CYANATION IN THE PYRIDINE SERIES: SYNTHETIC APPLICATIONS OF THE REISSERT-HENZE AND RELATED REACTIONS

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Abstract - This review provides an up-to-date summary of the Reissert-Henze reaction, as applied to the cyanation of pyridine derivatives. It highlights recent studies that have established some highly efficient, regioselective methods for the synthesis of 2- and 4-pyridinecarbonitriles.

Contents

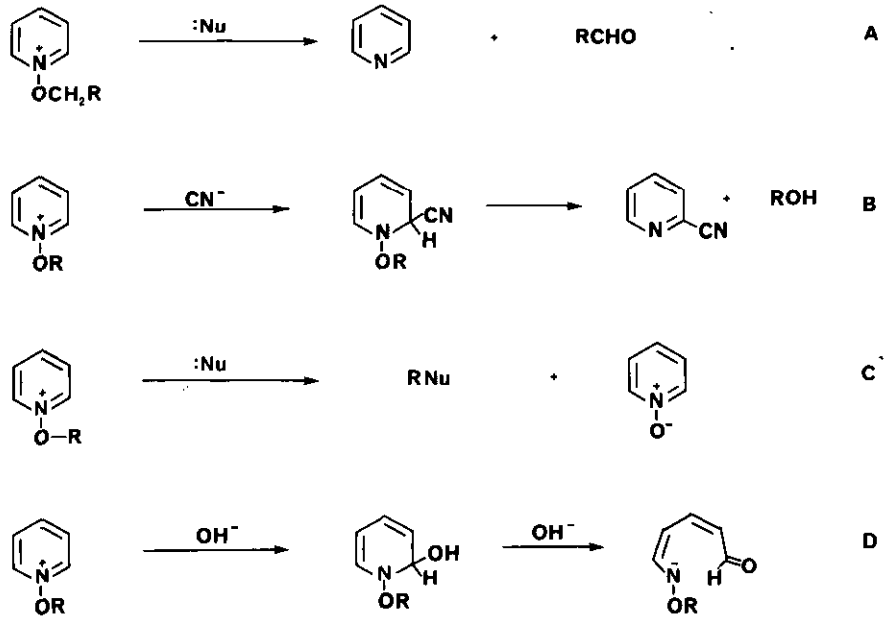
1. INTRODUCTION

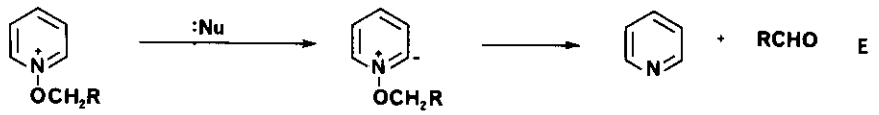
Henze reported[1], that the hydrochloride of quinoline 1-oxide, when treated with benzoyl chloride and potassium cyanide gave 2-quinolinecarbonitrile (Scheme 1).

Scheme 1

Such cyanations of quinoline and isoquinoline N-oxides have become known since as the Reissert-Henze[2] reaction, because they are an extension of the well known Reissert reaction (see 5.2). Unlike the Reissert reaction, which has been the subject of several reviews,[2-8] the Reissert-Henze reaction has not been the exclusive subject of a review. However, some extensions of this important reaction were reviewed in this journal a few years ago.[9] Here, we highlight new developments that extend the synthetic utility of this cyanation to the pyridine series.

First, it is useful to consider the Reissert-Henze reaction in the wider context of the reaction of N-alkoxy- and N-acyloxypyridiniums with nucleophiles. These were classified into four types (Paths A-D) by Katritzky[10]. A further category (Path E) was added subsequently by Abramovitch.[11]





The Reissert-Henze reaction provides an example of Path B. Attack by cyanide, of course, may take place also at C-4. In practice, one or more of the other pathways have been found to compete with cyanation. New ways of suppressing or avoiding such side reactions, and methods that lead to regiospecific α- or γ-cyanation have added greatly to the synthetic versatility of this reaction. The cyanation of N-alkoxy- and N-amino-pyridinium salts is also reviewed. The work is divided according to the nature of the element attached to the pyridine-nitrogen.

2. CYANATION OF N-OXIDES IN THE PRESENCE OF ACYLATING AGENTS

2.1. Under Two-Phase Conditions

Cyanation of pyridine 1-oxides under classical Reissert-Henze conditions[1] (i.e., treatment of the N-oxide and potassium cyanide in a well-stirred mixture of water and chloroform with benzoyl chloride Eq. 1) has proven to be a reaction of very limited synthetic value. The few reported examples of cyanation by this method are given in Table 1; note the exclusive α-orientation, and the beneficial effect of electron-withdrawing substituents on the yield.

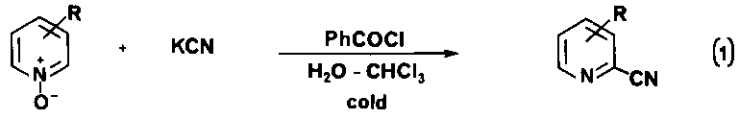


Table 1. Cyanation of Pyridine 1-Oxide with Aqueous Potassium Cyanide-Benzoyl Chloride

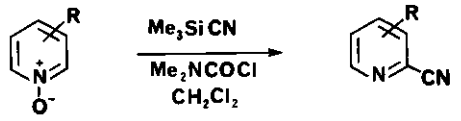
Substituent	% Yield of Isolation Products[a]			Reference
	2-CN	4-CN	6-CN	
H	5	—	—	12, 13
4-Cl	63	—	—	14
2-(2'-Pyridinyl)	—	—	62	15
2-CF_3	—	—	61	16
3-CF_3	17	—	34	16
4-CF_3	71	—	—	16

[a]Cyano compounds were sometimes characterized as the corresponding amide or carboxylic acid.

2.2. Under Non-Aqueous Conditions

2.2.1. In the presence of carbamoylating or benzoylating agents

Fife has recently reported the quantitative conversion of pyridine 1-oxides to 2-pyridinecarbonitriles by treatment of the N-oxide with equivalent amounts of trimethylsilanecarbonitrile and dimethylcarbamoyl chloride in dichloromethane solution (Eq. 2).[17] This new modification of the Reissert-Henze reaction provides experimentally easy access to a wide variety of substituted 2-pyridinecarbonitriles (Table 2).



(2)

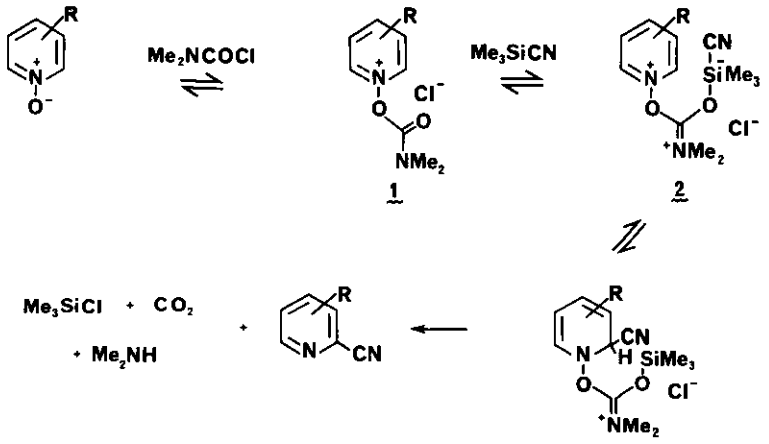
α-Cyanation predominates, unless both α-positions are blocked (Table 2), and no evidence was found for γ-cyanation under the conditions used. The effect of a 3-substituent in the N-oxide upon the orientation of cyanation is interesting. Methyl, methoxy, chloro, and hydroxy groups, attached at the 3-position of the starting N-oxide, direct cyanation predominantly, or exclusively (3-OH), to C-2. On the other hand, N-oxides bearing strongly electron-withdrawing groups (3-CO_2Me and 3-CN) undergo 2- and 6-cyanation with about equal facility.

Table 2. Cyanation of Pyridine 1-Oxides with Trimethylsilanecarbonitrile and Dimethylcarbamoyl Chloride[a]

Substituent	Position of Cyanation, %			% Yield
	2-CN	4-CN	6-CN	
H	100	—	—	94
2-Me	—	—	100	90
3-Me	90	—	10	95
4-Me	100	—	—	90
2,6-Me_2	—	—	—	0
2-MeO[13]	—	—	100	90
3-MeO	98	—	2	87
2-Cl[13]	—	—	100	90
3-Cl	89	—	11	90
3-OH	100	—	—	86
3-CO_2Me	40	—	60	70
3-CN	55	—	45	82

[a]See reference 17 unless otherwise noted.

The success of this new modification of the Reissert-Henze reaction may be attributed to several factors. The use of a non-aqueous, non-nucleophilic solvent eliminates potential competing reactions such as solvolysis of the acyl chloride, ring attack by water, and ring-opening processes (Path D). Trimethylsilanecarbonitrile represents an excellent source of cyanide ion because of its high solubility in organic solvents and its relative inertness to acyl chlorides.[17] Its particular effectiveness in cyanation may be attributable in part to a unique interaction with the acyloxypyridinium intermediate, 1 (Scheme 2). Intermediates such as 2 that include a trigonal bipyramidal silicon have been proposed by Corriu for a



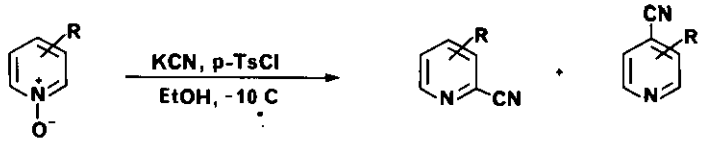
Scheme 2

number of reactions of silicon reagents.[18] Postulation of this type of intermediate provides an explanation for the high regioselectivity of the reaction. The selectivity is also accommodated by an irreversible deprotonation step via 3.

Benzoyl chloride has been shown to be clearly inferior to dimethylcarbamoyl chloride in effecting cyanation of pyridine 1-oxides by trimethylsilanecarbonitrile.[17] Although quantitative conversion of the N-oxide to the corresponding 2-pyridinecarbonitrile is possible with excess trimethylsilanecarbonitrile (5-fold) and benzoyl chloride (2-fold), yields of cyanation product are only 30-40% when equimolar quantities of all reagents are used. This difference is ascribed to a competing pathway involving intermediate 4 that leads to benzoyl cyanide by cyanide attack at the N-acyloxy carbonyl group. The more ketone-like carbonyl group of 4 is expected to be more susceptible to nucleophilic attack than the corresponding carbonyl group in 2.

2.2.2. In the presence of sulfonylating agents

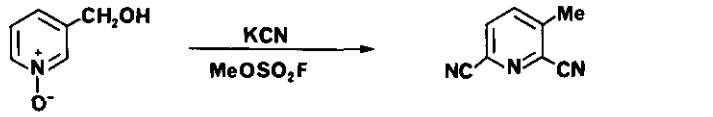
Cyanations of some pyridine 1-oxides in the presence of p-toluenesulfonyl chloride have been less successful than those described in the last section (Eq. 3).[19] However, treatment of quinoline 1-oxides with potassium cyanide and p-toluenesulfonyl chloride leads to some fascinating rearrangements.[9]



(3)

R =	H	4-Cl	4-NO_2
	18%	27	0
	trace	-	-

Warawa[20] has described the novel 2,6-dicyanation of 3-(hydroxymethyl)pyridine 1-oxide with potassium cyanide and methyl fluorosulfonate (Eq. 4). This reaction is restricted to pyridine 1-oxides bearing 3-substituents that can form an anhydrobase during the course of reaction.

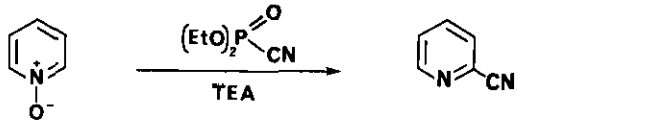


(4)

33%

2.2.3. In the presence of phosphorus agents

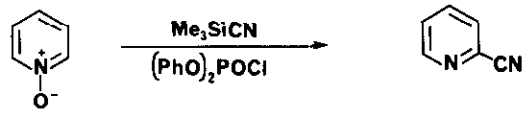
Shioiri and coworkers[21] have reported the cyanation of a series of N-oxides, for example, pyridine 1-oxide (Eq. 5), using diethyl phosphorocyanidate (DEPC).



(5)

24.5%

More recently, Fife[17] has obtained a comparable result with diphenyl phosphorochloridate and trimethylsilanecarbonitrile as reagents (Eq. 6). This suggests the possibility of a common intermediate, 5, in these apparently closely related processes.



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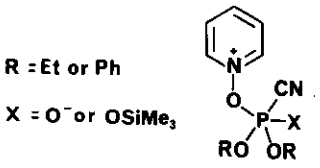

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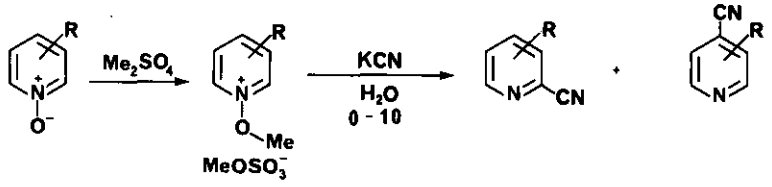
3. CYANATION OF SALTS OF N-OXIDES

3.1. 1-Akoxypyridiniums

The most widely used laboratory method for the preparation of pyridinecarbonitriles has been the cyanation of 1-methoxypyridiniums with potassium cyanide in cold aqueous solution (Scheme 3). This reaction was discovered independently, and at about the same time, by Okamoto and Tani,[22] and Feely and Beavers.[23] Their work has been discussed quite extensively in the major reviews of N-oxide chemistry.[11,24,25]



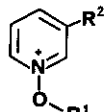
Scheme 3

Despite wide-spread and frequent utilization, the Feely-Beavers/Okamoto-Tani method has certain drawbacks. Yields are often under 50% and are distributed among several products (Paths A - D). Pyridine

1-oxides bearing substituents such as -OH, $-NH_2$ and -COOH that are readily alkylated, of course, undergo multiple alkylation prior to cyanation. Nonetheless, as a result of extensive investigations, Tani and others have demonstrated considerable control over product composition.[11,24,25]

Cyanation at an α-position of 1-alkoxypyridinium ions can be reliably predicted for the 2- and 4- substituted derivatives; i.e. 4-substituted 1-alkoxypyridinium ions cyanate only at the 2-position and the 2-substituted analogues cyanate predominantly, if not exclusively, at the 6-position. The reactions of 3-substituted 1-alkoxypyridiniums present a more complex situation. Cyanation can occur at the 2-, 4-, or 6-position, with or without hydrolysis of the pyridinecarbonitrile so formed (Table 3, also see references 11, 24, 25, 31).

Ferles and Jankovsky[26-28] have carefully investigated the influence of substituent size on cyanation



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product distribution in a series of 1-alkoxy-3-alkylpyridiniums, 6 (Table 3). There is progressive enhancement of cyanation in the 4-position at the expense of the 2-position as the steric demands of 1- and 3-substituents increase. Predictably, the 6-position remains relatively insensitive to these changes.

The employment of N-t-alkoxypyridiniums in cyanations, in order to avoid proton-loss and side-reaction by Path A, is limited by the difficulty in making such salts. Sliwa and Tartar[33] have overcome this problem by using activated halides (e.g. α-halo-acids and esters) to form alkoxyquaternaries which then are cyanated. In the example below (Eq. 7), 2-pyridinecarbonitrile was the main product, and no pyridine (the Path A product) was detected.

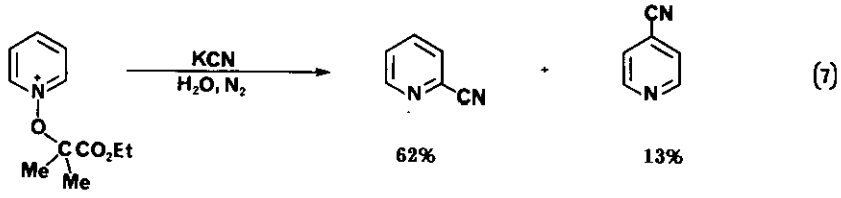

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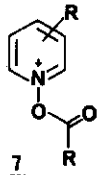
Table 3. Cyanation of 1-Alkoxy-3-alkylpyridiniums

Substituents		Conditions[a]	% Yield of Isolated Products				Reference
1-	3-	Temperature, °C	2-CN	4-CN	6-CN	6-$CONH_2$	
OMe	Me	-5 to 0°	36	6	6	-	23
OMe	Me	-5 to +1°	19	7.6	2	13	26
OMe	Et	-5 to +1°	-[d]	38	-[d]	12.8	26
OMe	Et	r.t.[b]	-[e]	36	-[e]	-	32
OMe	Bu-i	-5 to +1°	44	41	-	15	27
OMe	CH_2COOEt	23 to 25°[c]	-[d]	36	-[d]	-	29
OEt	Me	-5 to +1°	23	40	4.4	17.5	26
OEt	Me	50°	-[d]	60	-[d]	-	30
OEt	Et	-5 to +1°	-[d]	47	-[d]	12.5	26
OEt	Pr-i	-5 to +1°	-[d]	38.2	-[d]	24.8	26
OEt	Bu-i	0°	30	55	-	15	27
OPr-n	Me	-5 to +1°	7.9	35.5	14.0	10.5	26
OPr-n	Et	-5 to +1°	-[d]	43.5	-[d]	10	26
OPr-n	Bu-n	5°	-[f]	40	-[f]	-	28
OPr-n	Bu-i	0°	24	61	-	15	27
OPr-i	Me	-5 to +1°	3.9	57.6	10.5	7.2	26
OBu-n	Me	-5 to +1°	0	25.4	9.0	10.4	26
OBu-n	Et	-5 to +1°	-[d]	54	-[d]	27	26
OBu-n	Pr-i	-5 to +1°	-[d]	62.4	-[d]	19.5	26
OBu-n	Bu-i	0°	25	60	-	15	27
OPen-i	Me	-5 to +1°	0	51.0	15.5	21	26

[a]Reactions were run in water with iodide salts unless otherwise noted. [b]Solvent: Dioxane-water. [c]The methylsulfate salt was used. [d]2-CN and 6-CN yields were not determined. [e]2-CN and 6-CN were not separated, but together represented a product yield of 30%. [f]2-CN and 6-CN were not separated, but chromatographic separation (Al_2O_3) of corresponding acids indicated 10% of each had been formed.

3.2. 1-Acyloxypyridiniums

Although 1-acyloxypyridinium ions of the type 7 have long been presumed to be the reactive intermediate in the few documented examples of cyanation of pyridine 1-oxides in the presence of benzoyl chloride,[14-16] the very recent report of Fife[34] represents the first use of previously prepared and isolated 1-acyloxypyridinium ions for preparation of 2-pyridinecarbonitriles in high yield (Eq. 8).



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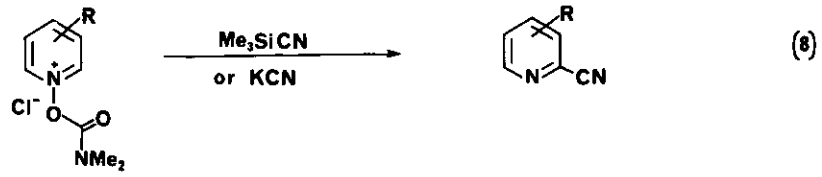

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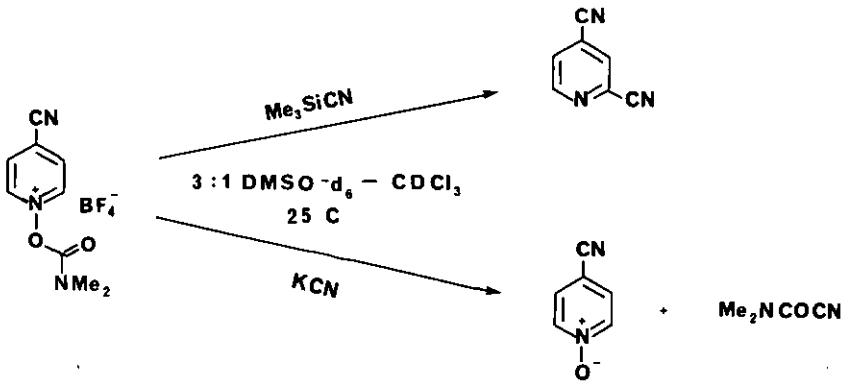
Product mixtures from cyanation of these ions closely resemble those obtained by treatment of the related pyridine 1-oxides with trimethylsilanecarbonitrile and dimethylcarbamoyl chloride (Table 4). Furthermore, rates of cyanation of 1-acyloxypyridinium ions appear to be relatively insensitive to the nature of ring substituents. In contrast, cyanation of the pyridine 1-oxides follows the order expected for ease of acylation: 3-Me = H > 3-$COOCH_3$.[34] Therefore, it seems likely that cyanation of pyridine 1-oxides with trimethylsilanecarbonitrile in the presence of dimethylcarbamoyl chloride proceeds by way of a 1-acyloxypyridinium ion, and there are now two essentially equivalent procedures for preparing substituted 2-pyridinecarbonitriles in high yield under very mild conditions. The particular effectiveness of trimethylsilanecarbonitrile in ring cyanation is demonstrated in its reaction with the 4-cyano derivative to form 2,4-pyridinedicarbonitrile (Table 4, Scheme 4)[13]. In contrast, attempted cyanation with potassium cyanide gave only deacylation products (Path C).[13]



Scheme 4

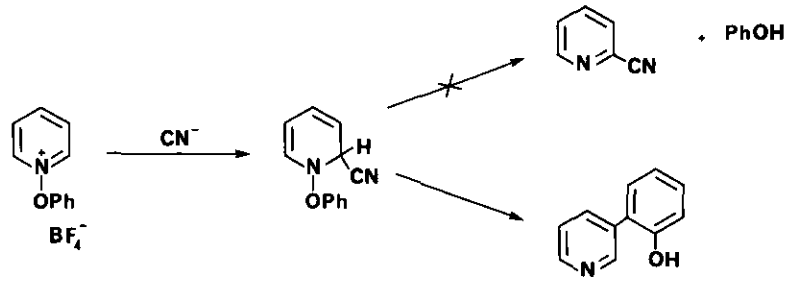
Table 4. Cyanation of 1-Dimethylcarbamoyloxypyridinium Chlorides at Room Temperature[a]

Substituent	Reagent	Solvent	Position of Cyanation, % 2-CN	4-CN	6-CN
H[b]	Me_3SiCN	CH_2Cl_2	100	—	—
	KCN	MeCN	100	—	—
	KCN	H_2O	100	—	—
3-Me[b]	Me_3SiCN	CH_2Cl_2	90	—	10
	KCN	MeCN	86	—	14
	KCN	H_2O	89	—	11
3-CO_2Me[b]	Me_3SiCN	CH_2Cl_2	40	trace	60
	KCN	MeCN	48	10	42
	KCN	D_2O	55	2	43
4-Me[c]	Me_3SiCN	CH_2Cl_2	100	—	—
	KCN	MeCN	100	—	—
	KCN	H_2O	100	—	—
4-Ph[c]	Me_3SiCN	CH_2Cl_2	100	—	—
	KCN	MeCN	100	—	—
	KCN	H_2O	100	—	—
4-CN[c]	Me_3SiCN	DMSO-d_6:$CDCl_3$(3:1)	100	—	—
	KCN	DMSO-d_6:$CDCl_3$	—[d]	—[d]	—[d]

[a]Yields of isolated cyano-products usually exceed 90%. [b]See reference 34. [c]W. K. Fife, unpublished work. [d]Pyridinecarbonitrile 1-oxide formed (Path C).

3.3. 1-Aryloxypyridiniums

In view of the utility of 1-alkoxy- and 1-acyloxy-pyridiniums in the synthesis of pyridinecarbonitriles, it is somewhat surprising that 1-aryloxypyridinium ions do not form cyano products when treated with cyanide ion.[35] Instead, after initial attack by cyanide at C-2, a 3,5-sigmatropic rearrangement takes place (Scheme 5), rather than elimination (Path B).



Scheme 5

3.4. 1-Silyloxypridiniums

The recently reported method of Vorbrüggen and Krolikiewicz[36] for cyanation of pyridine 1-oxides with trimethylsilanecarbonitrile in the presence of triethylamine provides high yields (70% or greater) of the 2-cyano-product when R is H, 3-Me, 4-Me, 3-OH, 3-CN, 5-COOH, and 5-$CONH_2$ (Scheme 6, Table 5).

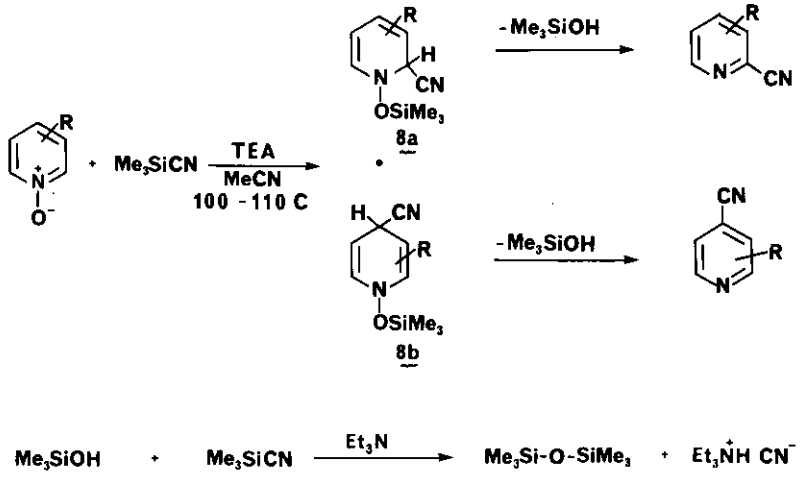
Table 5. Cyanation of Pyridine 1-Oxides with Trimethylsilanecarbonitrile/Triethylamine at 100-110°.[a]

Substituent	Reagents	Reaction Time	% Yield of Isolated Product 2-CN	4-CN	6-CN
H	2.5 eq Me_3SiCN/1.5 NEt_3/ CH_3CN	12 hr	80	< 0.5	0
	3 eq Me_3SiCl/3 eq NaCN/ 4 eq NEt_3/DMF	18 hr	76	1.3	0
2-Me	5 eq Me_3SiCl/4 eq NaCN/ 6 eq NEt_3/DMF	72 hr	41	0	0
3-Me	3 eq Me_3SiCl/3 eq NaCN/ 4 eq NEt_3/DMF	52 hr	40	0	40
4-Me	4 eq Me_3SiCN/2 eq NEt_3/ CH_3CN	20 hr	89	0	0
3-OH	3.5 eq Me_3SiCN/2.5 eq NEt_3/ CH_3CN	8 hr	73	0	0
	4 eq Me_3SiCl/2 eq NaCN/ 5 eq NEt_3/DMF	12 hr	90	0	0
3-CN	3 eq Me_3SiCl/3 eq NaCN/ 4 eq NEt_3/DMF	8 hr	53	0	27
	3 eq Me_3SiCN/4 eq NEt_3/ 0.1 eq $n\text{-}Bu_4N^+F^-$/THF	1 hr/5°C	48	0	18
3-COOH	4 eq Me_3SiCl/3 eq NaCN/ 5 eq NEt_3/DMF	10 hr	0	0	76
3-$CONH_2$	5 eq Me_3SiCl/3 eq NaCN/ 6 eq NEt_3/DMF	12 hr	0	0	70

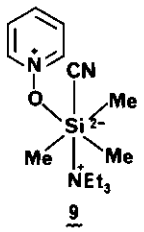
[a]See reference 36.

Unsuccessful efforts by Fife and co-workers[13] to cyanate pyridine 1-oxides with trimethylsilanecarbonitrile in the absence of a base or with transition metal cyanides provide additional evidence for the role of triethylamine in deprotonation of addition intermediates, 8. The requirement of triethylamine to effect reaction also suggests the intervention of an octahedral complex such as 9. This complex enables one to

rationalize the high specificity of the reaction for cyanation at the 2-position and resembles intermediates proposed by Fife[17] for cyanation by Me_3SiCN/Me_2NCOCl as well as those proposed earlier for other reactions of silicon compounds.[18]



Scheme 6



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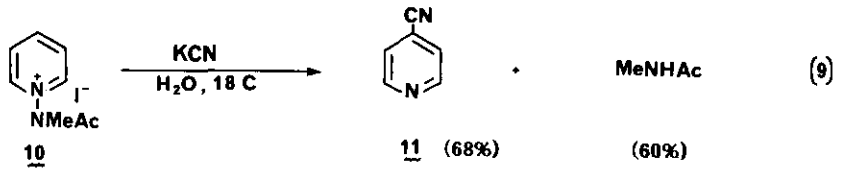
The product distributions, 2,3- vs. 2,5- observed for 3-CN, 3-COOH and $3\text{-}CONH_2$ substituted pyridine 1-oxides (Table 5) provides additional evidence for the involvement of a bulky intermediate. The 3-COOH and $3\text{-}CONH_2$ groups are expected to be silylated quickly under the conditions of the reaction, and hence make substantial steric demands around the 3-position.

4. CYANATION OF N-AMINOPYRIDINIUM SALTS

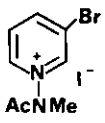
4.1. N-Acetylaminopyridiniums

Okamoto and his school[37] found that the cyanation of N-acetylaminopyridinium salts, 10, takes place at C-4 rather than C-2 as in alkoxy quaternary salts (Eq. 9).

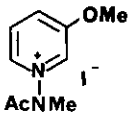


10 — 11 (68%) — (60%)

When methanol is used as the reaction solvent 2-cyanation predominates over 4 - almost two-fold.[38] A little of the 2-cyano-isomer (7%) may be obtained by raising the cyanide excess from 4:1 (Eq. 9) to 13.2:1 over the salt, 10, but the yield of the major product, 11, is raised to 76%. The effect of raising the cyanide excess used is spectacular for the cyanations of the 3-bromo and 3-methoxy salts, 12 and 13 (Table 6).

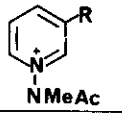


12



13

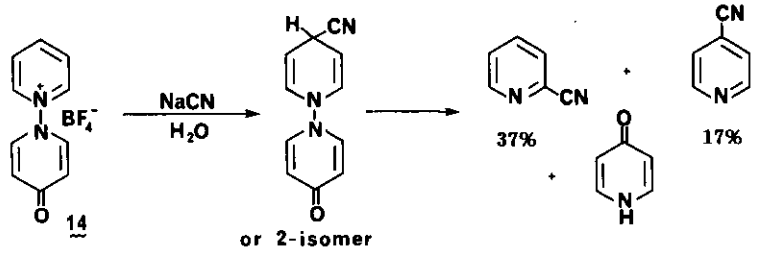
Table 6. Cyanation of N-Acetylaminopyridinium Salts in Aqueous Potassium Cyanide

	Salt/KCN	% Yield of Isolated Product	
		2-CN	4-CN
R = 3-Br	1:1·13	23	69
3-Br	1:5·45	90	trace
3-OMe	1:3	20	60
3-OMe	1:21·25	97	trace

Treatment of the corresponding 3-methyl- and 3-phenyl-pyridinium salts with a large excess of potassium cyanide results in over 90% 4-cyanation in each case. The attachment of an alkyl (or allyl) group, and an electron-withdrawing substituent (e.g. p-nitrophenyl or methylsulfonyl) is required (to facilitate the elimination step) for salts of this type to participate in these reactions.

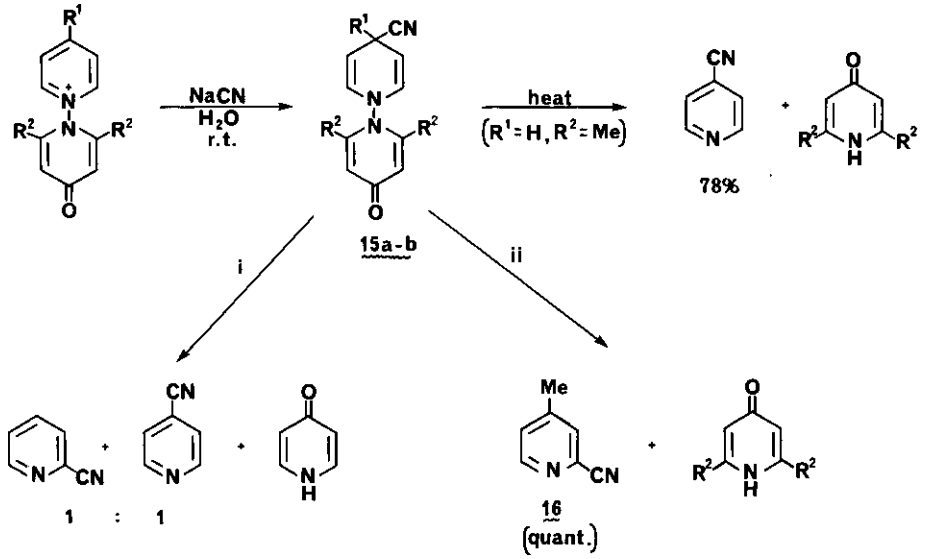
4.2. N-Pyridinio-4-pyridones

Katritzky and coworkers[39] found that N-pyridinio-4-pyridone, 14, unlike Okamoto's salts, undergoes α- and γ- rather than mainly γ-cyanation in the presence of aqueous sodium cyanide (Scheme 7). Reaction was shown to proceed via a 1,4-adduct, and 4-pyridone is formed as a by-product. The 3-methyl analogue of 14 cyanates at the 2-(40%), 4-(13%), and 6-(7%) positions. Although a decrease in the cyanide excess did promote 4- at the expense of 2-cyanation in the series, overall yields fell and synthetically useful selectivity was not achieved.



Scheme 7

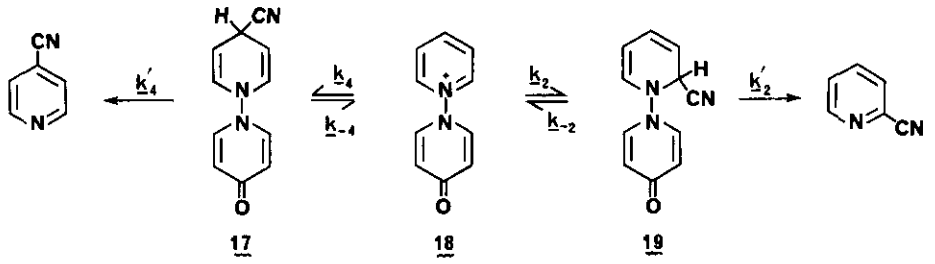
On the other hand, pyridinio-4-pyridone salts, bearing methyl groups at C-2 and C-6 in the pyridone moiety, were found to undergo regiospecific C-4 addition of cyanide in high yield,as C-2 attack was blocked. (Scheme 8). These adducts proved to be remarkably stable compounds as compared to those lacking 2- and 6-methyl groups. Nevertheless, they readily underwent elimination on heating to afford the corresponding 4-pyridinecarbonitriles and 2,6-dimethyl-4-pyridone.



i, excess NaCN aq. on 15a (R^1=R^2=H); ii, excess NaCN aq. on 15b (R^1=R^2=Me)

Scheme 8

The reversibility of 1,4-dihydro-compound formation was demonstrated by stirring either 15a or 15b with sodium cyanide at room temperature. The former gave a 1:1 mixture of 2- and 4-pyridinecarbonitriles, and the latter gave 16. These and the results of other experiments allowed the authors to explain the increase in 2- over 4-cyanation with increase in cyanide ion excess (Scheme 9) by the requirement that $k_2 > k_4$ (kinetically controlled attack at C-2), and that $k_{-4} < k_{-2}$ (intermediate 17 is thermodynamically more stable than intermediate 19).



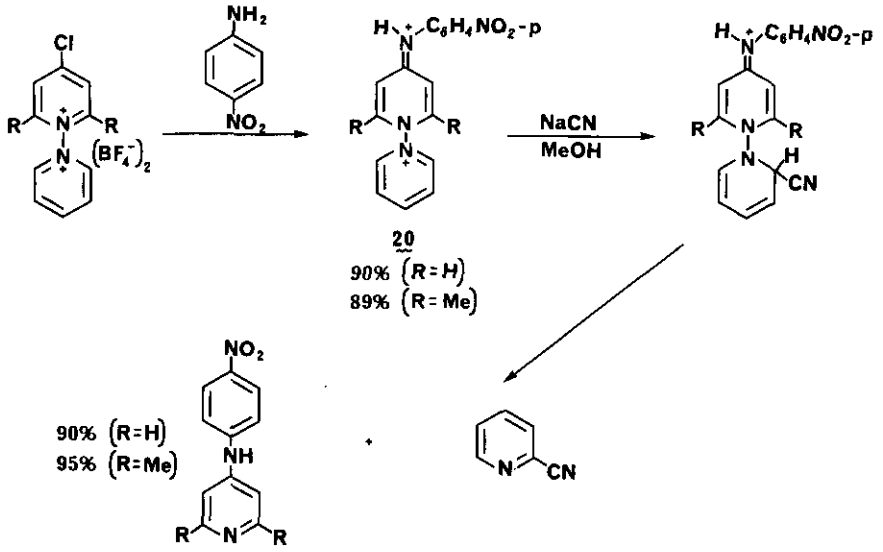
17 18 19

Scheme 9

Therefore, at high cyanide concentrations formation of 19, and elimination are fast; thus formation of 2-pyridinecarbonitriles is favored. At lower cyanide concentration, elimination (k'_2) is slower and equilibration 17 ⇌ 18 ⇌ 19 becomes possible allowing an increase in the rate of production of 4-pyridinecarbonitrile.

4.3. 4-Aryliminiumpyridiniopyridiniums

Recently, the Katritzky-Sammes group has reported an excellent new synthesis of 4-pyridyl(aryl)amines from



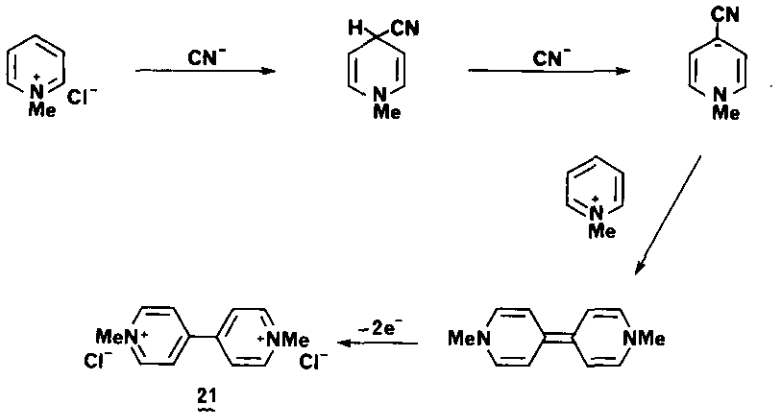
Scheme 10

4-chloro-1-pyridiniopyridinium salts (Scheme 10).[40] Of interest to us here is the nature of the second product, 2-pyridinecarbonitrile, that is formed concomitantly with the 4-pyridyl(aryl)amine. In contrast to the work with pyridiniopyridones (4.2), no 4-pyridinecarbonitrile was formed on treatment of iminium salts of the type 20 with sodium cyanide even when R = Me. This striking difference was tentatively attributed to two factors. Lengthening of the N-N bond in 20, due to the extra positive charge on the salt, would reduce the steric effect of the methyl groups. The higher charge density at the pyridinium α-positions should also favor 2-cyanation.

5. CYANATION OF N-ALKYL AND N-ACYL QUATERNARY SALTS

5.1. Reissert-Kaufmann Reaction

Quite soon after the discovery of the Reissert reaction,[41] Kaufmann and Albertini[42] showed that potassium cyanide adds 1,4- to the 1-methylquinolinium ion. However, as methyl is a poor leaving group forcing conditions were needed for its removal, and pseudobase formation interfered. Consequently, this does not provide a synthetically useful approach to cyano-heterocycles. N-Alkylpyridiniums, bearing an electron-withdrawing 3-substituent, readily undergo 1,4-addition of cyanide, and such processes that are of great biochemical significance have been reviewed elsewhere.[43] The 1,4-addition of cyanide to 1-methylpyridinium chloride has an interesting outcome, leading ultimately to the formation of the herbicide paraquat, 21, (Scheme 11).[44]

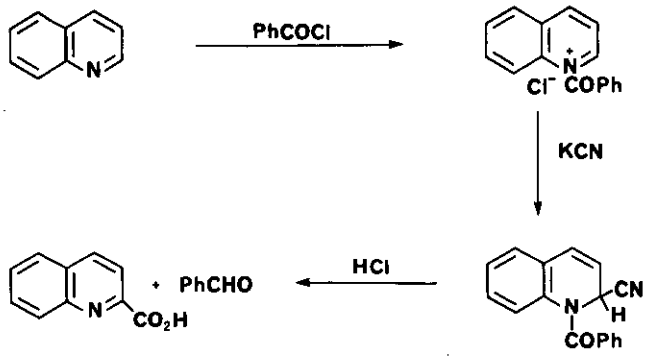


21

Scheme 11

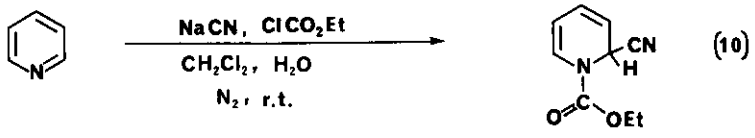
5.2. Reissert Reaction

The Reissert reaction (Scheme 12), discovered in the quinoline series,[41] provides a classical method for the synthesis of aldehydes.[2] Reissert reaction in isoquinolines yields Reissert compounds which are important precursors for alkaloid synthesis.[3-7]



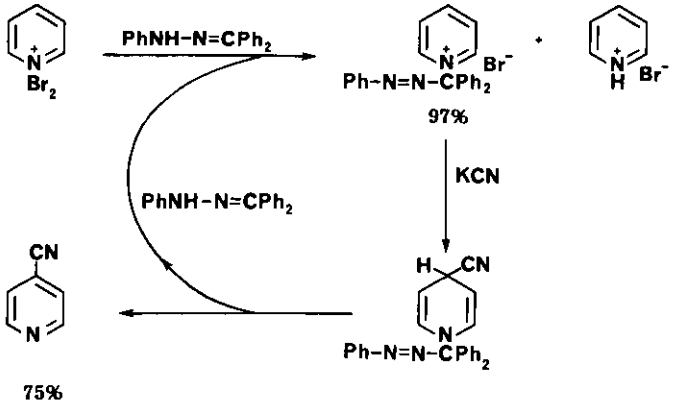
Scheme 12

The Reissert reaction, however, has not proved very useful in the pyridine series. Only one example of Reissert compound formation has been reported to date.[45] (Eq. 10)



(10)

A process for the regiospecific synthesis of 4-pyridinecarbonitrile was described a few years ago (Scheme 13).[46]

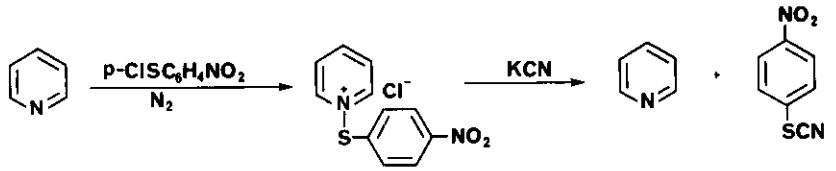


Scheme 13

This procedure illustrates the advantage of having a sufficiently good leaving group on nitrogen to facilitate the elimination step, but one that is not so strongly electron-withdrawing that 2-cyanation is preferred.

6. CYANATION OF N-THIOPYRIDINIUMS

N-Thiopyridinium salts are extremely rare compounds that have been adequately described only recently by Abramovitch and coworkers.[47] Treatment of 22 with potassium cyanide yielded an isothiocyanate (by Path C) rather than a pyridine-ring substituted product (Scheme 14).



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Scheme 14

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