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THE PREPARATION OF 4- AND 6-CHLORO-2-CHLOROMETHYLPYRIDINE

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Abstract—6-Chloro-2-chloromethylpyridine is prepared from 6-chloro-2-methylpyridine by a route in which the 2-Me substituent was successively converted to 2-acetoxymethyl, 2-hydroxymethyl and finally to the required 2-chloromethyl substituent. Attempts to simultaneously monochlorinate the Me group and reduce the N-oxide function of 6-chloro-2-methylpyridine-N-oxide with methanesulphonyl chloride and *p*-toluenesulphonyl chloride gave only very small yields of 6-chloro-2-chloromethyl-pyridine. 4-Chloro-2-chloromethylpyridine is prepared from 2-methylpyridine-N-oxide by nitration, followed by substitution of the 4-nitro group by chloro using conc HCl; side chain chlorination of the 2-Me group using *p*-toluenesulphonyl chloride yields 4-chloro-2-chloromethylpyridine. Phosphoryl chloride reacts with 2-chloromethylpyridine-N-oxide hydrochloride to yield only 14.4% of 4-chloro-2-chloromethylpyridine, together with 2-chloromethylpyridine (2.2%), 2-dichloromethylpyridine (41.6%) and 6-chloro-2-chloromethylpyridine (41.8%). Attempts to N-oxidise 2-chloromethylpyridine with peracids led to either 2-hydroxymethylpyridine (peracetic, *m*-chloroperbenzoic and performic acid) or no reaction (pertrifluoroacetic acid); none of the peracids led to any detectable N-oxidation.

We required both 6- and 4-chloro-2-chloromethylpyridine in connection with a programme concerned with the preparation of pyridine compounds containing thiol substituents. The 6-isomer has not previously been prepared whereas the 4-isomer has been prepared by methanesulphonyl chloride chlorination of 4-chloro-2-methylpyridine-N-oxide[1], which can be obtained in a two step reaction from 2-methylpyridine-N-oxide. Here we report the synthesis of the hitherto unknown 6-isomer, together with an improved preparation of the 4-isomer.

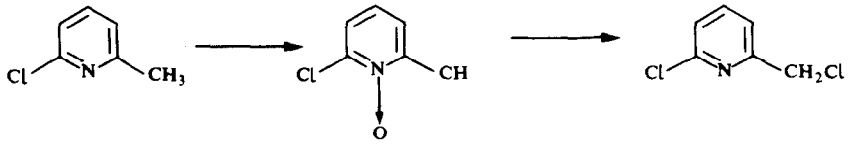
Synthesis of 6-chloro-2-chloromethylpyridine. Initial attempts to synthesise 6-chloro-2-chloromethylpyridine from 6-chloro-2-methylpyridine were based on oxidation of 6-chloro-2-methylpyridine followed by a search for reagents that would monochlorinate the Me side chain with simultaneous reduction of the N-oxide function (reaction 1). Both methanesulphonyl chloride and *p*-toluenesulphonyl chloride are known to effect similar reactions with analogous compounds (see Refs. 1 and 2 and below). However methanesulphonyl chloride gave only a 1% yield of the desired 6-chloro-2-chloromethylpyridine and *p*-toluenesulphonyl chloride gave only a trace, together with a small amount of 6-chloro-2-methylpyridine formed by reduction, but not side-chain chlorination, of the starting N-oxide.

6-Chloro-2-chloromethylpyridine was successfully synthesised from 6-chloro-2-methylpyridine in 18% overall yield by converting the 2-Me substituent successively to 2-acetoxymethyl, 2-hydroxymethyl and finally to the required 2-chloromethyl substiuent (Scheme 1).

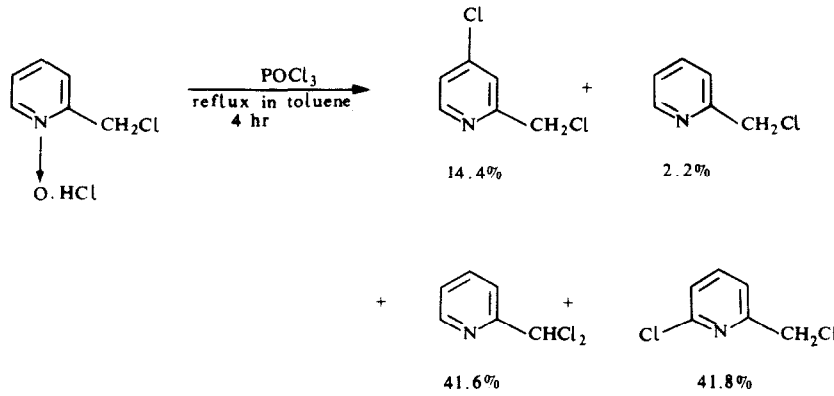
Synthesis of 4-chloro-2-chloromethylpyridine. 2-Methylpyridine-N-oxide is reported to react with phosphoryl chloride to yield 4-chloro-2-methylpyridine in 72, 28 and 22% yields.[3-5] When 2-chloromethylpyridine-N-oxide hydrochloride was treated with phosphoryl chloride a mixture of four products was obtained, in which the desired product was only a relatively minor component (reaction 2). Although the high yield of the hiteerto unknown 6-chloro-2-chloromethylpyridine was unexpected, it is noteworthy that one previous report[4] of the corresponding reaction of 2-methylpyridine-N-oxide did note the formation of small amounts of both 6-chloro-2-methylpyridine and 2-chloromethylpyridine.

Before reaction (2) could be studied in detail a source of 2-chloromethylpyridine-N-oxide was required. This is no longer made commercially. Two routes are described (reactions 3 and 4),[6,7] and both have been used by others.[8] The first starts with 2-hydroxymethylpyridine-N-oxide, which may be prepared by N-oxidation of 2-hydroxymethylpyridine with 35% hydrogen peroxide. This oxidation has led to a number of explosions,[9] and accordingly we examined reaction (4). However when this was carried out using the conditions described[7] the product was not that shown in reaction (4) but rather a 15% yield of 2-hydroxymethylpyridine, (reaction 5). Attempts to modify the conditions of reaction (5) only resulted in modifications to the yield of 2-hydroxymethylpyridine; no conditions under which reaction (4) occurred could be found. Accordingly alternative peracid oxidants were examined. These gave either 2-hydroxymethylpyridine (*m*-chloroperbenzoic acid at 50° and performic acid at 100°) or no reaction at all (*m*-chloroperbenzoic acid between 4 and 25°[10] and pertrifluoracetic acid at 100°); none of the peracids led to any detectable N-oxidation.

4-Chloro-2-chloromethylpyridine was finally synthesised (Scheme 2) from 2-methylpyridine-N-oxide by



(1)



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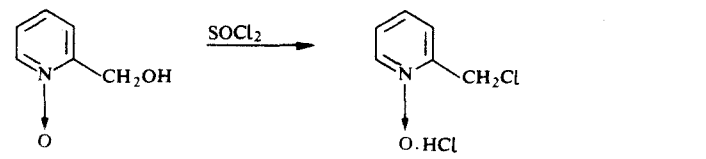

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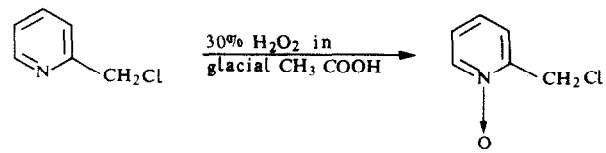

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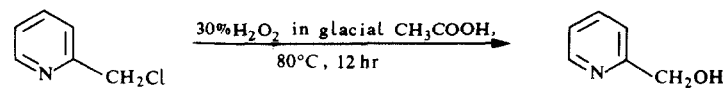
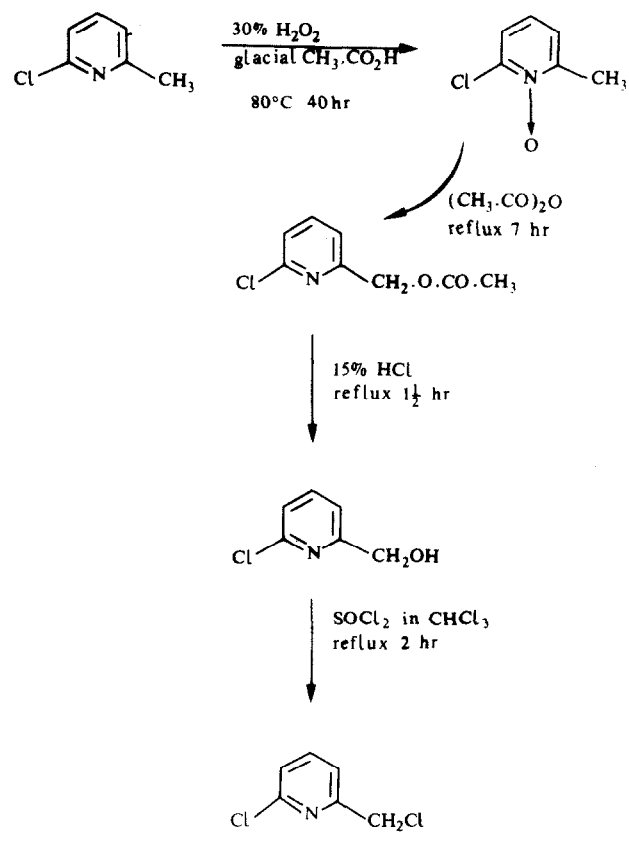
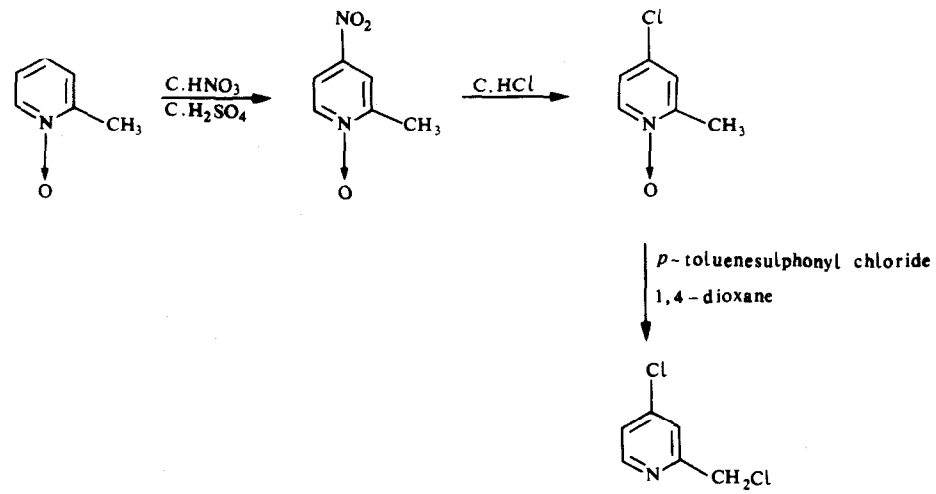


(5)

Scheme 1.





Scheme 2.

nitration to yield the 4-nitro derivative,[13] followed by treatment with conc HCl[14] to give the 4-chloro product in 84% yield. An alternative route for replacing the 4-nitro group by a chloro group using acetyl chloride[15] gave only a 16% yield. The side chain Me group was chlorinated in 35% yield using *p*-toluenesulphonyl chloride. This was better than the methanesulphonyl chloride route previously recommended[1] which gave only 14% 4-chloro-2-chloromethylpyridine.

EXPERIMENTAL

Ir spectra were recorded with a Perkin–Elmer 577 spectrometer. ^{1}H NMR spectra were run on a Perkin–Elmer R32 90 MHz spectrometer in $CDCl_3$ using TMS as an internal standard. Combined gas chromatography-mass spectrometry data were obtained by Dr. A. Gilbert in the Chemistry Department at Reading University using a Pye 104 chromatograph fitted with a 150 × 0.65 cm glass column packed with SE 30 (10%) on siliconised celite (85–100 mesh) coupled to an AEI MS-12 single focussing spectrometer. Microanalyses were performed either by Dr. F. Strauss at Oxford or the Butterworth Microanalytical Laboratory in Teddington.

6-Chloro-2-methylpyridine-N-oxide was prepared by peracetic acid oxidation of 6-chloro-2-methylpyridine,[5] 4-nitro-2-methylpyridine-N-oxide was prepared by nitration of 2-methylpyridine-N-oxide[13] and 4-chloro-2-methylpyridine-N-oxide was prepared by refluxing 4-nitro-2-methylpyridine-N-oxide with HCl.[14]

6-Chloro-2-chloromethylpyridine. 6-Chloro-2-methylpyridine-N-oxide (41.84 g; 0.29 mol) was gently refluxed in Ac_2O (223 ml) for 7 hr. After workup vacuum distillation (b.p. 87–88°; 0.02 mm Hg) yielded 24.60 g (49.8%) of bright yellow 6-chloro-2-acetoxymethylpyridine; ^{1}H NMR: δ 7.66 (t, 1H, H^4), δ 7.30 (d, 1H, H^3), δ 7.21 (d, 1H, H^5), δ 5.16 (s, 2H, $-CH_2-$), δ 2.15 (s, 3H, $-CH_3$); strong IR peaks were observed at 1747, 1230 and 1054 cm^{-1}.

A soln of 6-chloro-2-acetoxymethylpyridine (24.50 g; 0.13 mol) was hydrolysed by gently refluxing for 1.5 hr in 15% HCl aq (70 ml). After workup a pale green oil was obtained, which was purified by column chromatography using alumina; elution was effected by diethyl ether to yield 11.37 g (60% yield) of yellow 6-chloro-2-hydroxymethylpyridine. ^{1}H NMR: δ 7.63 (t, 1H, H^4), δ 7.31 (d, 1H, H^3), δ 7.18 (d, 1H, H^5), δ 4.72 (s, 2H, $-CH_2-$) and δ 1.20 (t, 1H, –OH).

A soln of $SOCl_2$ (14.30 g; 0.21 mol) in $CHCl_3$ (10 ml) was added dropwise to a soln of 6-chloro-2-hydroxymethylpyridine (15.15 g; 0.11 mol) in $CHCl_3$ (10 ml). The mixture was gently refluxed with stirring for 2 hr. Workup gave a pale brown solid which was purified by column chromatography using alumina. Elution was effected by EtOH to give golden yellow platelets of 6-chloro-2-chloromethylpyridine (11.58 g; 68% yield). ^{1}H NMR: δ 7.78 (t, 1H, H^4), δ 7.51 (d, 1H, H^3), δ 7.36 (d, 1H, H^5) and δ 4.72 (s, 2H, $-CH_2-$). (Found: C, 44.7; H, 3.2; N, 8.4. $C_6H_5NCl_2$ requires: C, 44.5; H, 3.1; N, 8.6%).

When 6-chloro-2-chloromethylpyridine was prepared directly from 6-chloro-2-methylpyridine-N-oxide without special purification of the intermediates an overall yield of 18% was achieved.

Attempts were made to convert 6-chloro-2-methylpyridine-N-oxide to 6-chloro-2-chloromethylpyridine directly using both methanesulphonyl chloride and *p*-toluenesulphonyl chloride. A soln of 6-chloro-2-methylpyridine-N-oxide (20.0 g; 0.14 mol) in 1,4-dioxane (200 ml) was gently refluxed with stirring for 16 hr with either methanesulphonyl chloride (31.6 g; 0.28 mol) or *p*-toluenesulphonyl chloride (53.0 g; 0.28 mol). After workup vacuum distillation of the product obtained using methanesulphonyl chloride yielded two fractions: The first fraction (2.32 g; 12% yield) boiled between 60 and 65° (0.07 mm Hg) and was identified as 6-chloro-2-methylpyridine-N-oxide (I/R strong band at 1262 cm^{-1} due to N→O, ^{1}H NMR: δ 7.42 (t, 1H, H^4), δ 7.25 (d, 1H, H^3), δ 7.10 (d, 1H, H^5) and δ 2.55 (s, 3H, $-CH_3$). The second fraction (0.2 g; 1% yield) boiled between 51 and 53° (0.15 mm Hg) and was identified spectroscopically as 6-chloro-2-chloromethylpyridine. The product obtained using *p*-toluenesulphonyl chloride was vacuum distilled at 0.06 mm Hg to yield 2.82 g of a colourless liquid boiling between 60 and 63°. Preparative tlc (Merck, silica gel 60 F_{254} pre-coated incorporating an UV fluorescent indicator) using toluene:MeOH (90:10) to elute a $CHCl_3$ (1 ml) soln of the distillate (1 g) showed three components, unreacted 6-chloro-2-methylpyridine-N-oxide, 6-chloro-2-methylpyridine and 6-chloro-2-chloromethylpyridine, the last being identified spectroscopically and by microanalysis (Found: C, 44.7; H, 3.2; N, 8.4. $C_6H_5NCl_2$ requires: C, 44.5; H, 3.1; N, 8.6%).

4-Chloro-2-chloromethylpyridine. The chlorination of 4-chloro-2-methylpyridine-N-oxide by both methanesulphonyl chloride and *p*-toluenesulphonyl chloride was examined using a procedure identical to that just described for 6-chloro-2-chloromethylpyridine. 4-Chloro-2-chloromethylpyridine (b.p. 75–78° at 4.0 mm Hg) was obtained in 14% yield using methanesulphonyl chloride and in 35% yield using *p*-toluenesulphonyl chloride. ^{1}H NMR: δ 8.45 (d, 1H, H^6), δ 7.48 (s, 1H, H^3), δ 7.22 (d, 1H, H^5) and δ 4.63 (s, 2H, $-CH_2-$). The picrate derivative was prepared and found to melt at 116°C (lit[1] 123–125°) (Found: C, 37.1; H, 2.3; N, 14.4. $C_{12}H_8O_7N_4Cl_2$ requires: C, 36.8; H, 2.1; N, 14.3%).

Attempts to N-Oxidise 2-Chloromethylpyridine.

(1) *Peracetic acid.* A mixture of freshly distilled 2-chloromethylpyridine (17.5 g; 0.14 mol) and 30% H_2O_2 (14 ml) in glacial AcOH (60 ml) was stirred at 80° for 3 hr, cooled, and after adding a further 10 ml of 30% H_2O_2 stirred at 80° for a further 9 hr. After workup a dark brown liquid was distilled under vacuum at 60–61° (0.45 mm Hg) to give 2.60 g (15% yield) of colourless 2-hydroxymethylpyridine identified by IR (strong, broad-OH stretch in the region 3700–3100 cm^{-1}), ^1H NMR: δ 8.41 (d, 1H, H^6), δ 7.62 (t, 1H, H^4), δ 7.35 (d, 1H, H^3), δ 7.10 (t, 1H, H^5), δ 5.46 (s, 1H, -OH), δ 4.73 (s, 2H, $-CH_2-$) and microanalysis (Found: C, 64.9; H, 6.5; N, 12.6. C_6H_7NO requires: C, 66.0; H, 6.5; N, 12.8%).

(2) *m-Chloroperbenzoic acid.* No reaction occurred when it was carried out between 4 and 25° as described.[10] A soln of *m*-chloroperbenzoic acid (12.52 g; 0.07 mol) in $CHCl_3$ (130 ml) was added over 2 hr to a stirred soln of 2-chloromethylpyridine (9.25 g; 0.07 mol) in $CHCl_3$ (15 ml) and the mixture then stirred at 50° for 3 days. Following workup vacuum distillation yielded 1.20 g (15% yield) of 2-hydroxymethylpyridine.

(3) *Pertrifluoroacetic acid.* When 2-chloromethylpyridine was treated with 30% H_2O_2 in trifluoroacetic acid for 4 hr over a steam bath no reaction took place; workup yielded only the initial reactant.

(4) *Performic acid.* 30% H_2O_2 (26 ml) was added slowly with stirring to a soln of freshly distilled 2-chloromethylpyridine (32.5 g; 0.26 mol) in formic acid (110 ml, 98–100%) and the mixture then heated over a steam bath for 3 hr. After cooling, addition of further 30% H_2O_2 (20 ml) and heating over a steam bath for a further 9 hr, workup yielded 16.30 g (59% yield) of 2-hydroxymethylpyridine.

Reaction of phosphoryl chloride with 2-chloromethylpyridine-N-oxide hydrochloride

A soln of $POCl_3$ (40.0 g; 0.26 mol) and 2-chloromethylpyridine-N-oxide hydrochloride (53.0 g; 0.29 mol) in dry toluene (60 ml) was refluxed gently for 4 hr. After workup vacuum distillation (b.p. 57–60°; 0.35 mm Hg) yielded 10.98 g of a pale yellow liquid. Combined gas chromatography-mass spectrometry indicated four peaks of relative areas 2.2:41.6:14.4:41.8 containing components whose parent ions had masses of 127, 162, 162 and 162 respectively.

Preparative tlc (Merck, silica gel $60F_{254}$ pre-coated incorporating an UV fluorescent indicator) of a soln of the pale yellow liquid (0.5 g) in $CHCl_3$ (4.0 ml) using chloroform as eluent resulted in the separation of 4 bands, each of which was removed, extracted with $CHCl_3$ and evaporated to an oil. On dilution with $CDCl_3$ the four components were identified by combining the previous gas chromatography-mass spectrometry data with ^1H NMR data as follows: Component 1: 2-chloromethylpyridine (MW 127) δ 8.55 (d, 1H, H^6), δ 7.70 (t, 1H, H^4), δ 7.45 (d, 1H, H^3), δ 7.20 (t, 1H, H^5), δ 4.67 (s, 2H, $-CH_2-$). Component 2: 2-dichloromethylpyridine (MW 162) δ 8.55 (d, 1H, H^6), δ 7.76 (*m*, 2H, H^3H^4), δ 7.35 (t, 1H, H^5), δ 6.74 (s, 1H, -CH=). Component 3: 4-chloro-2-chloromethylpyridine (MW 162) δ 8.46 (d, 1H, H^6), δ 7.50 (d, 1H, H^3), δ 7.25 (d, 1H, H^5), δ 4.64 (s, 2H, $-CH_2-$). Component 4: 6-chloro-2-chloromethylpyridine (MW 162) δ 7.70 (t, 1H, H^4), δ 7.42 (d, 1H, H^3), δ 7.28 (d 1H, H^5), δ 4.64 (s, 2H, $-CH_2-$).

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