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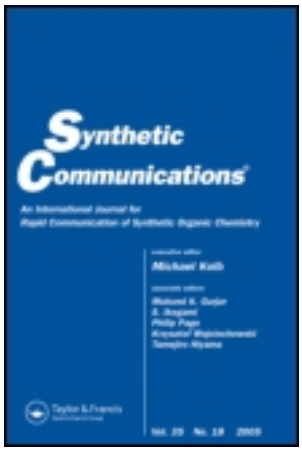

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PREPARATION OF 2-CHLOROPYRIDINE

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PREPARATION OF 2-CHLOROPYRIDINE

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ABSTRACT

Regiospecific chlorination of pyridine-*N*-oxide to give 2-chloropyridine was achieved in 90% yield with 99.2% selectivity by treatment with phosphorus oxychloride in the presence of a stoichiometric amount of triethylamine. Other chlorinating agents such as sulfuryl chloride, *p*-toluenesulfonyl chloride, trichloroacetyl chloride, benzenesulfonyl chloride and methanesulfonyl chloride produced 2-chloropyridine also under these conditions, albeit in moderate yield.

2-Chloropyridine derivatives are useful for the synthesis of pharmaceutical compounds and dyes.[1] The two most commonly used methods for the synthesis of 2-chloropyridine are the direct chlorination of pyridine with acetyl hypochlorite,[2] which is unsatisfactory in yield, and the chlorination of pyridine-*N*-oxide using $POCl_3$,[3] SO_2Cl_2,[4] phosgene in DMF,[5] trichloroacetyl chloride,[6] benzenesulfonyl chloride[7] or *p*-toluenesulfonyl chloride.[8] The yields for the reactions using trichloroacetyl chloride

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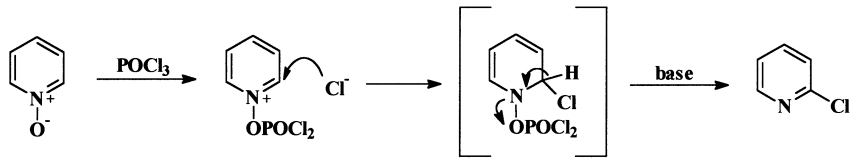
and the sulfonyl chlorides were acceptable but the waste disposal problems associated with the organic chlorinating agents and their higher cost over inorganics precluded their use in the preparation of large quantities of 2-chloropyridine. The reaction between $POCl_3$ and pyridine-*N*-oxide produces a mixture of 2-chloropyridine and 4-chloropyridine approximately in the ratio of 7:3 in around 70% yield.[9] Recovery of pure 2-chloropyridine is not very effective because of difficult separation. A mechanism involving an addition-elimination sequence was proposed to account for the reaction of pyridine-*N*-oxide with $POCl_3$. The oxygen of pyridine-*N*-oxide is coordinated with phosphorus of $POCl_3$. This complexation activates the adjacent carbon atom to chloride ion attack. Then elimination of phosphorus moiety from this system leads to overall substitution of hydrogen by chlorine. Considering this reaction mechanism, addition of a stoichiometric amount of base such as triethylamine should promote the elimination of hydrogen at C-2 and phosphorus moiety and result in getting higher yield and selectivity (Scheme).



Scheme.

An evalution of several potential chlorinating agents was undertaken and the results are shown in the Table. We now wish to report the conversion of pyridine-*N*-oxide to 2-chloropyridine utilizing phosphorus oxychloride in the presence of a stoichiometric amount of triethylamine.

The chlorination of pyridine-*N*-oxide with sulfuryl chloride and thionyl chloride in the presence or absence of base gave disappointingly low yields and selectivities. The reactions of pyridine-*N*-oxide with *p*-toluenesulfonyl chloride, chloroacetyl chloride, benzenesulfonyl chloride and methanesulfonyl chloride in the presence of triethylamine gave us 2-chloropyridine in moderate yield and selectivity, whereas phosphorus oxychloride in the presence of triethylamine gave a 90% yield with 99.2% selectivity. The latter reaction doesn't require any purification method such as distillation or chromatography.

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Table. Reaction of Pyridine-*N*-Oxide with Several Chlorinating Agents

Reagents	Base	Temp.[a] (°C)	Time (hour)	Solvents	Yield[b] (%)	Selectivity[c] (%)
Sulfuryl chloride	none	40	16	CH_2Cl_2	56	45
Sulfuryl chloride	Et_3N	40	3	CH_2Cl_2	64	78
Thionyl chloride	none	80	6	DMF	48	60
Thionyl chloride	Et_3N	80	3	DMF	52	66
Phosphorus oxychloride	none	90	24	dioxane	36	61
Phosphorus oxychloride	K_2CO_3	80	3	DMF	84	82
Phosphorus oxychloride	Et_3N	40	1	CH_2Cl_2	90	99.2
Chloroacetyl chloride	Et_3N	40	1	CH_2Cl_2	59	66
Methanesulfonyl chloride	Et_3N	40	3	CH_2Cl_2	73	89
Benzenesulfonyl chloride	Et_3N	40	3	CH_2Cl_2	76	86
p-Toluenesulfonyl chloride	Et_3N	40	3	CH_2Cl_2	80	79

[a]Temperature; [b] Isolated yields. The product showed spectral data in accord with the literature[10] values; [c] GC-analyzed selectivity.

In summary, selective chlorination of pyridine-*N*-oxide to give 2-chloropyridine can be achieved reacting phosphorus oxychloride with pyridine-*N*-oxide in the presence of a stoichiometric amount of triethylamine.

EXPERIMENTAL

Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM reagents and visualized with 254-nm UV light or ceric sulfate-ammoniummolybdate-sulfuric acid spray. ^1H NMR and ^{13}C NMR spectra were recorded on a Brucker DPX 300 at 300 MHz and 76 MHz, respectively. The chemical shifts are reported in parts

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per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. IR spectra were obtained on a Jasco FT/IR-300E spectrometer. GC analyses were recorded with a Shimadzu-14-D GC system. When necessary, chemicals were purified according to the reported procedure.[11]

General Procedure for the Reaction of Pyridine-*N*-Oxide with Chlorinating Agent

A solution of the chlorinating agent (72 mmol) in solvent (32 mL) was added dropwise at 10°C to a stirred solution of pyridine-*N*-oxide (5.7 g, 60 mmol) and base (72 mmol) in solvents (48–66 mL). The reaction mixture was heated for the length of time listed in Table. The mixture was concentrated *in vacuo* and treated with dichloromethane. The product was analyzed with GC to determine the conversion and selectivity of the reaction.

Preparation of 2-Chloropyridine Reacting Pyridine-*N*-Oxide and Phosphorus Oxychloride in the Presence of Triethylamine

A solution of phosphorus oxychloride (18.7 g, 120 mmol) in dichloromethane (50 mL) was added dropwise at 10°C to a stirred solution of pyridine-*N*-oxide (9.5 g, 100 mmol) and triethylamine (12.1 g, 120 mmol) in dichloromethane (76–100 mL). The reaction mixture was stirred for 30 minutes at room temperature and then refluxed for 1 h. The mixture was poured into water (30 mL) and neutralized with 2*M* NaOH. The organic layer was separated and aqueous layer was extracted with dichloromethane. The combined dichloromethane layer was washed with brine, dried and concentrated at reduced pressure to give colorless liquid (10.2 g, 90%). In the GC analysis, the product exhibited 99.2% selectivity to 2-chloropyridine. Bp 176–177°C/760 torr (*lit.*[12] 166°C/714 torr, *lit.*[13] 173–175°C/760 torr); IR (ν_{max}, KBr) 3053, 1578, 764, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.56 (dd, $J = 4.74$ Hz, $J = 1.58$ Hz, 1H, C_6), 7.98 (ddd, $J = 6.67$ Hz, $J = 4.78$ Hz, $J = 1.24$ Hz, 1H, C_4), 7.52 (dd, $J = 7.96$ Hz, $J = 0.71$ Hz, 1H, C_3); 7.60 (ddd, $J = 7.37$ Hz, $J = 4.86$ Hz, $J = 0.89$ Hz, 1H, C_5); ^{13}C NMR ($CDCl_3$) δ 206.29, 150.83, 140.19, 125.31, 123.67.

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