

REGIOSELECTIVE CYANATION OF 3-SUBSTITUTED PYRIDINE 1-OXIDES¹

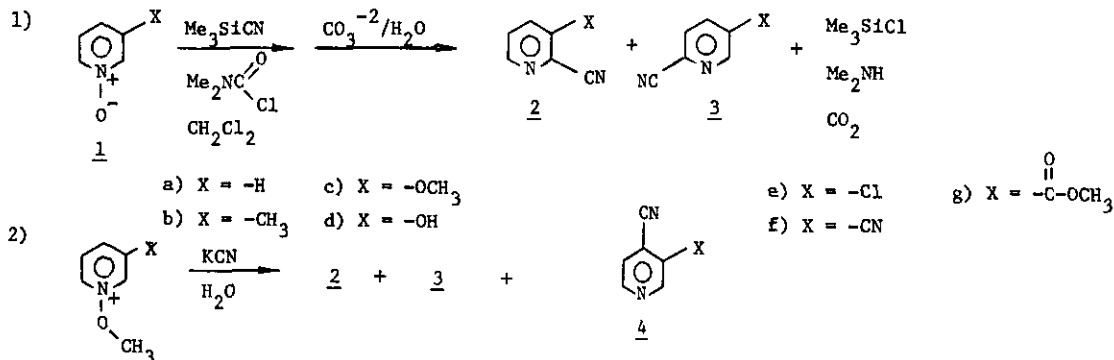
Wilmer K. Fife

Indiana University-Purdue University at Indianapolis

Indianapolis, IN 46223, U.S.A.

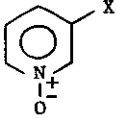
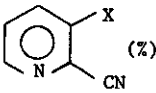
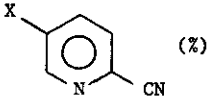
Abstract — Cyanation of 3-X-pyridine 1-oxides with trimethylsilanecarbonitrile and dimethylcarbamoyl chloride occurs quantitatively to give 3-X-2-pyridinecarbonitriles in $\geq 90\%$ isolated yields when X = -CH₃, -OCH₃, -OH and -Cl, and approximately equal amounts of the 3- and 5-X derivatives when X = -CN and -COOCH₃.

The recently reported reaction of pyridine 1-oxides with trimethylsilanecarbonitrile and dimethylcarbamoyl chloride in dichloromethane solution selectively produces 2-pyridinecarbonitriles in nearly quantitative yield.² This reaction has now been extended to a series of 3-substituted pyridine 1-oxides 1, eq. 1, Table 1. Cyanation of 1 via the 1-methoxypyridinium ion typically has produced mixtures of products, 2 and/or 3 as well as 4, eq. 2.³



In some cases, eg. 1b, all three isomeric products have been obtained,⁴ in others, eg. 1f, the products, 2 and 3 are found;^{5,7} and yet for some substituents, eg. -OCH₃, only one product, 2, has been reported.⁷ The results summarized in Table 1 show two different substitution patterns. One group of substituents despite considerable variation in electronic character and steric requirement, ie. -CH₃, -OCH₃, -OH, and -Cl, direct cyanation to the 2-position of pyridine (90% or greater). The second group of substituents, -CN and -COOCH₃, direct substitution in roughly equal amounts to the 2- and 6-positions, the two ring positions adjacent to nitrogen. The pure substituted 2-pyridinecarbonitriles are now readily available after column chromatography on Florisil (Eluants: Hexane-Dichloromethane Mixtures) and recrystallization (Hexane-Ether).

Table 1. Cyanation of 3-Substituted Pyridine 1-Oxides with Trimethylsilanecarbonitrile and Dimethylcarbamoyl Chloride^{a,b}

	Total Isolated Yield (%) ^c	 (%)	 (%)
X = -H ²	94	100	---
-CH ₃ ²	95	90	10
-OCH ₃	87	98	2
-OH	86	70 ^d	---
-Cl	90	89	11
-CN	82	55	45
	70 ^e	40	60 ^f

^aReaction mixtures contained equimolar quantities (0.002 mole) of N-oxide, trimethylsilanecarbonitrile and dimethylcarbamoyl chloride in 10 mL dichloromethane. Following reaction at room temperature for 1-10 days, product composition was determined by VPC analysis (OV-1 5% on Chromosorb W) at 160° after work-up with 10% aqueous potassium carbonate.

^bAll products gave melting points and/or IR and NMR spectra that were in excellent agreement with literature data unless otherwise noted.

^cTotal isolated yields are based on total amounts of pure products obtained after column chromatographic separations (Florisil-Hexane/Dichloromethane) and recrystallization (Hexane-Ether).

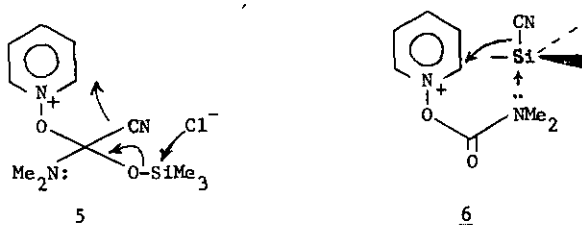
^dA second product (16%) gave spectral data consistent with 3-dimethylcarbamoyloxy-2-pyridinecarbonitrile, IR(neat) $\nu_{\max}$ = 2940, 2240, 1740, 800, 670 cm^{-1} . NMR(CDCl₃) δ 8.53 (q, 1H, 6-H, $J_{5,6}$ = 4 Hz, $J_{4,6}$ = 1 Hz); 7.90 (q, 1H, 4-H, $J_{4,5}$ = 8 Hz); 7.40 (q, 1H, 5-H); 3.12 (d, 6H, -NMe₂). mp 95-96°C. Found: C, 56.33; H, 4.73; N, 21.72%. Calcd for C₉H₉N₃O₂: C, 56.54; H, 4.74; N, 21.98%.

^eYields of isolated products were diminished by hydrolysis of the 2,3-isomer during column chromatographic separations.

^fMethyl 6-cyano-3-pyridinecarboxylate, mp 86-87°C (Ether-Hexane); NMR(CDCl₃) δ 9.26 (d, 1H, 2-H, $J_{2,4}$ = 1.5 Hz); 8.47 (q, 1H, 4-H, $J_{4,5}$ = 9 Hz); 7.81 (d, 1H, 5-H); 4.03 (s, 3H, -OCH₃). Found: C, 59.05; H, 3.66; N, 17.02%. Calcd for C₈H₆N₂O₂: C, 59.26; H, 3.73; N, 17.28%.

Variations in temperature, Table 2, were found to have little influence on cyanation of 1b. The product always consists of 90% or more 2b. In contrast, cyanation of 1g at low temperature (-7°C) gives exactly a 1:1 ratio of 2g and 3g, but at higher temperature a 2:3 ratio is found.

The lack of cyanation at the 4-position, even by compound 1g which is expected to behave similarly to ethyl 3-pyridinecarboxylate 1-oxide, a compound known to cyanate predominantly at carbon-4,⁷ strongly suggests "intramolecular delivery" of cyanide ion from an intermediate such as 5 or a complex such as 6. Complexes similar to 6 have been invoked in recent studies of silanes.⁸



The moderate sensitivity of product isomer ratio to temperature in the cyanation of lg is consistent with an intramolecular pathway that includes intermediates 5 or 6 as well as 7 and 8 whose relative populations vary according to the extent of kinetic vs. thermodynamic control.

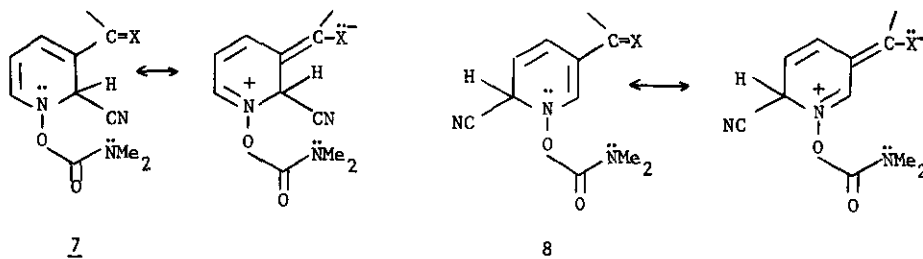
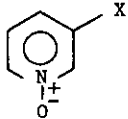
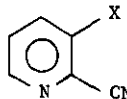
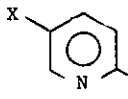
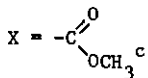


Table 2. Temperature Effect - Cyanation of 3-Substituted Pyridine 1-Oxides^{a,b}

	Temperature (°C)	 (%)	 (%)
X = -CH ₃	-7°	96	4
	27°	90	10
	40°	93	7
	-7°	50	50
	27°	40	60
	40°	41	59

^aReaction mixtures contained equimolar quantities of N-oxide, trimethylsilanecarbonitrile and dimethylcarbamyl chloride in dichloromethane solution.

^bTemperatures were maintained to $\pm 1^\circ\text{C}$ throughout the reaction period.

^cTrace amounts of methyl 4-cyano-3-pyridinecarboxylate are found in the product mixture at room temperature and above. Careful VPC analysis of the reaction run at -7°C did not reveal even a trace of the 4-cyano product.

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REFERENCES AND NOTES

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