A Simple Procedure for the Preparation of 2-Cyano-4-chloropyridines

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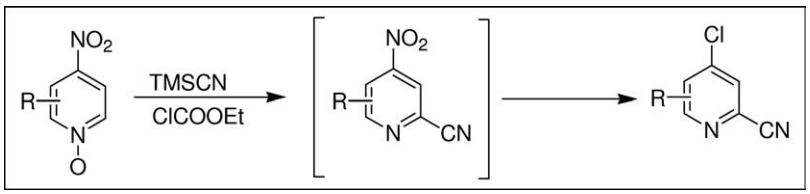

4-Nitro-pyridine-*N*-oxides are reacted with ethylchloroformate and trimethylsilyl cyanide to give 4-chloro-2-cyanopyridine.

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INTRODUCTION

Among many heterocyclic compounds, pyridine and its derivatives are important compounds and are present in many biological systems [1,2]. Substituted pyridines, among the different applications, the pharmaceutical [3] and agrochemical [3] applications are more important. Extensive studies have been carried out on the synthesis of substituted pyridine compounds owing to their wide importance as drugs, biologically active natural products, and for other applications. Preparation of 2-cyanopyridine derivatives is an important activity because of the versatility of the group for further conversions [4] to acids [5,6], aldehydes [7,8], ketones [9], and amines. Some substituted cyanopyridines are themselves biologically active [10].

4-Substituted 2-cyanopyridines are prepared by different methods. Japanese [11] team prepared 2-cyano-4-substituted pyridine oxides **2** from picoline oxides **1**, with acetyl chloride. Compound **2** is deoxygenated with PCl_3 to give 4-chloro-2-cyanopyridines **3** with overall yields of 31.5% (Scheme 1).

Matsumura et al. [12c] prepared 2-cyano-4-substituted pyridines **7**, using the Reissert–Kaufmann-type reaction on 4-nitropyridine-*N*-oxide **4** (Scheme 2).

Later, Yamanaka and coworkers [12b,d–g] reported trimethylsilylcyanide as a versatile reagent for converting pyridine-*N*-oxides to 2-cyanopyridine derivatives (Scheme 3).

Desjardins et al. [12a] and Hiroshi et al. [12h] reported trimethylsilylcyanide in combination with dimethylcarbamoyl chloride to convert substituted pyridines-*N*-oxides to 2-cyanopyridine derivatives at room temperature (Scheme 4).

The chloro-*N*-oxide pyridines **8** are usually prepared from 4-nitro-*N*-oxide pyridines **4** in the presence of acid chlorides such as acetyl chloride and chloroformate esters.

RESULTS AND DISCUSSION

In our medicinal chemistry program, we were in need of several 4-chloro-2-cyanopyridine building blocks. We hereby report our serendipitous discovery of preparing 4-chloro-2-cyanopyridines **9**, from 4-nitropyridine-*N*-oxide **8**, in a one-step process. In our interest to replace dimethylcarbamoyl chloride reagent with ethylchloroformate in conversion of 4-nitropyridine-*N*-oxide **4** to 4-nitro-2-cyanopyridine **11**, surprisingly we found that 4-chloro-2-cyanopyridine **12** is the major product. The ethyl chloro formate not only served as a reagent to replace dimethylcarbamoyl chloride in cyanation but also converted the 4-nitro to chloro compounds (Scheme 5).

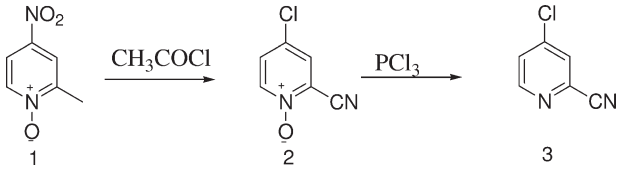
To see the generality of this reaction, we studied number of substituted derivatives of nitropyridine-*N*-oxides and found that the reaction is a general one. The best results were obtained when pyridine ring is substituted with benzyl ester (Entry **10**). The results are tabulated in Table 1.

In conclusion, we have developed a simple and convenient method for the preparation of 2-cyano-4-chloropyridines.

EXPERIMENTAL

All reagents were obtained commercially and were of the highest commercial quality and used without further

Scheme 1

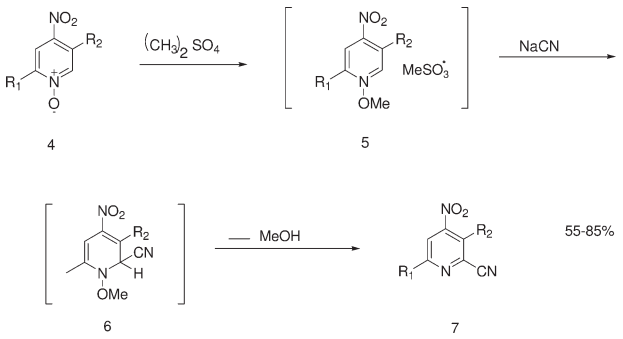


purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. The purity of all compounds was routinely checked by TLC on silica gel-coated plates. IR spectra were recorded on a Perkin-Elmer model 2000 instrument in KBr phase. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded in $CDCl_3$ using Brucker instrument, and mass spectra were recorded on a Perkin-Elmer mass spectrometer operating at 70 eV.

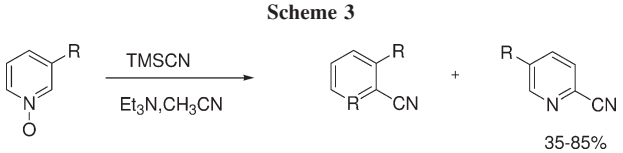
General procedure for the preparation of 4-chloro-2-cyanopyridines. To a solution of 5.0 g (0.032 mol) of 4-nitropyridine-*N*-oxide and 7.0 g of (0.064 mol) ethylchloroformate in 20 mL of 1,2-dichloroethane (EDC)/acetonitrile (CH_3CN) was added 3.17 g (0.032 mol) of trimethylsilylcyanide at 40–45°C over a period of 30 min, and then the reaction mixture was stirred at 60–65°C for 1 h. After the completion of reaction, the reaction mixture was cooled to 10°C, and the chilled DM water was added (10 mL) at 10–20°C over a period of 15 min and stirred for 30 min at 25–30°C. The separated organic layer was dried over sodium sulfate, and the solvent was removed *in vacuo* to get the crude product, which was purified by column chromatography or by recrystallization to yield 1.44 g (32%), mp 82–85°C.

4-Chloro-2-cyanopyridine (13). mp 82–85°C; IR (KBr): 3086.38, 2467.90, 2239.82 (CN), 1963.38, 1547.75, 1380.86, 1214.74, 885.96, 846.76 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.6 (s, 1H), 7.7 (d, J = 5.3 Hz, 1H), 7.3 (d, J = 6.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$): δ 116.06 (CN), 127.4, 128.68, 134.75, 145.18, 1 51.78; ms: m/z 139.0 (M^+) and 141.0 (M+2).

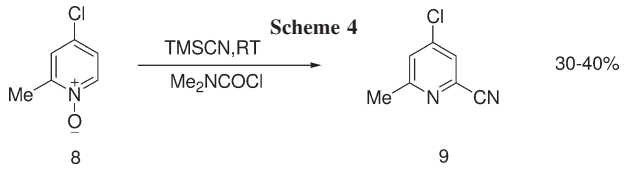
Scheme 2



Scheme 3



Scheme 4



4-Chloro-3-methyl-2-cyanopyridine (14). mp 70–72°C; IR (KBr): 3068.24, 2925.79, 2222.89 (CN), 1562.57, 1545.56, 1389.87, 1222.53, 1222.53, 1015.37, 858.18, 804.61 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.62 (s, 3H), 7.5 (d, J = 5.16 Hz, 1H), 8.44 (d, J = 5.12 Hz, 1H); ^{13}C-NMR ($CDCl_3$): δ 16.61, 115.70 (CN), 127.32, 135.11, 137.11, 145.42, 148.80; ms: m/z 153.0 (M^+) and 154.7 (M+2).

4-Chloro-3,5-dimethyl-2-cyanopyridine (15). mp 70–72°C; IR (KBr): 3427.14, 2925.13, 2231.98 (CN), 1544.76, 1452.53, 1213.25, 1017.33, 809.01 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.48 (s, 1H), 2.60 (s, 1H), 8.37 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 16.99, 17.70, 116.04 (CN), 132.40, 136.28, 136.62, 145.13, 149.63; ms: m/z 166.8 (M^+) and 169.1 (M+2).

4-Chloro-6-methyl-2-cyanopyridine (16). mp 78–79°C; IR (KBr): 3444.58, 3072.65, 2927.37, 2242.75 (CN), 1573.30, 1411.00, 1261.54, 1114.42, 881.88, 849.45 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.60 (s, 3H), 7.39, (s, 1H), 7.5 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 24.15, 116.22 (CN), 125.83, 126.98, 133.98, 144.93, 161.92; ms: m/z 153.0 (M^+) and 155.0 (M+2).

4-Chloro-3,5,6-trimethyl-2-cyanopyridine (17). mp 47–49°C; IR (KBr): 2926.90, 2229.31 (CN), 1571.10, 1539.48, 1440.93, 1410.32, 1235.65, 1012.47, 815.63 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.46 (s, 3H), 2.56 (s, 3H), 2.56 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 16.55, 17.19, 23.34, 116.29 (CN), 130.69, 134.45, 134.53, 144.94, 157.56; ms: m/z 180.9 $(M)^+$ and 183.11 (M+2).

4-Chloro-5,6-dimethyl-2-cyanopyridine (18). IR (KBr): 2985.24, 2928.64, 2241.58 (CN), 1557.70, 1372.09, 1242.38, 1126.41, 1023.70, 758.23 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.56 (s, 1H), 2.43 (s, 3H), 2.61 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 13.95, 15.92, 116.45 (CN), 126.75, 130.03, 134.89, 148.3, 151.98.

6-Bromo-4-chloro-2-cyanopyridine (19). mp 80–84°C; IR (KBr): 3064.30, 1560.38, 1382.0, 1163.23, 980.71, 889.58, 817.98 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.65 (s, 1H), 7.76 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 114.9 (CN), 127.56, 128.20, 133.94, 146.91, 153.3.

3-Bromo-4-chloro-6-methyl-2-cyaonopyridine (20). mp 83–85°C; IR (KBr): 067.58, 2242.25 (CN), 1561.51, 1407.17, 1340.85, 1037.9, 875.65, 849.23 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.47 (s, 1H), 2.56 (s, 3H); ^{13}C-NMR (CDCl3): δ 23.58, 115.47 (CN), 122.17, 127.911, 135.89, 145.68, 159.70; ms: m/z 233.2 (M^+) and 235.1 (M+2).

6-Bromo-4-chloro-3-methyl-2-cyaonopyridine (21). IR (KBr): 3072.82, 2242.57 (CN), 1560.87, 1417.46, 1227.32, 1101.18, 1026.83, 833.84 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.58 (s, 1H), 2.63, (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 2.59, 114.64 (CN),

Scheme 5

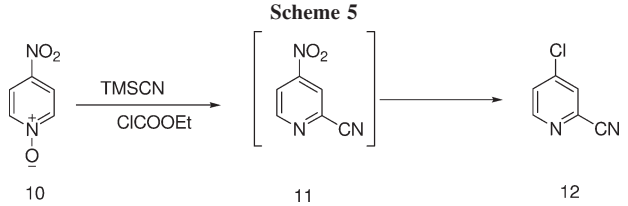
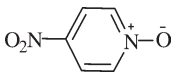
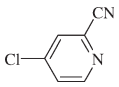
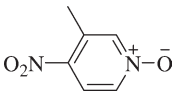
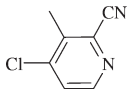
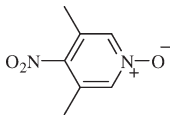
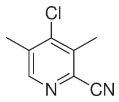
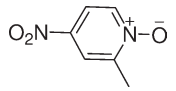
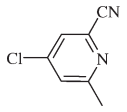
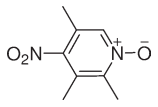
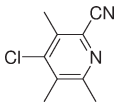
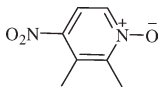
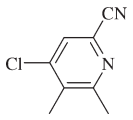
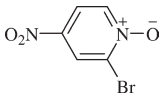
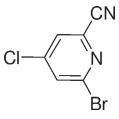
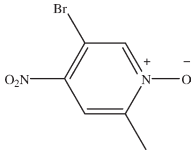
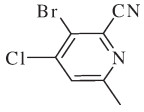
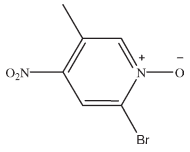
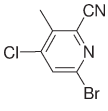


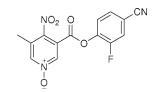
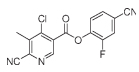
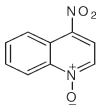
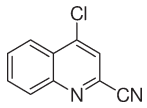
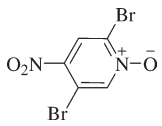
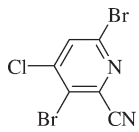
Table 1

Preparation of 2-cyano-4-chloropyridine.

				Reaction conditions				
Entry	Nitro compound	Entry	Product	Solvent	Temp (°C)	Time (h)	mp (°C)	Yield (%)
1		**13**		EDC	60–65	1	82–85 (84–85) [13]	32
2		**14**		EDC	25–30	3	70–72	30
3		**15**		EDC	25–30	3	47–49	30
4		**16**		EDC	25–30	3	78–80 (NR) [11h]	10
5		**17**		EDC	5–10	2	74–78	18
6		**18**		EDC	–5 to 10	1	NR	18
7		**19**		EDC	60–65	5	80–84	19
8		**20**		CH_3CN	80–83	6	83–85	17
9		**21**		CH_3CN	80–83	6	NR	15

(*Continued*)

Table 1
(*Continued*)

Entry	Nitro compound	Entry	Product	Reaction conditions: Solvent	Temp (°C)	Time (h)	mp (°C)	Yield (%)
10		**22**		EDC	60–65	2	88–93	48
11		**23**		EDC	60–65	1	106–108 (109) [13a,b]	25
12		**24**		CH_3CN	80–83	6	101–103	31

EDC, ethylene dichloride; CH_3CN, acetonitrile; NR, mp not reported.

127.93, 133.92, 136.32, 147.27, 150.01; ms: *m/z* 232.2 (M^+) and 234.2 (M+2).

4-Chloro-6-cyano-5-methylnicotinic acid-4-cyano-2-fluro benzyl ester (22). mp 88–93°C; IR (KBr): 2928.35, 2238.01 (CN), 1575.69, 1418.35, 1294.55, 1215.83, 1150.25, 757.59 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.9 (s, 1H), 7.95 (d, J = 9.94 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 8.56 Hz, 1H), 5.5 (s, 2H), 2.49 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 17.19, 61.16, 114.29 (CN), 115.17, 116.93, 119.3, 127.5, 128.34, 131.33, 136.88, 138.34, 145.11, 149.61, 158.96, 161.48, 162.52.

4-Chloro-2-cyanoquinoline (23). mp 106–108°C; IR (KBr): 3093.86, 2344.01, 2239.84 (CN), 1570.54, 1491.74, 1402.69, 1292.47, 1023.82, 907.86, 853.94 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.28 (d, J = 8.6 Hz, 1H), 8.19 (d, J = 8.44 Hz, 1H), 7.92 (t, J = 7.48 Hz, 1H,), 7.82 (t, 7.76 Hz, 1H), 7.78 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 116.53 (CN), 123.17, 124.1, 127.04, 130.41, 131.97, 133.12, 144.0, 148.65; ms: *m/z* 189.1 $(M)^+$ and 191.2 (M+2).

3,6-Dibromo-4-chloro-pyridine-2-carbonitrile (24). mp 101–103°C; IR (KBr): 3092.448, 3051.8, 2245.1 (CN), 1524.00, 1537.81, 1385.75, 1210.82, 1137.60, 885.88, 836.98, 817.79 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 114.31 (CN), 124.48, 128.74, 35.71, 147.84, 151.09.

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REFERENCES AND NOTES

[1] Jones, G. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 167.

[2] Balasubrahmanian, M.; Keay, J. G. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 245.

[3] (a) Gavin, D. H. Tetrahedron 2004, 60, 6043; (b) Baily, T. D.; Geo, G. L.; Scriven, E. F. V. Chem Heterocycl Compd 1984, 14, 1; (c) Thummel, R. P. Chem Heterocycl Compd 1984, 14, 253; (d) Kumar, R.; Chandra, R. Adv Heterocycl Chem 2001, 78, 269; (e) Hanket, T.; Brunne, R. M.; Miller, H.; Rechel, F. Angew Chem Int Ed 1999, 38, 643; (e) Lukevits, E. Chem Heterocycl Compd 1995, 31, 639.

[4] (a) Katrizky, A. R.; Scriven, E. F. V.; Majumdar, S.; Tu, H.; Vakulenko, A. V.; Akhmedov, N. Z.; Murugan, R. Synthesis 2005, 993; (b) Abraca, B.; Ballesteros, R.; Chadlaoui, M. ARKIVOV 2002, 10, 52; (c) Brun, E. M.; Gil, S.; Parra, M. ARKIVOC 2002, 10, 80.

[5] Werstiuk, N. H.; Ju, C. Can J Chem 1989, 67, 5.

[6] Belokon, Y. N.; Tararov, V. I.; Savel'eva, T. F.; Vitt, S. V.; Paskonova, E. A.; Dotdayev, S. C.; Borisov, Y. A.; Struchkov, Y. T.; Batasanor, A. S.; Balikov, V. M. Inorg Chem 1988, 27, 4046.

[7] Cha, J. S.; Yoon, M. S. Tetrahedron Lett 1989, 30, 3677.

[8] Uno, T. Jpn Pat. 10259180 (1988); Chem Abstr 1998, 129, 260349.

[9] Reimann, E.; Ziegon, H.-L. Liebigs Ann Chem 1976, 1351.

[10] Murugan, R.; Scriven, E. F. V.; Hillstrom, G. F.; Ghoshal, P. K. PCT WO Pat. 2002090328 (2002); Chem Abstr 2002, 137, 352895.

[11] (a) Hamano, M.; Saeki, S.; Hatano, Y.; Nagakura, M. Yakugaku Zasshi 1963, 83, 348; (b) Kato, T.; Hayashi, H. Yakugaku Zasshi 1963, 83, 352.

[12] (a) Desjardins, S. Y.; Cavell, K. J.; Hoare, J. L.; Skelton, B. W.; Sobolev, A. N.; White, A. M.; Keim, W. J Organomet Chem 1997, 544, 163; (b) Sakamato, T., Kaneda, S.; Nishimura, S.; Yamanaka, H. Chem Pharm Bull 1985, 33, 565; (c) Matsumura, E.; Agira, M.; Ohfuji, T. Bull Chem Soc Jpn 1970, 43, 3210; (d) Vorbruggen, H.; Krolikiewicz, K. Synthesis 1983, 316; (e) Fife, W. K. J Org Chem 1983, 48, 1375; (f) Fife, W. K. Heterocycles 1984, 22, 93; (g) Fife, W. K.; Boyer, R. Heterocycles 1984, 22, 1211; (h) Hiroshi, S.; Tadashi, N.; Hiroshi, H.; Akira, M.; Takahiro, A. Eur Pat. 1,236,717 (2002).

[13] Bisagni, E.; Rautureau, M.; Huel, C. Heterocycles 1989, 29, 1815.