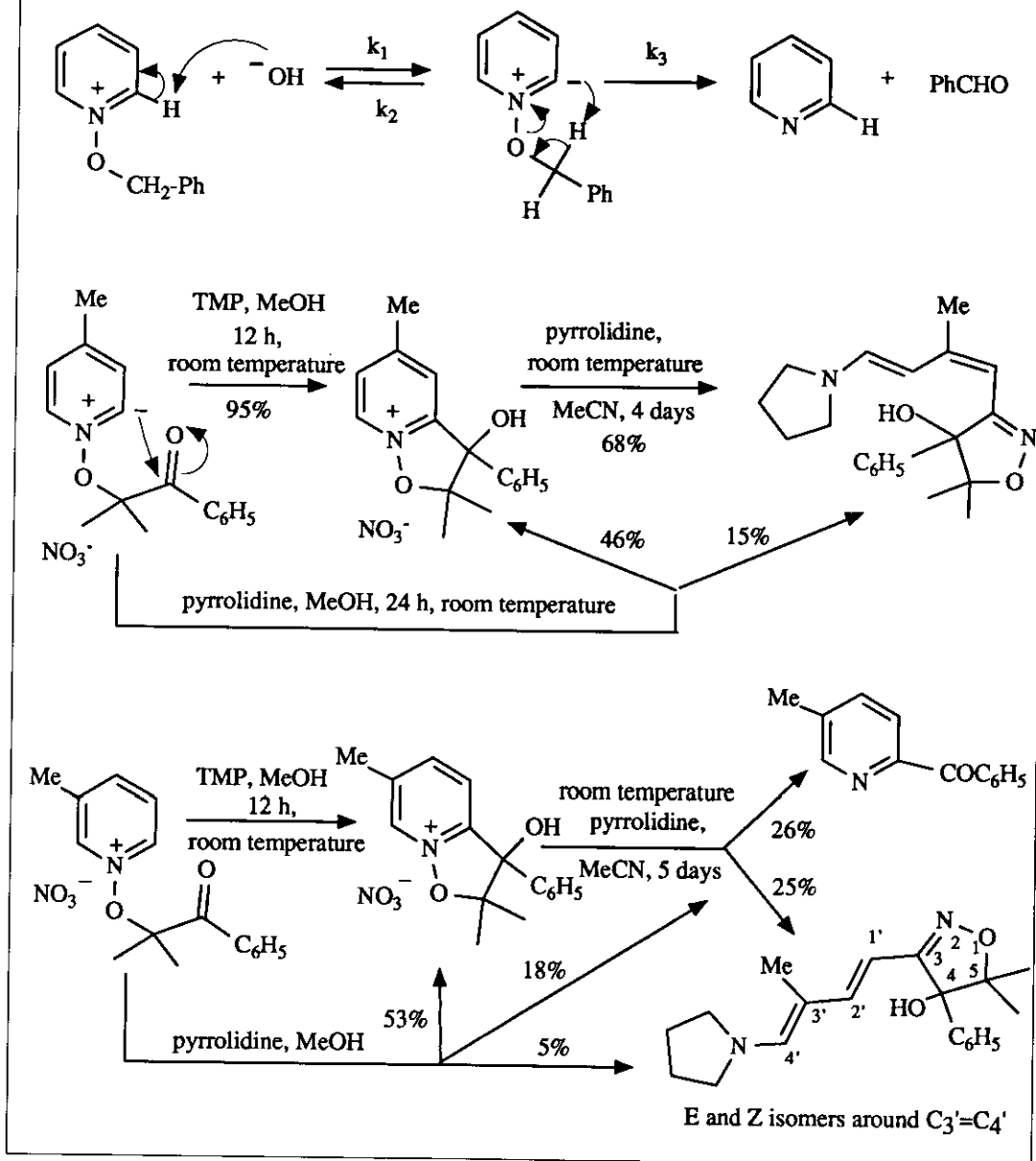


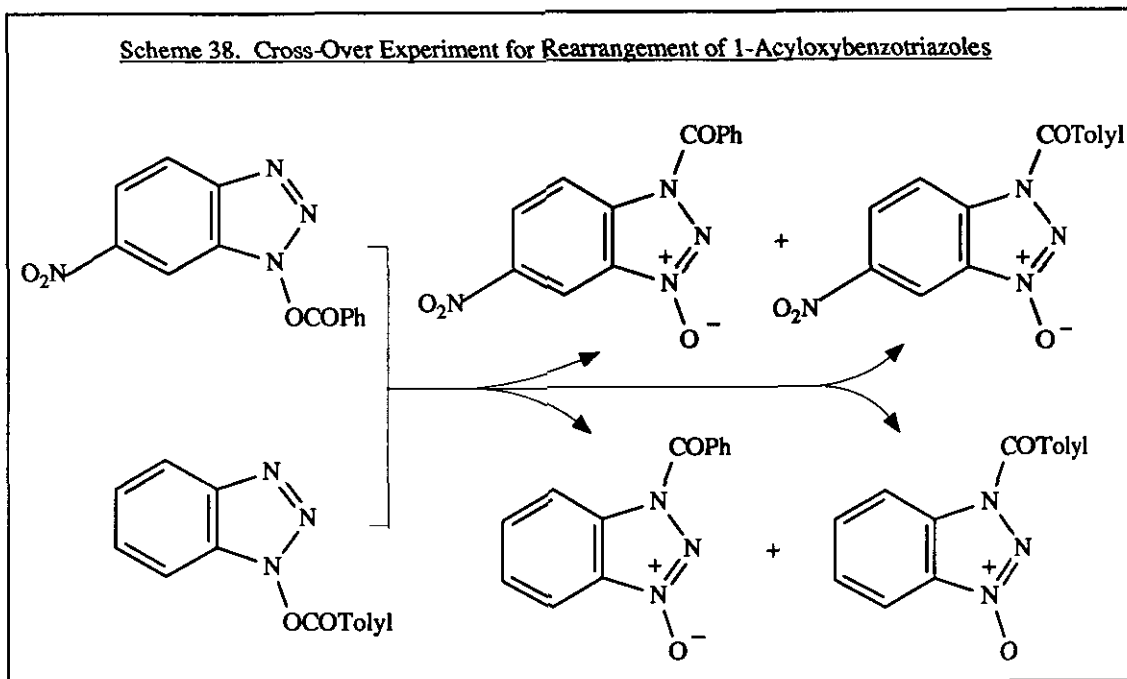
The isoxazoline pyridinium cation reacts with secondary amines to give stable ring-opened products⁷⁰ (Scheme 36) and many further extensions of this type of reaction have been reported by Sliwa [eg. ref.71].



There are additional modes for the reaction of *N*-alkoxy pyridinium salts which involve proton loss at the 2-position of the pyridine ring, followed by simple⁷² or complex⁷³ reactions (Scheme 37).

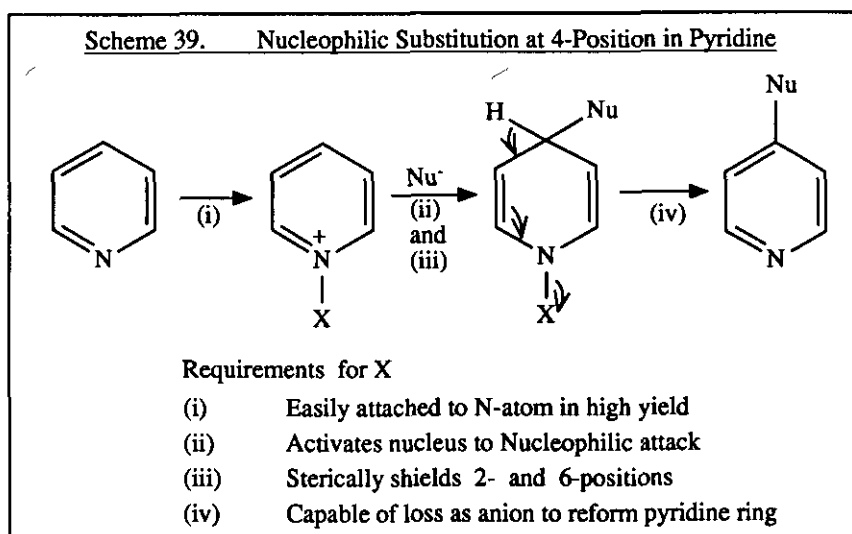
Acyl derivatives of 1-hydroxybenzotriazole have been widely used in peptide synthesis: the 1-hydroxybenzotriazole anion is a good leaving group. There has been considerable uncertainty regarding the structure of these compounds: we have recently shown⁷⁴ that *O*-acyl derivatives are initially formed and rearrange, (in a processes shown to be intermolecular by a crossover experiment), into the *N*-acyl compounds (Scheme 38).

Scheme 37. 2 Additional Modes of Reaction of *N*-Alkoxy pyridinium Salts^{72,73}

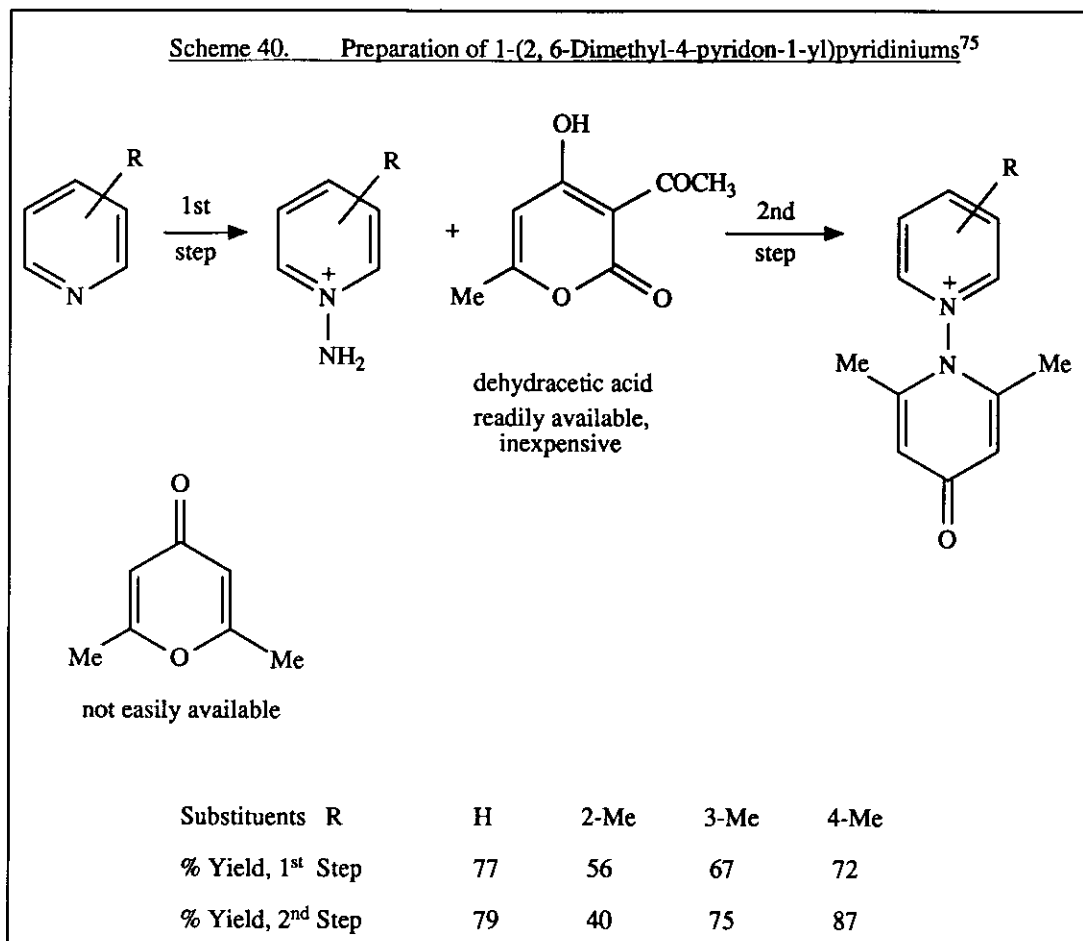


7. Regio Specific Nucleophilic Substitution at the 4-Position of Pyridine

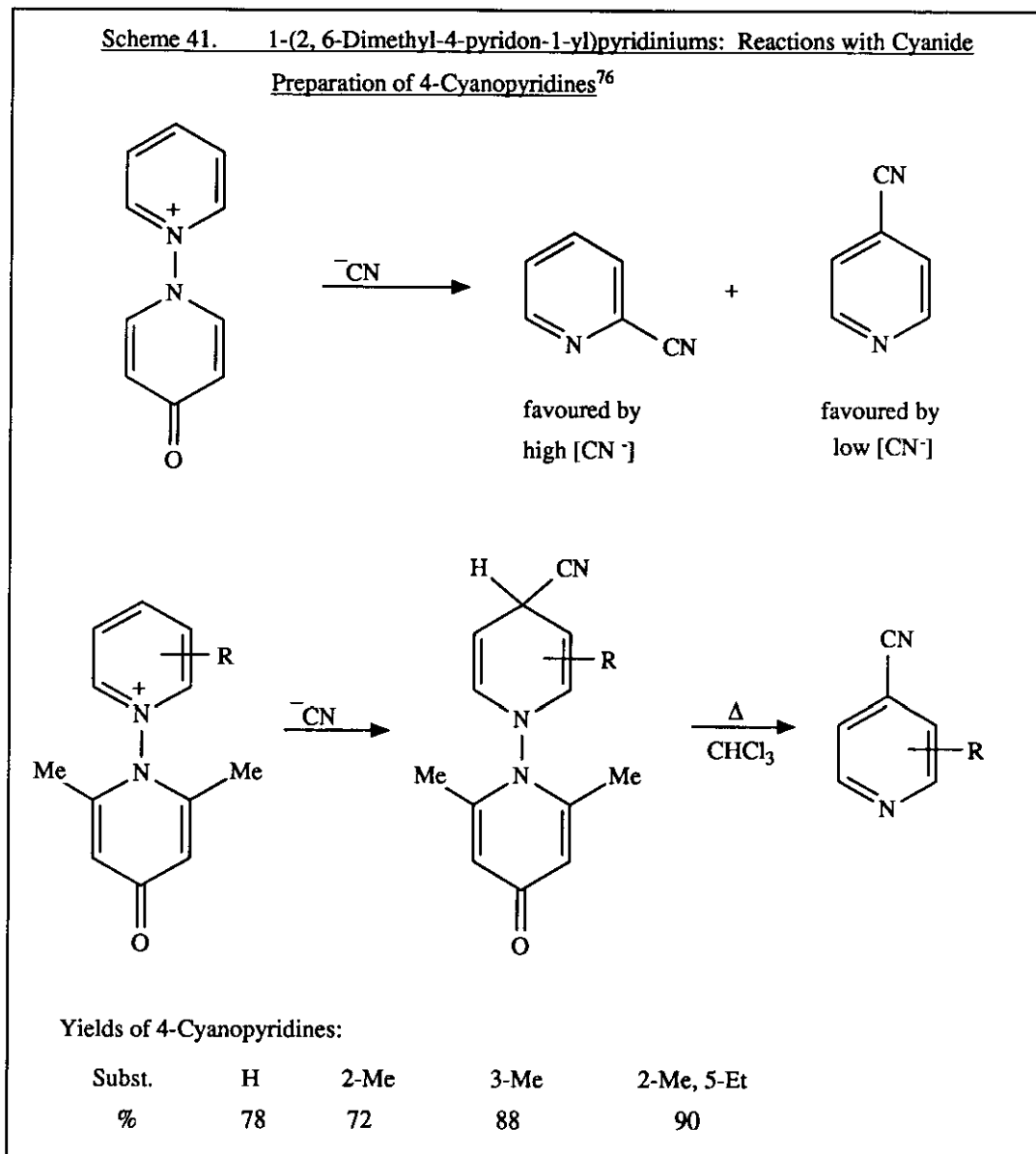
The differentiation between nucleophilic attack at the 2- and 4-positions in a pyridine ring is normally difficult and such reactions frequently lead to mixtures of products, or to exclusively 2-position substitution. One set of conditions for getting regioselective substitution at the 4-position is shown in Scheme 39.



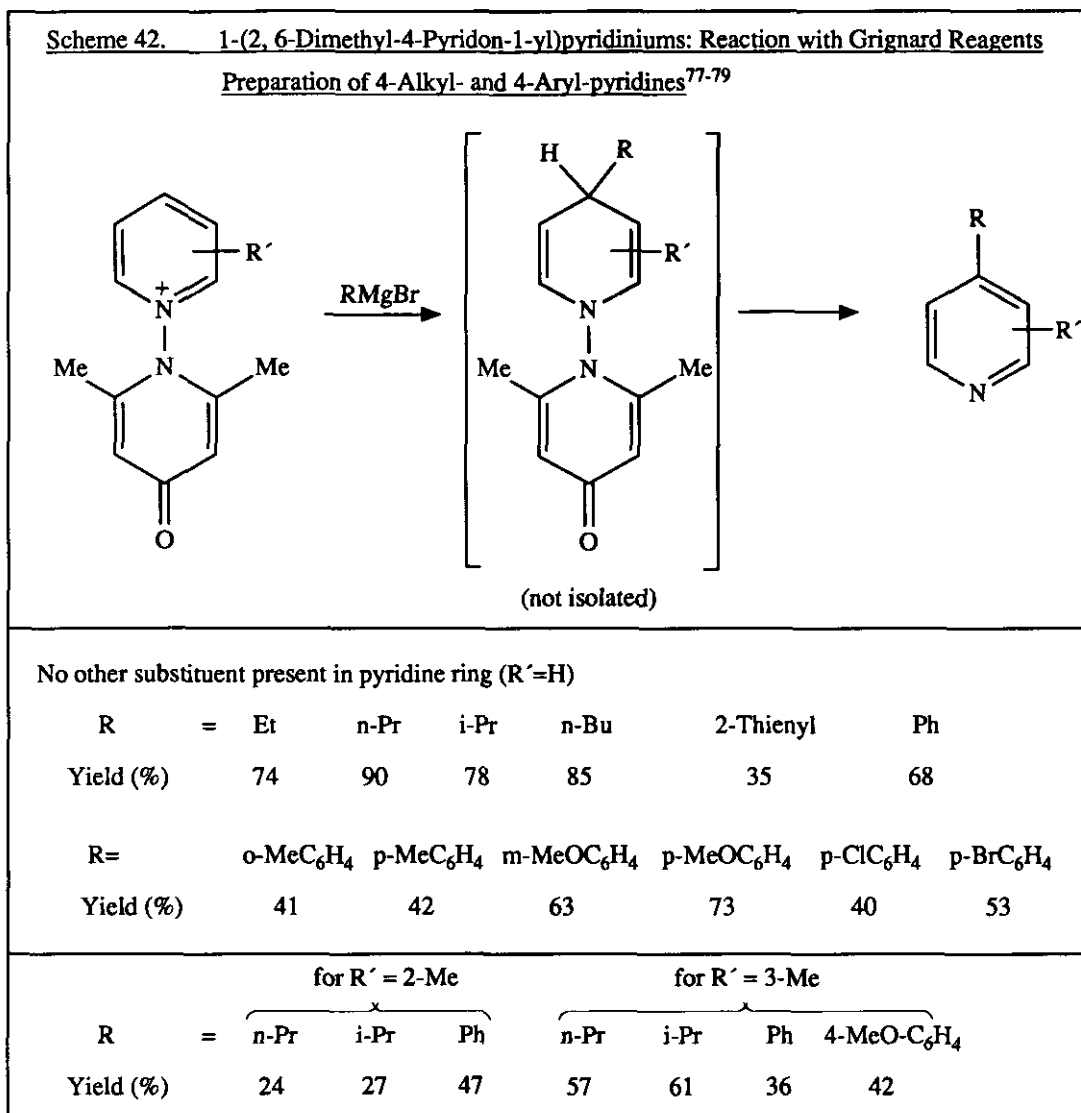
A substituent that satisfies the conditions of Scheme 33 is the 2,6-dimethyl-4-pyridon-1-yl group. It can be attached to the nitrogen atom of a pyridine in two simple stages, as shown in Scheme 40.



The 1-(2,6-dimethyl-4-pyridon-1-yl)pyridinium compounds of Scheme 40 give the 4-cyanopyridine as the only products isolated on reaction with cyanide - see Scheme 41. The 2,6-dimethyl groups are essential as the corresponding compounds without methyl groups on reaction with cyanide give mixtures of 2-cyano- and 4-cyanopyridines in proportions which depend on the cyanide ion concentration.

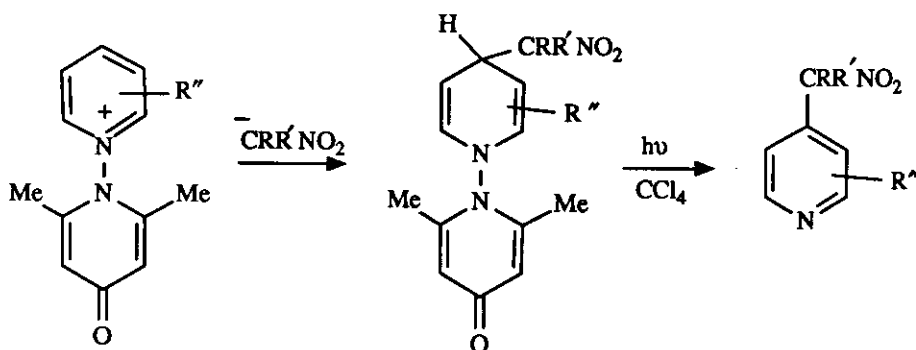


Synthetically useful transformations of this type have been extended to a wide range of nucleophiles. This is illustrated for reactions with Grignard reagents^{77,79} in Scheme 42, with nitroalkane cations^{77,80} in Scheme 43, and with ketone enolate anions^{77,81} in Scheme 44.



Scheme 43. 1-(2,6-Dimethyl-4-pyridon-1-yl)pyridiniums: Reaction with Nitroalkane Anions

Preparation of 4-(Nitroalkyl)pyridines^{77,80}

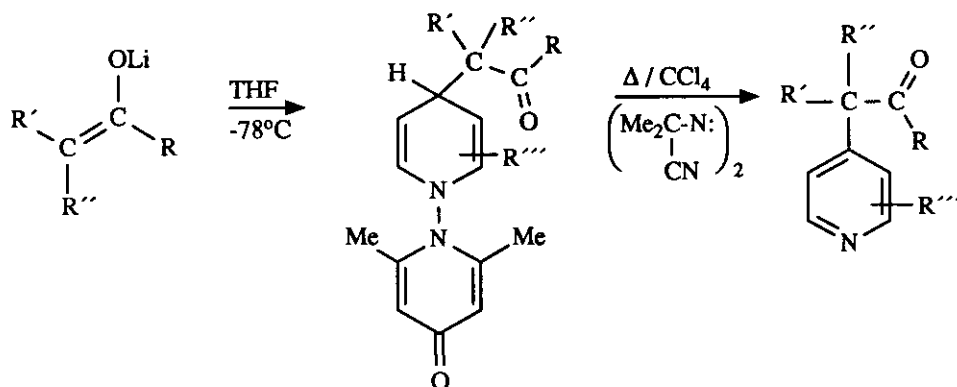


No other substituent present in pyridine ring ($R'' = H$)

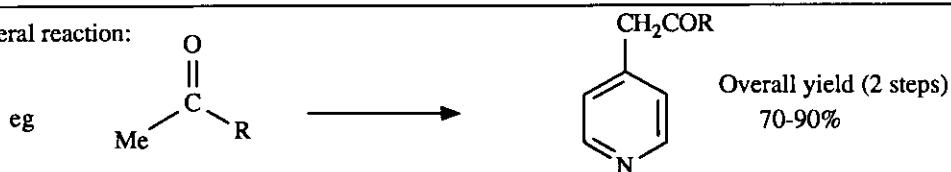
CRR'NO ₂	CH ₂ NO ₂	CHMeNO ₂	CMe ₂ NO ₂	CMe(CH ₂ Ph)NO ₂	CMe(2,4-Cl ₂ C ₆ H ₃ CH ₂)NO ₂	
Yield (%)	intermediate	65	90	92	71	72
	product	-	31	75	52	46

CRR'NO ₂		for R'' = 2-Me CMe ₂ NO ₂	for R'' = 3-Me CMe ₂ NO ₂
Yield (%)	intermediate	52	80
	product	51	55

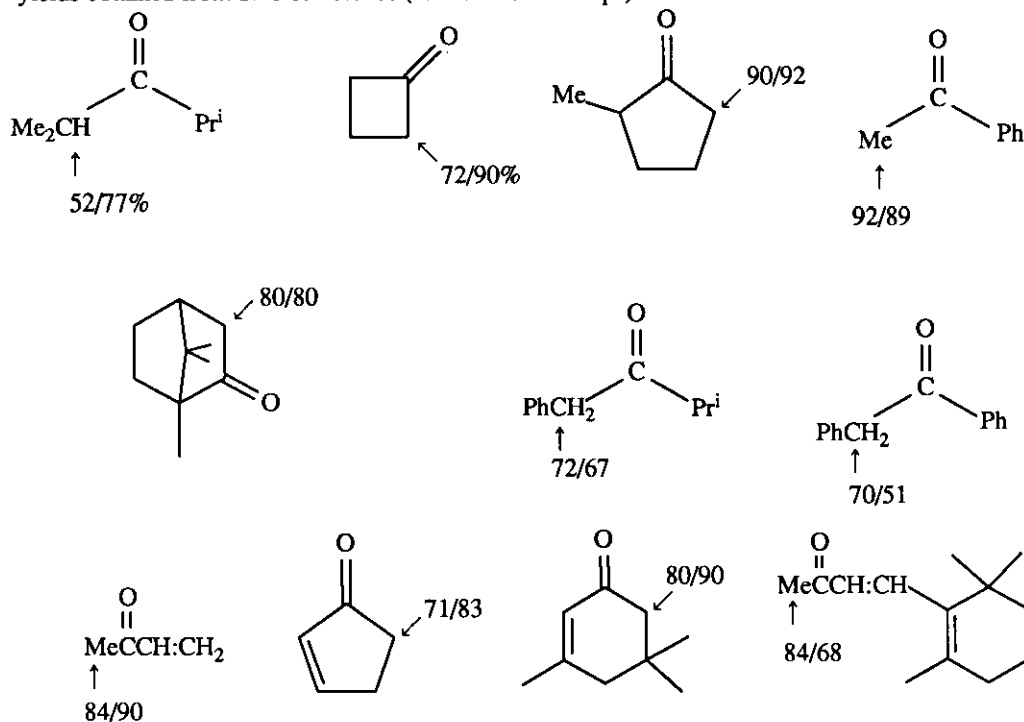
Scheme 44. 1-(2, 6-Dimethyl-4-pyridon-1-yl)pyridiniums: Reaction with Ketone Enolate Anions

Preparation of 4-(α -Acylalkyl)pyridines^{77,81}

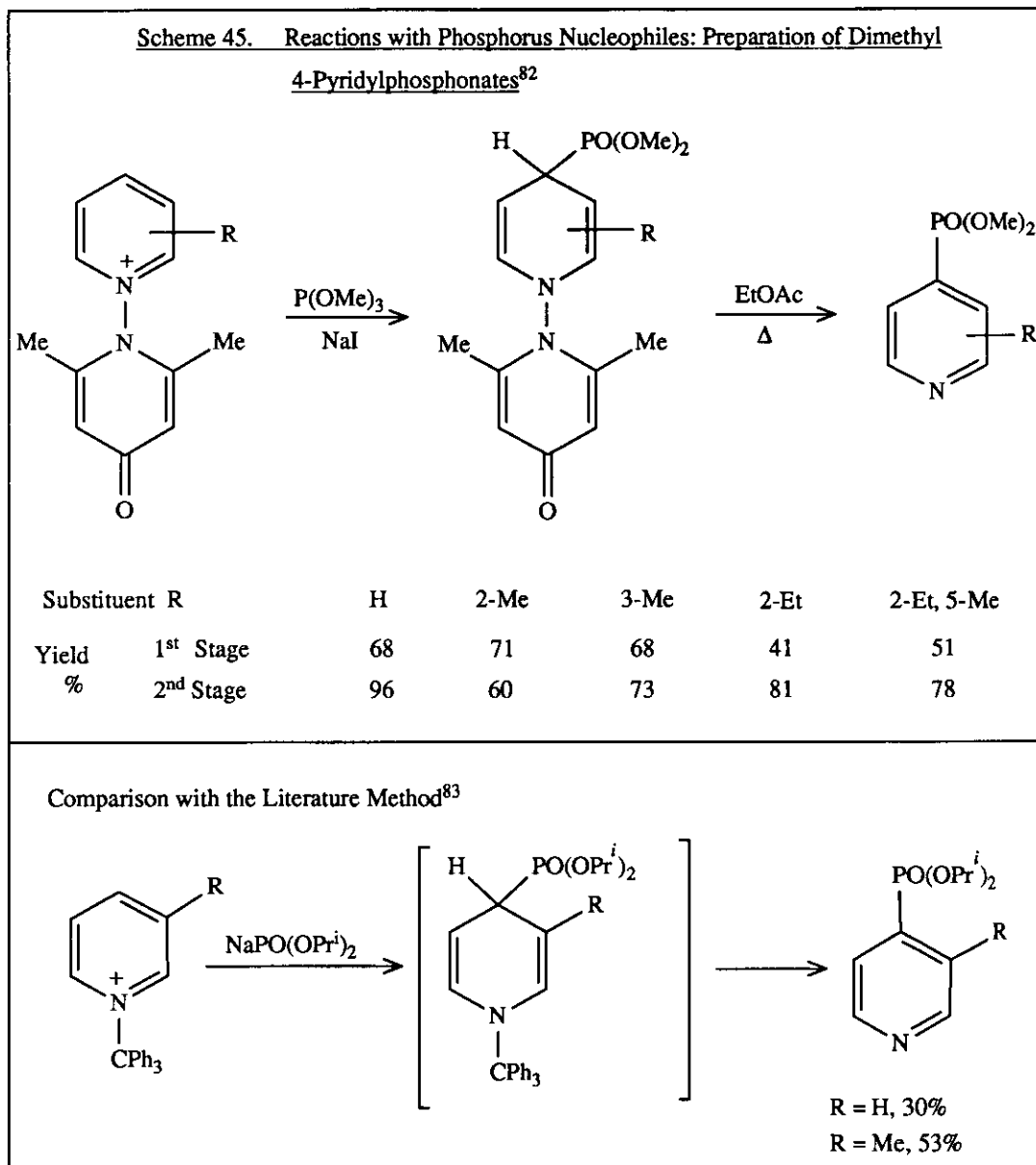
general reaction:



yields obtained from diverse ketones (for 1st and 2nd steps)



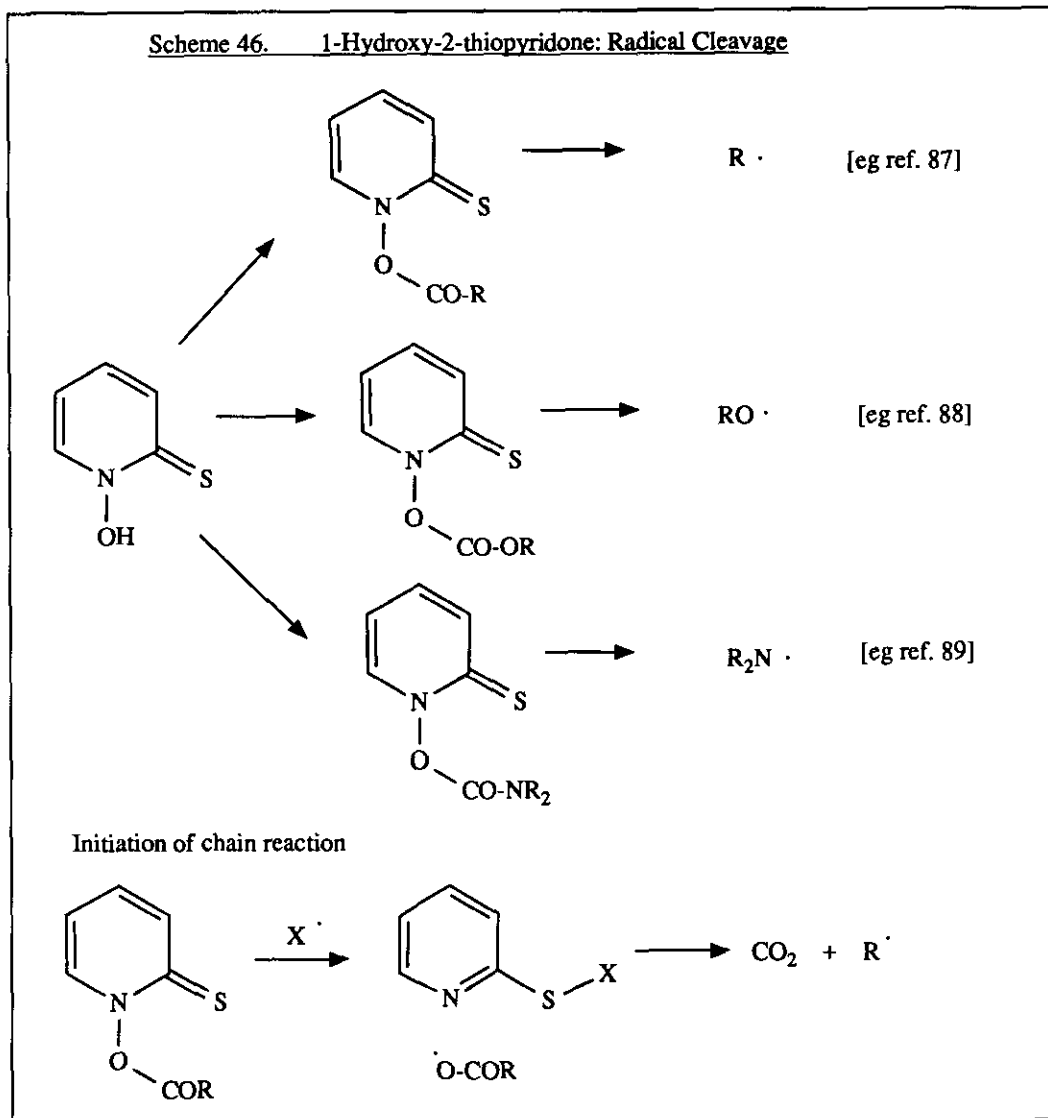
Scheme 45 shows similar work with trimethyl phosphite as a phosphorus nucleophile. It is of interest to compare these results with the corresponding work on 1-tritylpyridinium which was reported earlier and this is done in Scheme 45.



Similar regioselective attacks are also observed by thioalkoxide ions,⁸⁴ by ester and nitrile anions,⁸⁵ and also by carbanions derived from carbon acids⁸⁶ to afford 4-substituted pyridines.

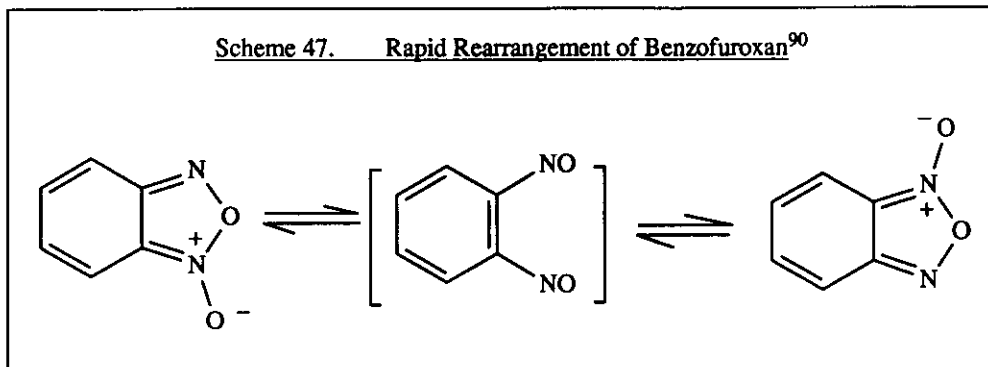
8. Radical Reactions

Any account of *N*-oxide chemistry must mention the great importance of 1-hydroxy-2-thiopyridone (Scheme 46) as a precursor for radicals: leading references are given in the scheme.

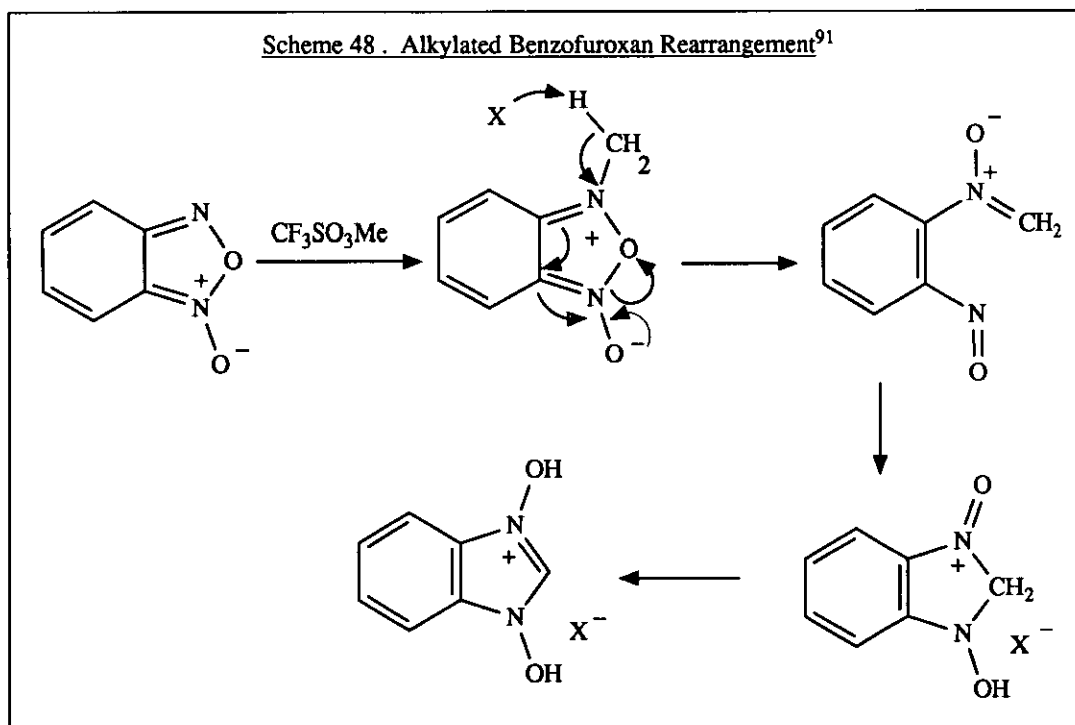


9. Rearrangement reactions

Benzofuroxan has been shown to equilibrate rapidly between the two alternative *N*-oxide structures (Scheme 47).



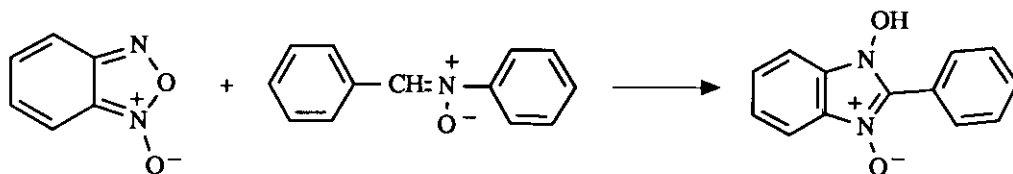
The reaction of benzofuroxan with methyl triflate involves a fascinating rearrangement (Scheme 48).



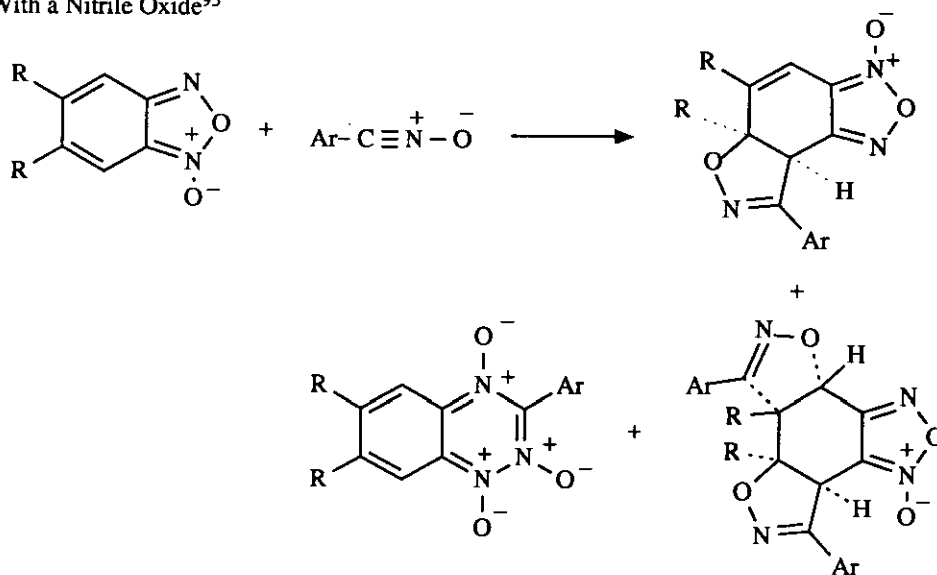
The versatility of benzofuroxan chemistry is illustrated by its totally different reactions with a nitron and a nitrile oxide (Scheme 49).

Scheme 49. Reactions of Benzofuroxans

With a Nitron⁹²



With a Nitrile Oxide⁹³



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