The Synthesis of 2-Chloromethylpyridine from 2-Picoline-*N*-Oxide

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Phosphoryl chloride reacts with 2-picoline-*N*-oxide in the presence of triethylamine to give 2-chloromethylpyridine in 90% conversion with 98% selectivity. Diethylchlorophosphate, ethyl chloroformate, chloroacetyl chloride and phosgene also react with 2-picoline-*N*-oxide to give 2-chloromethylpyridine in moderate yields. Other potential chlorinating agents, titanium tetrachloride, zinc chloride, magnesium chloride and sulfuryl chloride, did not convert 2-picoline *N*-oxide into 2-chloromethylpyridine.

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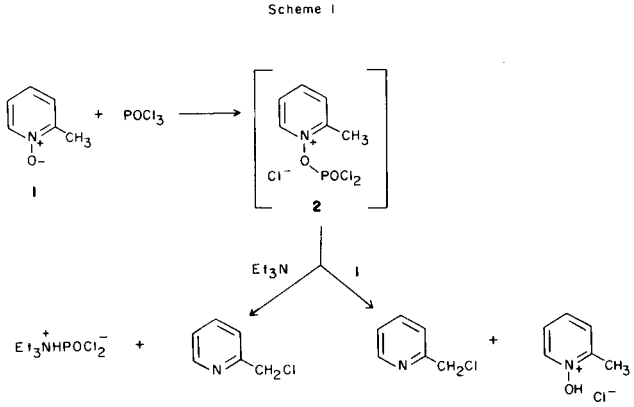
2-Chloromethylpyridine has been prepared by the direct chlorination of α-picoline but the yields were low due to the formation of large amounts of di- and trichloromethylated pyridines (1). 2-Chloromethylpyridine has also been obtained from 2-picoline-*N*-oxide using phosphoryl chloride (2), trichloroacetyl chloride (3), benzenesulfonyl chloride (4), or *p*-toluenesulfonyl chloride (5) in yields of 25%, 70%, 72%, and 90%, respectively. The yields for the reactions using trichloroacetyl chloride 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-chloromethylpyridine. We now wish to report the conversion of 2-picoline-*N*-oxide to 2-chloromethylpyridine utilizing phosphoryl chloride in the presence of a base, triethylamine.

2-Picoline-*N*-oxide was known to react with acetic anhydride to give 2-pyridylmethyl acetate (6). Sulfur and butyl mercaptan have been reported to deoxygenate

Scheme I



2-picoline-*N*-oxide to yield 2-picoline (7) as have thionyl chloride and phoshorus trichloride (4). A preliminary evaluation of other potential chlorinating agents was undertaken and the results of those experiments are shown in Table I.

Zinc chloride, titanium tetrachloride with and without triethylamine, and anhydrous magnesium chloride with

Table I

The Results of the Reaction Between 2-Picoline-*N*-Oxide and Chlorinating Agents

Reagent	Triethylamine (mmole)	Solvent	Temperature °C	Time (hour)	Conversion 2-Picoline *N*-oxide (percent)	Selectivity to 2-Chloromethylpyridine (percent)
$TiCl_4$	none	EDC (a)	50	2	98	0
$TiCl_4$	9.17	EDC	50	4	98	0
$ZnCl_2$	none	EDC	50	2	0	0
$MgCl_2$	9.17	EDC	50	4	0	0
Sulfuryl Chloride	9.17	Benzene	60	3	95	0 (b)
Diethyl chlorophosphate	none	CH_2Cl_2	40	0.75	95	10
Diethyl chlorophosphate	9.17	CH_2Cl_2	40	1	65	5
Ethyl chloroformate	none	CH_2Cl_2	25	1.5	82	5
Phosphoryl chloride in DMF (c)	none	DMF	65	14	75	40
Phosgene	9.17	CH_2Cl_2 acetonitrile	25	1	57	61
Chloroacetyl chloride	9.17	$CHCl_3$ (d)	60	14	50	73
Phosphoryl chloride	9.17	CH_2Cl_2	40	0.25	90	98

(a) Ethylene Dichloride. (b) Major product was 2-Picoline. (c) *N,N*-Dimethylformamide. (d) Prior to heating the chloroform was removed *in vacuo*.

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triethylamine failed to convert 2-picoline-*N*-oxide into 2-chloromethylpyridine. Sulfuryl chloride deoxygenated 2-picoline-*N*-oxide to give greater than a 90% yield of α-picoline. Although diethyl chlorophosphate, ethyl chloroformate in the presence and absence of triethylamine, and *N,N*-dimethylformamide gave good conversions of the 2-picoline-*N*-oxide, the selectivities to the 2-chloromethylpyridine were low. Modest conversions and selectivities for the reactions of phosgene or diethyl chlorophosphate with 2-picoline-*N*-oxide in the presence of triethylamine and of chloroacetyl chloride with 2-picoline-*N*-oxide gave disappointingly low overall yields of 2-chloromethylpyridine. The highest overall yield of 2-chloromethylpyridine was obtained from the reaction of 2-picoline-*N*-oxide with phosphoryl chloride in the presence of triethylamine.

Phosphoryl chloride reacted with 2-picoline-*N*-oxide (**1**) in the presence of triethylamine to give 2-chloromethylpyridine in 90% conversion with a 98% selectivity. The use of an external base in the reaction was critical since deprotonation of **2** by unreacted 2-picoline-*N*-oxide, as shown in the Vozza mechanism (4), could lead to no greater than 50% conversion of starting materials (Scheme I). When **2** was formed prior to the addition of any triethylamine, the product mixture contained 4- and 6-chloro-2-picoline as the major products. These products may have arisen via aromatic nucleophilic substitution by a chloride ion on **2**. If the phosphoryl chloride were added to a mixed solution of the triethylamine and **1**, the phosphoryl chloride preferentially reacted with the triethylamine rather than with **1**.

A delicate balance had to be met between the rates of the three major reactions: 2-picoline-*N*-oxide with phosphoryl chloride to yield the initial complex **2**, phosphoryl chloride with triethylamine to lower conversion and the initial complex with triethylamine to yield 2-chloromethylpyridine. This was accomplished by forming and maintaining a small amount of **2** in solution during the addition of the triethylamine. The addition of a solution of phosphoryl chloride in methylene chloride to a solution of 2-picoline-*N*-oxide in methylene chloride was begun. After approximately one tenth of the phosphoryl chloride solution had been added, the addition of a solution of triethylamine in methylene chloride commenced. The rate of addition of the two solutions was equivalent and was such that the exotherm from the reaction held the methylene chloride at reflux. In this manner there was an excess of **2** always present. This complex reacted with the triethylamine quickly and had little time to decompose to give the 4- and 6-chloro-2-picolines. The triethylamine appeared to react faster with **2** than with the phosphoryl chloride, and thus, the phosphoryl chloride was present to react with the 2-picoline-*N*-oxide. In this manner, consistent conversions of 89-90% with selectivities of 96-98% 2-chloromethylpyridine were realized.

EXPERIMENTAL

The ^{1}H-nmr spectra were run on a Varian T-60 Spectrometer using tetramethylsilane as the internal standard. VPC analysis were carried out on a Hewlett-Packard 5710A gas chromatograph equipped with thermal conductivity detectors using paired 6′ × ¼″ glass columns packed with 3% SE-30 on Chromosorb G and fitted into the injection port so that on-column injection occurred. Product analyses were calculated using response factors obtained relative to the internal standards: *o*-dichlorobenzene, 1,2,4-trichlorobenzene, or 1,2,3,4-tetrachlorobenzene.

General Procedure for the Reactions of **1** with Chlorinating Agents.

In an atmosphere of dry nitrogen a solution of the chlorinating agent in 10 ml of solvent was added dropwise to a stirred solution of **1** (1.00 g, 9.17 mmoles) in 10 ml of solvent. Triethylamine was added dropwise to the resulting solution which was heated for the length of time listed in Table I. A known amount of internal standard was added and VPC analysis was performed.

Reaction of 1 with Phosphoryl Chloride and Triethylamine.

To a stirred solution of **1** (0.88 g, 8.1 mmoles) in methylene chloride (5 ml) under a nitrogen atmosphere, the addition of a solution of phosphoryl chloride (1.46 g, 9.17 mmoles) in methylene chloride (5 ml) was begun. After one-tenth of the phosphoryl chloride solution had been added, simultaneously the addition of a solution of triethylamine (0.926 g, 9.17 mmoles) in methylene chloride (5 ml) was begun. The rate of addition of the phosphoryl chloride and the triethylamine solutions was the same and was set so that the heat of reaction caused the methylene chloride to reflux. After the addition of the phosphoryl chloride solution had been completed, the remaining one-tenth of the triethylamine solution was completed. VPC analysis of the resulting mixture showed 90% conversion of **1** and a 98% selectivity to 2-chloromethylpyridine.

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