HETEROCYCLES, Vol 22, No. 5, 1984

1-ACYLOXYPYRIDINIUM ION: THE REACTIVE INTERMEDIATE IN A MODIFIED REISSERT-HENZE REACTION

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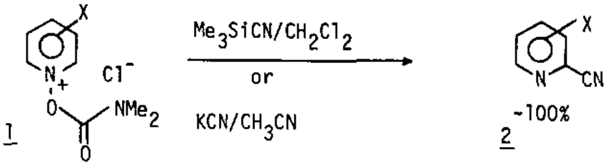
Abstract - Cyanation of 3-X-1-dimethylaminocarbonyloxypyridinium ions with trimethylsilanecarbonitrile or cyanide ion gives 3-methyl-2-pyridinecarbonitrile (~90%) contaminated with 5-methyl-2-pyridinecarbonitrile (~10%) when X = $-CH_3$, and approximately equal amounts of the 3- and 5-X derivatives when X = $-COOCH_3$. These product mixtures are identical to those obtained with the corresponding pyridine 1-oxides and dimethylcarbamoyl chloride in a modified Reissert-Henze reaction.

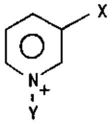
The recently reported quantitative conversion of pyridine 1-oxides to 2-pyridinecarbonitriles[3] has now been shown to involve the intermediacy of 1-acyloxypyridinium ion, eq. 1. 1-Acyloxypyridinium ions have been presumed to be the reactive intermediate in the few documented examples of Reissert-Henze cyanation of pyridine 1-oxides in the presence of benzoyl chloride.[4] Treatment of the 1-dimethylaminocarbonyloxypyridinium ion,[5] 1, formed by prior reaction between a pyridine 1-oxide and dimethylcarbamoyl chloride, with either trimethylsilanecarbonitrile in dichloromethane or potassium cyanide in acetonitrile (or water) furnishes the related 2-pyridinecarbonitrile, 2, in essentially quantitative yield (Table 1).

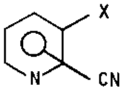
1)



X = $-H$, $3-CH_3$, $3-COOCH_3$

Table 1. Cyanation of Pyridine Derivatives[a]





(Yields %)[b]

X	Y	Cyanating Agent	Solvent	3-X 2-CN	5-X 2-CN	3-X 4-CN	Overall Isolated Yield (%)
H[3]	O^-	Me_3SiCN/Me_2NCOCl	CH_2Cl_2	100	—	0	94
H	$OOCNMe_2$	Me_3SiCN	CH_2Cl_2	100	—	0	95
		KCN	CH_3CN	100	—	0	90
		KCN	H_2O	100	—	0	88
CH_3[3]	O^-	$Me_3SiCN/MeNCOCl$	CH_2Cl_2	90	10	0	95
CH_3	$OOCNMe_2$	Me_3SiCN	CH_2Cl_2	94	6	0	91
		KCN	CH_3CN	86	14	0	90
		KCN	H_2O	89	11	0	87
$COOCH_3$[6]	O^-	Me_3SiCN/Me_2NCOCl	CH_2Cl_2	40	60	0	70
$COOCH_3$	$OOCNMe_2$	Me_3SiCN	4:1 DMSO-d_6-$CDCl_3$[c]	40	60	trace	—
		KCN	CH_3CN	48	42	10	90
		KCN	D_2O	55	43	2	—
CH_3	OCH_3	Me_3SiCN	1:1 DMSO-d_6-$CDCl_3$	0	0	0	0
		KCN	CH_3CN	22	5	73	50
		KCN	H_2O	24	7	69	65
$COOCH_3$	OCH_3	Me_3SiCN	1:1 DMSO-d_6-$CDCl_3$	0	0	0	0
		KCN	CH_3CN	16	26	58	60
		KCN	H_2O[d]	2	11	87	75

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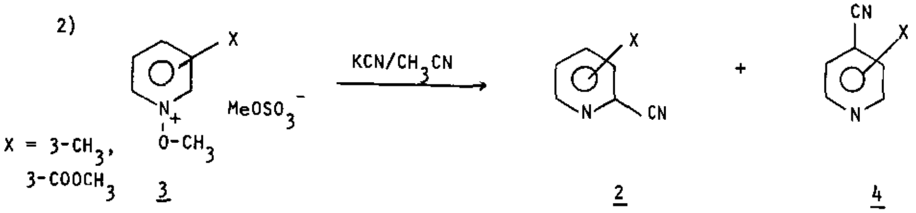
[a] Analytical experiments utilized reaction mixtures at room temperature ($\sim$27°C) that contained 2.5×10^{-4} mole pyridinium salt, 2.8×10^{-4} mole trimethylsilanecarbonitrile or 7.5×10^{-4} mole potassium cyanide in 0.50 mL solvent. Preparative experiments were conducted with the same proportions of reactants and 0.005-0.010 mole pyridinium salt. See reference 3 for experimental details. [b] Product compositions were determined by VPC analysis (OV-1 5% on Chromosorb W) at 160°C. All products were compared to samples that gave melting points and/or IR and NMR spectra that were in excellent agreement with literature data, or had appropriate elemental compositions. [c] 3-Carbomethoxy-1-dimethylaminocarbonyloxypyridinium chloride reverts to a mixture of the N-oxide and dimethylcarbamoyl chloride in chloroform-d. [d] The reported result was obtained by addition of an aqueous solution containing 10-fold excess potassium cyanide to an aqueous solution containing the pyridinium salt. A reversed order of addition produced the cyanation product mixture: 11% 2-CN, 18% 6-CN, 71% 4-CN (overall isolated yield of cyano product-70%).

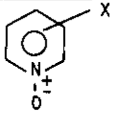
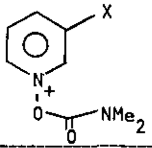
Product mixtures obtained by cyanation of 1 (X = 3-CH_3 and 3-$COOCH_3$) are identical to those obtained by treatment of related pyridine 1-oxides with trimethylsilanecarbonitrile and dimethylcarbamoyl chloride,[3] and they differ markedly from product mixtures derived from the corresponding 1-methoxypyridinium ions, 3, eq. 2. 1-Methoxypyridinium ions are not cyanated with trimethylsilanecarbonitrile in dichloromethane,

2)



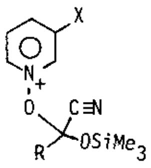
but they react with cyanide ion to give high percentages of 4 in agreement with the literature.[7] In contrast, products derived from 1, are almost exclusively the result of cyanation at a ring position adjacent to nitrogen. The only exception is the cyanation of the 3-$COOCH_3$ derivative with potassium cyanide in acetonitrile which gave 4 in 10% yield along with nearly equal amounts (48% and 42%, respectively) of 3- and 5-carbomethoxy-2-pyridinecarbonitrile.

Table 2. Relative Reactivity of 3-X-Pyridine 1-Oxide and 3-X-1-Dimethylaminocarbonyloxypyridinium Ion to Cyanation [a]

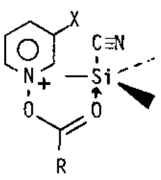
Pyridine Derivative		Cyanating Conditions	$t_{1/2}$	Rel. Rate
	X = H	$Me_3SiCN/Me_2NCOCl/CDCl_3$	15 min	20
	3-CH_3		20 min	15
	3-$COOCH_3$		5 hours	1
	X = 3-CH_3	Me_3SiCN/4:1 DMSO-d_6-$CDCl_3$	1 min	300
	3-$COOCH_3$		1 min	300

[a] Reactions were carried out at ambient probe temperatures (~32°C) in an NMR tube with equimolar mixtures (2.5 x 10^{-4} mole) of reactants in 0.50 mL solvent. The 3-carbomethoxy-1-dimethylaminocarbonyloxypyridinium ion was studied in 4:1 DMSO-d_6-$CDCl_3$ to avoid equilibration with N-oxide and dimethylcarbamoyl chloride. Half-lives ($t_{1/2}$) were estimated by integration of NMR signals of reaction mixtures.

The relative reactivity of 1 with trimethylsilanecarbonitrile is 15-300X that of related N-oxide-dimethylcarbamoyl chloride mixtures (Table 2). Furthermore, the reactivity of the 1-acyloxypyridinium ions is relatively insensitive to substituent, whereas the order of reactivity of the N-oxides toward cyanation parallels their ability to be acylated (3-CH_3 > H > -$COOCH_3$).[8] The inertness of 3 to trimethylsilanecarbonitrile and the appreciable amounts of product produced by attack of cyanide ion at the 4-position of 3 strongly supports the intervention of an intermediate such as 5 or 6 in reactions of 1.[9]



5



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Further work is currently underway to more fully characterize this reaction. Related studies in progress show that 1-acyloxypyridinium ions are extremely versatile intermediates for the synthesis of a wide-variety of pyridine derivatives. The results of these studies will be reported at a later date.

ACKNOWLEDGEMENT This research was supported by the gift of starting materials from Reilly Tar and Chemical Corporation.

REFERENCES AND NOTES

1. Author to whom correspondence should be addressed.
2. An undergraduate research participant *under the Consortium for Urban Education, Indianapolis.* Portions of this report were taken from the B.Sc. Thesis of B. D. Boyer.
3. W. K. Fife, *J. Org. Chem.*, 1983, **48**, 1375.
4. a) E. Ochiai and I. Nakayama, *Yakugaku Zasshi*, 1945 **65**, 582. b) Y. Kobayashi and I. Kumadaki, *Chem. Pharm. Bull.*, 1969 **17**, 510-514.
5. The preparation of 1-dimethylaminocarbonyloxypyridinium ions has been reported previously by: a) P. Bergthaller, *Ger. Offen.* 2, 408, 813 (Cl. C07D), Sept. 4, 1975, 25 pp., *Chem. Abstr.*, *84*, P43859p (1976); c) P. Bergthaller, W. Himmelmann, W. Sauerteig, and L. Rosenhahn, *Ger. Offen.* 2, 408, 814 (Cl. G03C), Sept. 4, 2975, 37 pp., *Chem. Abstr.*, *84*, P67803s (1975).
6. W. K.Fife, *Heterocycles*, in press.
7. E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam, 1974, p. 269. A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, London, 1971, p. 300. R. A. Abramovitch and E. M. Smith, "The Chemistry of Heterocyclic Compounds," A. Weissberger and E. C. Taylor, eds., John Wiley and Sons, New York, Vol. 14, Suppl. Part 2, 1974, pp. 114-117.
8. Studies currently in progress confirm that a wide variety of substituted 1-dimethylaminocarbonyloxypyridinium ions react rapidly with either trimethylsilanecarbonitrile or cyanide ion ($t_{1/2}$ 5 min. or less). Similar reactions with related pyridine-1-oxides and dimethylcarbamoyl chloride have half-lives that vary from 0.2 to 1.5 x 10^3 hours.
9. Complexes similar to 6 have been invoked in recent studies of silicon compounds. See R.J.P. Corriu and C. Guerin, *Adv. Organomet. Chem.*, 1982 **20**, 265.

Received, 12th December, 1983