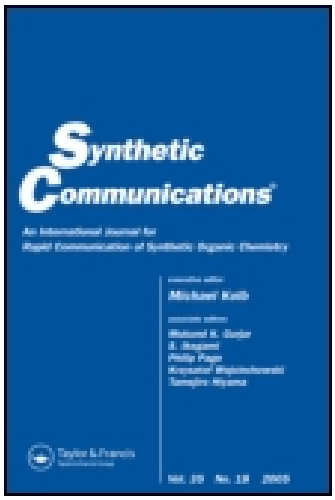

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Facile and Selective Synthesis of Chloromethylpyridines and Chloropyridines Using Diphosgene/Triphosgene

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Facile and Selective Synthesis of Chloromethylpyridines and Chloropyridines Using Diphosgene/Triphosgene[#]

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ABSTRACT

Diphosgene and triphosgene in the presence of amines were found to be an excellent chlorinating agents with high selectivity for the preparation of chloromethylpyridines and chloropyridines from picoline-*N*-oxides and pyridine-*N*-oxides respectively.

Key Words: Chloromethyl pyridine; Chloropyridine; Diphosgene; Triphosgene.

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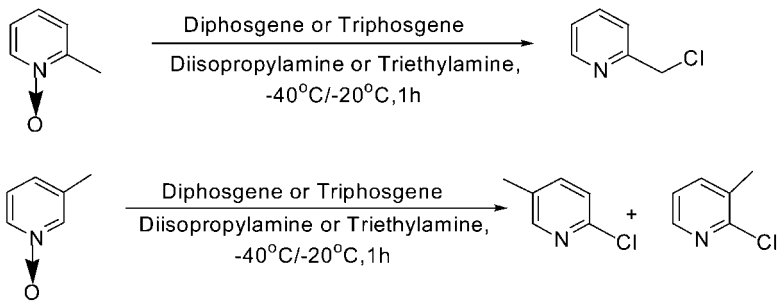
Chloromethylpyridines and chloropyridines constitute an important class of compounds in the preparation of pharmaceuticals, dyes,[1] and pesticides.[2] The most common method for the preparation of chloromethylpyridines and chloropyridines involve the chlorination of picolines[3] and pyridine-*N*-oxides[4] with reagents such as $POCl_3$,[5] SO_2Cl_2,[6] phosgene in DMF,[7] trichloroacetyl chloride,[8] and sulfonyl chlorides.[9] Chloromethylpyridines are prepared by the side-chain chlorination of picolines.[10] The reagents $POCl_3$, trichloroacetyl chloride and sulfonyl chlorides generate inorganic salts and possess environmental as well as disposal problems.

Diphosgene and triphosgene are safe and stable substitutes for toxic phosgene gas. Diphosgene used in various chemical transformations such as oximes to nitriles,[11] preparation of esters.[12] Triphosgene[13] also used in many organic reactions such as chloroformylation, carbonylation, dehydration and in the synthesis of imidazolidine-2-ones.[14] Our continuing interest in the synthesis of pesticides and pyridinecarboxaldehydes[15] using di- and triphosgenes,[16] lead us to report an efficient, mild and selective method for the preparation of chloromethylpyridines (**7–11**) and chloropyridines (**12–15**) from picoline-*N*-oxides (**1–5**) and pyridine-*N*-oxide (**6**) using diisopropylamine/triethylamine as bases in very good yields (Sch. 1).

2-Picoline-*N*-oxide (**1**) and lutidine-*N*-oxide (**2**) when reacted with triphosgene in presence of diisopropylamine at $-20^{\circ}C$ gave 2-chloromethylpyridine (**7**)[10c] in 90% yield and 2-chloromethyl-3-methylpyridine (**8**)[10d] in 80% yield respectively. Similarly collidine-*N*-oxide (**3**) gave two products namely 2-chloromethyl-4,6-dimethylpyridine (**9**)[10c] in 65% yield (82% selectivity) and 4-chloromethyl-2,6-dimethylpyridine (**10**)[10h] in 15% yield (18% selectivity). 4-Picoline-*N*-oxide (**4**) also gave two products, 4-chloromethylpyridine (**11**)[10f] in 61% yield by side chain chlorination (80% selectivity; isolated as a hydrochloride salt) and 2-chloro-4-methypyridine



Scheme 1.

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(**12**)[10g] in 14% yield by ring chlorination (20% selectivity). The mechanism of these chlorinated reactions are similar to the one proposed earlier. [5a,9a]

3-Picoline-*N*-oxide (**5**) under similar conditions gave two isomeric products 2-chloro-5-methylpyridine (**13**)[1a] in 70% yield (87% selectivity) and 2-chloro-3-methylpyridine (**14**)[1a] in 10% yield (13% selectivity). Pyridine-*N*-oxide (**6**) exclusively gave ring chlorinated 2-chloropyridine (**15**)[5a] in 80% yield. Table 1 clearly indicates the scope, generality and selectivity towards the formation side chain vs. ring chlorinated products.

In summary the method reported is very mild, efficient, environmentally benign and has high selectivity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Varian Gemini 200 MHz instrument in $CDCl_3$. The Mass spectra were measured on VG Micro mass 7070 H mass spectrometer.

General Procedure

A stock solution of triphosgene (2.97 g, 30 mmol) in dichloromethane (10 mL) was prepared of which 1 mL was added drop wise to 2-methylpyridine-*N*-oxide (**1**, 1.63 g, 15 mmol) in dichloromethane (15 mL) at -20°C. After 15 min the remaining solution was added drop wise along with diisopropylamine (3.03 g, 30 mmol) in dichloromethane (10 mL) over a period of 1 hr at -20°C. The contents were slowly brought to room temperature and stirred for another 45 min. The mass was quenched with water (10 mL), stirred for 30 min and the organic layer was separated. The aqueous layer was basified with NaOH solution (pH 7–8) and extracted with dichloromethane (2×50 mL). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure to give **7** (1.75 g) in 90% yield.

Spectral Data

2-Chloromethylpyridine (**7**): b.p.$_{10}$: 73–76°C.[10c] ^{1}H NMR ($CDCl_3$): δ4.7 (s, 2H), 7.3 (t, 1H), 7.55 (d, 1H), 7.95 (t, 1H), 8.6 (d, 1H). Mass (m/z): 127, 92, 78, 65, 51, 39.

2-Chloromethyl-3-methylpyridine (**8**): b.p.$_{1.4}$: 59–61°C.[10d] ^{1}H NMR ($CDCl_3$): δ2.4 (s, 3H), 4.62 (s, 2H), 7.15 (t, 1H), 7.42 (d, 1H), 8.39 (d, 1H). Mass (m/z): 141, 106, 79, 39.

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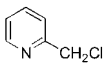
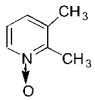
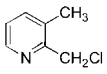
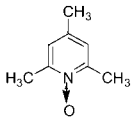
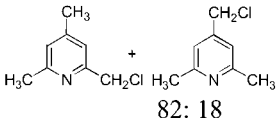
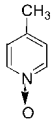
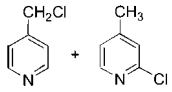
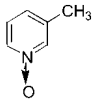
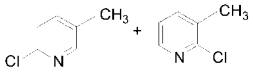
Table 1. Facile and selective synthesis of chloromethlpyridines and chloropyridines.

Entry	a	b	c	Temperature (°C)	% Y DIPA	% Y TEA
1	 **1**	DP TP	 **7**	−40 −20	92 90	90 88
2	 **2**	DP TP	 **8**	−40 −20	85 80	82 78
3	 **3**	DP TP	 82: 18 **9** **10**	−40 −20	75 80	72 78
4	 **4**	DP TP	 80: 20 **11** **12**	−40 −20	80 75	76 72
5	 **5**	DP TP	 87: 13 **13** **14**	−40 −20	85 80	82 78
6	 **6**	DP TP	 **15**	−40 −20	80 80	78 78

Note: All the products were well characterized by its ^{1}HNMR and GC/GCMS. a, Substrate; b, reagent; c, product; T, temperature; Y, yield; DIPA, diisopropyl-amine; TEA, triethylamine; DP, diphosgene; TP, triphosgene.

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2-Chloromethyl-4,6-dimethylpyridine (**9**): b.p.$_{1.4}$: 69–70°C.[10c] ^{1}H NMR ($CDCl_3$): δ2.3 (s, 3H), 2.45 (s, 3H), 4.55 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H). Mass (m/z): 155, 120, 93, 77, 51.

4-Chloromethyl-2,6-Dimethylpyridine (**10**): ^{1}H NMR ($CDCl_3$): δ2.45 (s, 6H), 4.35 (s, 2H), 6.85 (s, 2H). Mass (m/z): 155, 120, 77, 51.

2-Chloro-4-methylpyridine (**12**): b.p.$_{30}$ 97–99°C.[10g] ^{1}H NMR ($CDCl_3$): δ2.35 (s, 3H), 6.95 (d, 1H), 7.09 (s, 1H), 8.19 (d, 1H).

2-Chloro-5-methylpyridine (**13**): b.p.$_{2.5}$ 56°C.[1a] ^{1}H NMR ($CDCl_3$): δ2.31 (s, 3H), 7.15 (d, 1H), 7.45 (d, 1H), 8.19 (s, 1H). Mass (m/z): 127, 92, 65.

2-Chloro-3-methylpyridine (**14**): b.p. 192–193°C.[1a] ^{1}H NMR ($CDCl_3$): δ2.39 (s, 3H), 7.05 (t, 1H), 7.52 (d, 1H), 8.02 (d, 1H). Mass (m/z): 127, 91, 65.

2-Chloropyridine (**15**): b.p. 170°C.[5a] ^{1}H NMR ($CDCl_3$): δ7.15–7.5 (m, 2H), 7.6–7.9 (m, 1H), 8.45 (m, 1H).

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