Preparation of Cyanopyridines by Direct Cyanation

Alan R. Katritzky,*[a] Eric F. V. Scriven,[a] Suman Majumder,[a] Hongbin Tu,[a] Anatoliy V. Vakulenko,[a] Novruz G. Akhmedov,[a] Ramiah Murugan[b]

[a] Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA
E-mail: katritzky@chem.ufl.edu

[b] Reilly Industries, Inc, 1500 South Tibbs Avenue, P.O. Box 42912, Indianapolis, IN 46242-0912, USA
E-mail: rmurugan@reillyind.com

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Abstract: After pretreatment with nitric acid and trifluoroacetic anhydride, aqueous potassium cyanide converted pyridines **1a–l** into their corresponding 2-cyano derivatives **4a–l** in an average yield of 52%.

Key words: pyridines cyanation, concd nitric acid, TFAA, potassium cyanide

Cyanopyridines are widely used in the preparation of the corresponding acids,[1,2] aldehydes,[3,4] ketones,[5] and as important synthetic intermediates for the synthesis of herbicides, pesticides, fungicides,[6] and pharmaceuticals.[7] Some substituted cyanopyridines are themselves biologically active.[6] 2-Cyanopyridine is also useful as starting material for complex heterocyclic compounds.[8,9]

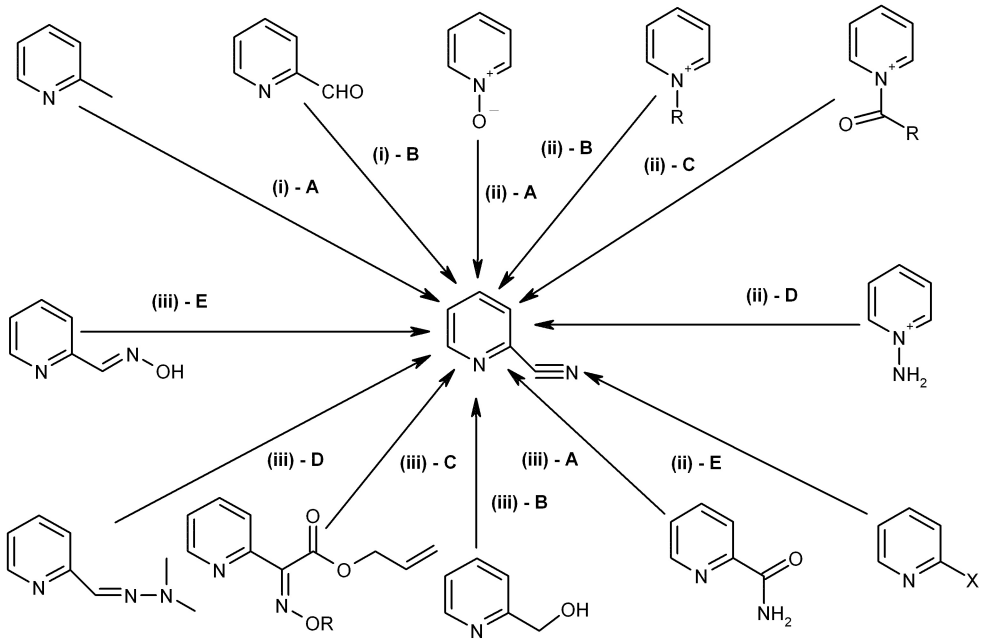
Three main approaches are currently available for the preparation of 2-cyanopyridines (Scheme 1):

i) Ammoxidation of **A**) 2-methylpyridines;[7,10] **B**) pyridine 2-aldehydes.[11–13]

ii) Reactions of cyanide ion with: **A**) activated pyridine *N*-oxides;[14–18] **B**) *N*-alkyl;[19] **C**) *N*-acyl-pyridinium cations;[14] **D**) *N*-aminopyridinium cations;[20] **E**) 2-halopyridines.[21]

iii) Dehydration, decarboxylation and/or oxidation of: **A**) primary amides;[22,23] **B**) primary alcohols;[24,25] **C**) 2-pyridylacetic esters, oximinocarbonates and carbamates;[26] **D**) pyridine-2-aldehyde and 2-acylpyridine *N*,*N*-dimethylhydrazones;[27] **E**) dehydration of pyridine-2-oximes.[28–33]

The parent 2-, 3- and 4-cyanopyridines are themselves each produced on an industrial scale in large quantities by ammoxidation of the corresponding picolines. However, this method shows poor selectivity with respect to a particular methyl group when applied to lutidines and it is not applicable to most functionalized methylpyridines.



Scheme 1

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On a laboratory scale, a cyano group is frequently introduced into the 2- and/or 4- position of a pyridine ring by a variant of method (ii), i.e., treatment of an activated pyridine ring with cyanide ion and the cyanopyridines formed result from an addition-elimination process. Commonly this has been achieved by treatment of pyridine-1-oxides with an alkylating or acylating agent plus a source of cyanide ions.

Recently methods have been reported for the one-pot conversion of pyridines to the 2-cyanopyridines by in situ activation: direct cyanation of pyridine with dicyanogen gives a mixture of 2-, 3- and 4-cyanopyridines.[34] Direct conversion of pyridine to 2-cyanopyridine in 27% yield was reported in a recent patent.[6]

The present research started with the objective of activating the pyridine nitrogen to generate a pyridinium species in situ, to promote subsequent nucleophilic attack by cyanide ion to produce cyanopyridines. Bakke and coworkers,[35] have described *N*-nitropyridinium ions as intermediates for the direct nitration of pyridines in nitromethane or sulfur dioxide to afford nitropyridines using dinitrogen pentoxide as the nitrating agent. While dinitrogen pentoxide, is difficult to prepare and unstable, it does ionize in organic solvents like CCl_4.

We sought to generate dinitrogen pentoxide in situ, under conditions in which it would react readily with a pyridine to give the corresponding *N*-nitropyridinium salt as an intermediate. This intermediate could then be treated with KCN to form the corresponding cyanopyridines (Scheme 2).

We now report a general one-pot conversion of a series of pyridines to 2-cyanopyridines, which avoids the preparation of *N*-oxides or isolation of any other intermediate. Moreover, the 2-cyanoderivatives are formed regioselectively. The conversion of pyridines **1a–l** with KCN to 2-cyanopyridines **4a–l**, pre-treated with nitric acid and in trifluoroacetic anhydride, were achieved in an average yield of 52%.

Dinitrogen pentoxide can be produced by removing one mole of water from two moles of nitric acid.[36] This prompted us to carry out the reaction in trifluoroacetic anhydride, which could act as a solvent and dehydrating agent. Indeed this sequence succeeds.

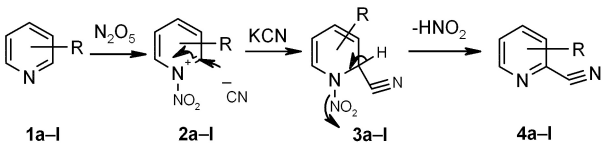
By standardizing with pyridine as substrate, it was found optimum to first dissolve the pyridine in trifluoroacetic anhydride under chilled conditions followed by slow addition of concentrated nitric acid to the mixture. This solution was then added dropwise to aqueous KCN buffered with NaOAc at 0 °C to give 2-cyanopyridine (Scheme 3).

The optimum reaction time was also standardized at 3 hours for the nitric acid treatment and the reaction mixture was allowed to stand at room temperature for 18 hours after addition to buffered KCN.

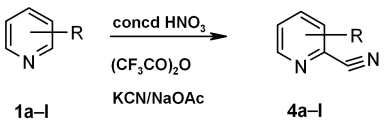
Cyanations, under the optimized reaction conditions, were carried out on picolines, lutidines, halopyridines, acylpyridines and even acid sensitive substrates like nicotinic acid ester, to afford one-pot syntheses of the corresponding 2-cyanopyridine (Table 1). All the products were characterized by comparison with melting points of the known compounds (wherever data is available) and by elemental analysis. The structures of all compounds were confirmed using 1D NOE difference, proton-coupled ^{13}C NMR, gHMQC and gHMBC experiments.

No direct cyanation of the pyridines (**4a–l**) has been reported. All previous methods used have involved multiple steps, with detriment to the final yield (see Table 1). For example, the reported syntheses of 3-chloro-2-cyanopyridine start with either (i) 2,3-dichloropyridine, not easily prepared in the laboratory from 3-chloropyridine or (ii) 3-chloropyridine *N*-oxide and which gives the desired 2,3-isomer in 45% yield mixed with the 3,5-isomer.

We consider a plausible mechanism for this reaction to involve initial formation of an *N*-nitropyridinium salt **1**, which is known to be formed in similar reactions of pyridines with dinitrogen pentoxide as shown by Bakke.[37] The *N*-nitropyridinium salt then undergoes a 1,2-addition of cyanide ion to give 'pseudocyanide' **2**. Intermediate **2** readily undergoes elimination with the formal loss of nitrous acid to form the cyanopyridine **3**. This mechanism is closely analogous to that of the Reissert–Henze reaction.[38] The NO_2 moiety is remarkable in that it as the nitronium ion attacks as an excellent electrophile, and departs as nitrite, a good leaving group.



Scheme 2



Scheme 3

Thus pyridines **1a–l**, pretreated with nitric acid and trifluoroacetic anhydride, were added to potassium cyanide–NaOAc buffer solution to give the corresponding 2-cyanopyridines **4a–l** in an average yield of 52%.

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra in $CDCl_3$ (TMS as internal standard) were recorded on a Varian Mercury 300 MHz NMR. The gHMQC and gHMBC experiments were performed without spinning and acquired with several spectral widths. The GARP pulse sequence was used for decoupling. The FID's were processed using Gauss and Gauss-shifted weighting functions before Fourier transformation.

Preparation of 2-Cyanopyridines; General Procedure

Trifluoroacetic anhydride (10 mL, 42 mmol) was chilled in an ice bath and the pyridine or substituted pyridine (17 mmol) was slowly

Table 1 Preparation of Cyanopyridines **4a–l** and Previous Literature

Product	R	Yield (%)	Literature		
			Yield (%)	Method (Scheme 1)	Ref.
4a	H	72	[f]	(ii)-**A**	39
			[f]	(ii)-**A**	40
4b	3-CH_3	75	[c]	(ii)-**A**	41
			[f]	(ii)-**A**	39
			[f]	(ii)-**A**	15
			[f]	(ii)-**E**	40
			[f]	(ii)-**A**	42
4c	4-CH_3	42	[f]	(ii)-**A**	39
			[f]	(ii)-**A**	40
4d	3,5-di-CH_3	82	[f]	(ii)-**A**	43
4e	3,6-di-CH_3	45	[f]	[a]	44
4f	3-C_2H_5	78	[d]	(ii)-**A**	41
4g	3-Cl	55	85[g]	(ii)-**A**	41
			47[g]	(ii)-**A**	45
4h	3-Br	81	86	(ii)-**A**	41
4i	5-$COCH_3$	10	25	(ii)-**A**	46
4j	4-$COCH_3$	53	26	[b]	47
4j′		22[e]			
4k	5-$CO_2C_2H_5$	20	51[g]	(ii)-**A**	41
4l	4-(4′-pyridyl)	20	90[g]	(ii)-**A**	48

[a] Prepared by ring cyclization.
[b] Prepared from dicyanopyridines.
[c] 93% Crude yield of mixture of isomers reported to be inseparable.
[d] 94% Crude yield of mixture of isomers reported to be inseparable.
[e] The product is a cyanohydrin.
[f] No yield quoted in the original reference.
[g] The reported yield is starting from pyridine-*N*-oxides, the overall yield from pyridine itself being comparable to our method.

added. After 1 h, concd nitric acid (1.9 mL, 36 mmol) was added dropwise under cooling. After stirring for 2–3 h at r.t., the solution was dripped slowly into chilled aq solution of KCN (8.4 g) and NaOAc (8.1 g). After 12 h, the pH of the solution was checked to be 6–7 and extracted with CH_2Cl_2 to give the pure cyanopyridines **4a–l**. All the compounds have been purified by column chromatography on silica gel using EtOAc–hexane (1:1).

2-Pyridinecarbonitrile (4a)
Yield: 72%; yellow oil.

^{1}H NMR: δ = 7.63 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.78 (ddd, *J* = 7.7, 1.3, 0.9 Hz, 1 H), 7.95 (td, *J* = 7.7 Hz, 1.8 Hz, 1 H), 8.76 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H).

^{13}C NMR: δ = 117.0, 126.8, 128.2, 133.3, 137.0, 151.0.

Anal. Calcd for $C_6H_4N_2$: C, 69.22; H, 3.87; N, 26.92. Found: C, 68.83; H, 3.80; N, 26.89.

3-Methyl-2-pyridinecarbonitrile (4b)
Yield: 75%; yellow prisms; mp 83.5 °C (Lit.[15] mp 84.0–86.0 °C).

^{1}H NMR: δ = 2.58 (s, 3 H), 7.43 (dd, *J* = 4.8, 8.0 Hz, 1 H), 7.69 (dd, *J* = 1.6, 8.0 Hz, 1 H), 8.55 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR: δ = 18.6, 116.3, 126.5, 134.0, 138.0, 138.4, 148.4.

Anal. Calcd for $C_7H_6N_2$: C, 71.19; H, 5.12; N, 23.73. Found: C, 71.41; H, 5.11; N, 23.76.

4-Methyl-2-pyridinecarbonitrile (4c)
Yield: 42%; yellow prisms; mp 87.0 °C.

^{1}H NMR: δ = 2.44 (s, 3 H), 7.34 (d, *J* = 4.9 Hz, 1 H), 7.53 (br s, 1 H), 8.57 (d, *J* = 4.9 Hz, 1 H).

^{13}C NMR: δ = 20.8, 117.3, 127.8, 129.3, 133.7, 148.7, 150.7.

Anal. Calcd for $C_7H_6N_2$: C, 71.19; H, 5.12; N, 23.73. Found: C, 71.41; H, 5.15; N, 23.81.

3,5-Dimethyl-2-pyridinecarbonitrile (4d)
Yield: 82%; yellow prisms; mp 61.5 °C.

^{1}H NMR: δ = 2.39 (s, 3 H), 2.52 (s, 3 H), 7.48 (dq, *J* = 1.3, 0.7 Hz, 1 H), 8.35 (dq, *J* = 1.3, 0.7 Hz, 1 H).

^{13}C NMR: δ = 18.4, 18.5, 116.5, 131.0, 137.2, 137.8, 138.3, 149.0.

Anal. Calcd for $C_8H_8N_2$: C, 72.68; H, 6.10; N, 21.20. Found: C, 72.11; H, 6.03; N, 21.21.

3,6-Dimethyl-2-pyridinecarbonitrile (4e)
Yield: 45%; yellow oil.

^{1}H NMR: δ = 2.52 (s, 3 H), 2.56 (s, 3 H), 7.29 (br d, *J* = 7.9 Hz, 1 H), 7.57 (br d, *J* = 7.9 Hz, 1 H).

^{13}C NMR: δ = 18.0, 23.7, 116.5, 126.6, 132.8, 135.3, 138.2, 145.2, 157.5.

Anal. Calcd for $C_8H_8N_2$: C, 72.68; H, 6.10; N, 21.20. Found: C, 72.80; H, 6.10; N, 21.23.

3-Ethyl-2-pyridinecarbonitrile (4f)
Yield: 78%; yellow oil.

^{1}H NMR: δ = 1.33 (t, *J* = 7.6 Hz, 3 H), 2.90 (q, *J* = 7.9 Hz, 2 H), 7.47 (dd, *J* = 7.9, 4.6 Hz, 1 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 8.55 (d, *J* = 4.6 Hz, 1 H).

^{13}C NMR: δ = 14.8, 26.1, 116.2, 127.1, 133.6, 136.9, 144.5, 148.7.

Anal. Calcd for $C_8H_8N_2$: C, 72.68; H, 6.10; N, 21.20. Found: C, 72.13; H, 6.15; N, 21.30.

3-Chloro-2-pyridinecarbonitrile (4g)
Yield: 55%; yellow prisms; mp 83.0–84.0 °C (Lit.[49] mp 83.0–84.0 °C).

^{1}H NMR: δ = 7.53 (dd, *J* = 8.2, 4.6 Hz, 1 H), 7.90 (dd, *J* = 1.2, 8.2 Hz, 1 H), 8.63 (dd, *J* = 1.2, 4.6 Hz, 1 H).

^{13}C NMR: δ = 114.5, 127.5, 133.1, 135.9, 137.6, 148.7.

Anal. Calcd for $C_6H_3ClN_2$: C, 52.01; H, 2.18; N, 20.22. Found: C, 52.09; H, 2.02; N, 20.02.

3-Bromo-2-pyridinecarbonitrile (4h)
Yield: 81%; yellow prisms; bp 119.5 °C/3 Torr (Lit.[41] bp 120.0 °C/3 Torr).

^{1}H NMR: δ = 7.43 (dd, *J* = 8.2, 4.5 Hz, 1 H), 8.04 (d, *J* = 8.2 Hz, 1 H), 8.66 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR: δ = 115.6, 124.5, 127.6, 135.2, 140.6, 149.0.

Anal. Calcd for $C_6H_3BrN_2$: C, 39.38; H, 1.46; N, 15.07. Found: C, 39.56; H, 6.15; N, 21.30.

5-Acetyl-2-pyridinecarbonitrile (4i)
Yield: 10%; yellow prisms; mp 54.5 °C (Lit.[46] mp 55.0–56.0 °C).

^{1}H NMR: δ = 2.70 (s, 3 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 8.36 (dd, *J* = 8.1, 2.2 Hz, 1 H), 9.23 (dd, *J* = 2.2, 1.1 Hz, 1 H).

^{13}C NMR: δ = 26.9, 116.5, 128.4, 133.8, 136.5, 136.8, 150.7, 195.1.

Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.37; H, 4.05; N, 19.03.

4-Acetyl-2-pyridinecarbonitrile (4j)
Yield: 53%; yellow prisms; mp 101.5 °C (Lit.[47] mp 101.0–102.0 °C).

^{1}H NMR: δ = 2.68 (s, 3 H), 7.95 (dd, *J* = 5.1, 1.7 Hz, 1 H), 8.13 (dd, *J* = 1.7, 0.8 Hz, 1 H), 8.94 (dd, *J* = 5.1, 0.8 Hz 1 H).

^{13}C NMR: δ = 26.6, 116.6, 124.4, 126.1, 143.6, 152.4, 194.9.

Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.75; H, 4.03; N, 18.99.

4-Pyridineglycolonitrile, α-Methyl (4j′)
Yield: 22%; white prisms; mp 121.0 °C.

^{1}H NMR: δ = 1.86 (s, 3 H), 7.51 (br s, OH, 1 H), 7.53 (AA′BB′, J_{AB} = 6.1 Hz, 2 H), 8.42 (AA′BB′, J_{AB} = 6.1 Hz, 2 H).

^{13}C NMR: δ = 31.0, 69.1, 119.9, 120.9, 149.1, 151.8.

Anal. Calcd for $C_8H_8N_2O$: C, 64.83; H, 5.44; N, 18.91. Found: C, 64.89; H, 5.35; N, 18.82.

5-Ethoxycarbonyl-2-pyridinecarbonitrile (4k)
Yield: 20%; yellow prisms; mp 47.0 °C.

^{1}H NMR: δ = 1.44 (t, *J* = 7.1 Hz, 3 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 8.45 (dd, *J* = 8.0, 2.1 Hz, 1 H), 9.29 (dd, *J* = 2.1, 1.1 Hz, 1 H).

^{13}C NMR: δ = 14.1, 62.3, 116.5, 128.0, 128.9, 136.8, 138.0, 151.8, 163.6.

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.31; H, 4.55; N, 15.78.

4-(4′-Pyridyl)-2-pyridinecarbonitrile (4l)
Yield: 20%; yellow prisms; mp 238.5 °C (Lit.[48] mp 238.0–240.0 °C).

^{1}H NMR: δ = 7.55 (AA′BB′, J_{AB} = 6.0 Hz, 2 H), 7.77 (dd, *J* = 8.2, 5.2 Hz, 1 H), 7.95 (s, 1 H), 8.82 (AA′BB′, J_{AB} = 6.0 Hz, 2 H), 8.86 (d, *J* = 5.2 Hz, 1 H).

^{13}C NMR: δ = 116.9, 121.2, 124.5, 126.2, 135.0, 143.3, 147.2, 151.0, 151.9.

Anal. Calcd for $C_{11}H_7N_3$: C, 72.91; H, 3.90; N, 23.19. Found: C, 72.04; H, 3.90; N, 22.86.

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