REGIOSELECTIVE CYANATION OF 3-SUBSTITUTED PYRIDINE 1-OXIDES[1]

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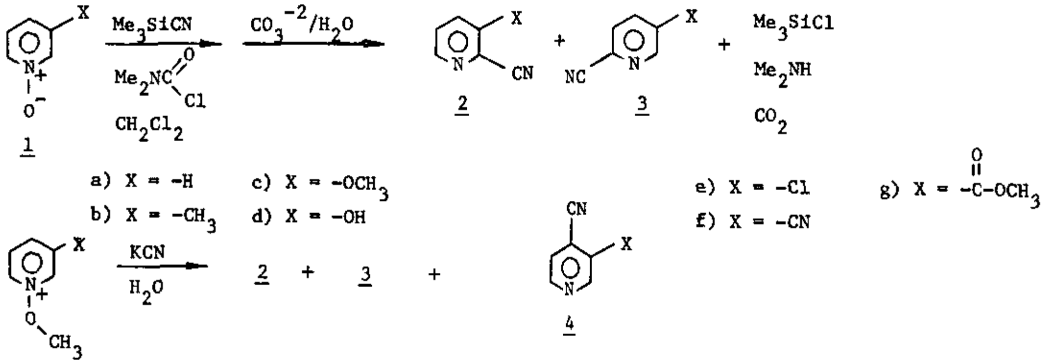
Abstract — Cyanation of 3-X-pyridine 1-oxides with trimethylsilanecarbonitrile and dimethylcarbamoyl chloride occurs quantitatively to give 3-X-2-pyridinecarbonitriles in ≥ 90% isolated yields when X = -CH_3, -OCH_3, -OH and -Cl, and approximately equal amounts of the 3- and 5-X derivatives when X = -CN and -$COOCH_3$.

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]

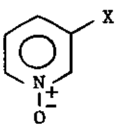
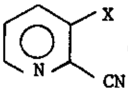
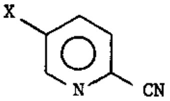
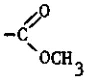
1)

2)



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. -OCH_3, 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. -CH_3,-OCH_3, -OH, and -Cl, direct cyanation to the 2-position of pyridine (90% or greater). The second group of substituents, -CN and -$COOCH_3$, 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
 $-C(=O)OCH_3$	70[e]	40	60[f]

[a] Reaction 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 postassium carbonate.

[b] All products gave melting points and/or IR and NMR spectra that were in excellent agreement with literature data unless otherwise noted.

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

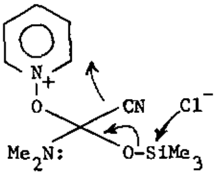
[d] A second product (16%) gave spectral data consistent with 3-dimethylcarbamoyloxy-2-pyridinecarbonitrile, IR(neat) $_{max}$ = 2940, 2240, 1740, 800, 670 cm^{-1}. NMR($CDCl_3$) 8.53 (q, 1H, 6-H, $J_{5,6}$ = 4 Hz, $J_{4,6}$ = 1 Hz); 7.90(q, 1H, 4-H, $J_{4,5}$ = 8 Hz); 7.40(q, 1H, 5-H); 3.12(d, 6H, $-NMe_2$). mp 95-96°C. Found: C, 56.33; H, 4.73; N, 21.72%. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98%.

[e] Yields of isolated products were diminished by hydrolysis of the 2,3-isomer during column chromatographic separations.

[f] Methyl 6-cyano-3-pyridinecarboxylate, mp 86-87°C (Ether-Hexane); NMR($CDCl_3$) 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, $-OCH_3$). Found: C, 59.05; H, 3.66; N, 17.02%. Calcd for $C_8H_6N_2O_2$: 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]



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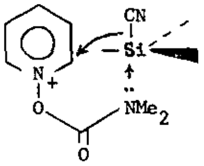

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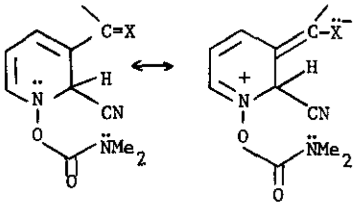
The moderate sensitivity of product isomer ratio to temperature in the cyanation of 1g is consistent with an intramolecular pathway that includes intermediates 5 or 6 as well as 7 and 8 whose relative populations vary according to the extent of kinetic vs. thermodynamic control.



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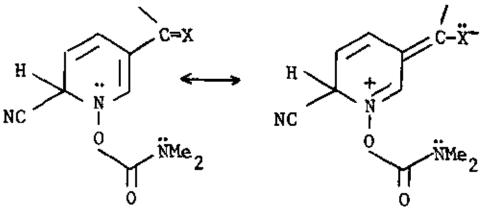

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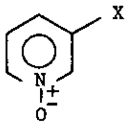
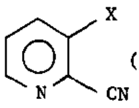
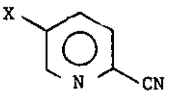
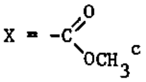
Table 2. Temperature Effect - Cyanation of 3-Substituted Pyridine 1-Oxides[a,b]

	Temperature (°C)	 (%)	 (%)
X = -CH$_3$	-7°	96	4
	27°	90	10
	40°	93	7
 X = -C(=O)OCH$_3$[c]	-7°	50	50
	27°	40	60
	40°	41	59

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[a] Reaction mixtures contained equimolar quantities of N-oxide, trimethylsilanecarbonitrile and dimethylcarbamyl chloride in dichloromethane solution.

[b] Temperatures were maintained to ± 1°C throughout the reaction period.

[c] Trace 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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