Synthesis of 6-Chlorofuro[2,3-*b*]pyridine-2-carboxylic Acid

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A new route was employed to synthesize methyl 6-chlorofuro[2,3-*b*]pyridine-2-carboxylate by concurrent dehydrohalogenation and dehydration of 3-chloro-3-(β,β-dichloro-β-ethoxycarbonylethyl)-2,6-piperidinedione using methyl phosphonyl chloride.

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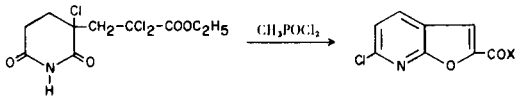
The current synthetic routes to furo[2,3-*b*]pyridine-2-carboxylic acid (1) are essentially based on the work of Snyder and Ebetino (2). Their synthesis rested upon condensation of a suitable 2,5-disubstituted furan derivative with either a 1,3-dicarbonyl compound or an α-alkoxymethylene derivative with subsequent ring closure of the intermediate to yield the pyridine nucleus.

We report herein a new synthesis of 6-chlorofuro-[2,3-*b*]pyridine carboxylic acid by an entirely different route and employing different starting materials than those previously described (1).

During the course of work on 3-alkylsubstituted 2,6-dichloro-pyridines (3) a facile synthesis of the ester **2** was developed starting from the cheap commercially available α-methyleneglutaronitrile, which is one of the dimers of acrylonitrile. It has previously been shown that the addition of ethyl trichloroacetate to the double bond of α-methyleneglutaronitrile is catalyzed by copper (I) chloride and yielded ethyl 4,6-dicyano-2,2,4-trichlorohexanecarboxylate (3). This ester was cyclized with gaseous hydrogen bromide followed by hydrolysis to yield 3,3-disubstituted piperidinedione **1** (3). When **1** was heated with excess methyl phosphonyl chloride (4) (Scheme 1) at 160°, aromatization of the 2,6-piperidinedione moiety followed

Scheme 1



1

2, X = OC_2H_5
3, X = OH
4, X = Cl

its expected course (3), while the side chain was simultaneously dehydrohalogenated and subsequently cyclized to a substituted furan ring (**2**) fused to the pyridine ring system. Alkaline saponification of **2** furnished the acid **3** which could be converted with thionyl chloride into the corresponding acid chloride **4**.

The products were identified as furo[2,3-*b*]pyridine derivatives by their spectral and analytical data and by their nmr assignments for the protons of the pyridine and the furan ring. The compounds **2** and **4**, respectively, showed two doublets each for H-4 and H-5, with a coupling constant of J_{4-5} = 8, and thus the nmr-pattern agrees with those of a number of 2,3,6-trisubstituted chloropyridines which have already been presented earlier in more detail (5). The singlet for H-3 at 7.47 is in good agreement with the reported value for the H-3 signal of a known furopyridinecarboxylic acid ester (both in deuteriochloroform solution) (1).

This result was quite in contrast to that found when phosphoryl chloride was employed to achieve aromatization of **1**, whereby a mixture of ethyl β-(2,6-dichloropyridyl)-β,β-dichloropropionate (**5**) and 3,7-dichloro-2*H*-pyrano[2,3-*b*]-2-pyridone (**6**) was obtained, albeit both in unsatisfactory yields (3).

Although phosphoryl chloride is usually employed to achieve dehydrative aromatization, it seems noteworthy that by using methyl phosphonyl chloride not only can the reaction temperature be raised considerably without using an autoclave, but also it possesses the distinct advantage of being able to differentiate between two apparently equivalent points of chlorination.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded in potassium bromide discs on a Perkin Elmer-221 instrument and the nmr spectra were determined on a Varian HA-100D instrument, using TMS as the internal standard.

6-Chlorofuro[2,3-*b*]pyridine-2-carboxylic Acid Ethyl Ester (**2**).

A stirred mixture of 120.0 g. (0.382 mole) of 3-chloro-3-(β,β-dichloro-β-ethoxycarbonylethyl)-2,6-piperidinedione (**1**) and 199.5 g. (1.5 mole) of methyl phosphonyl chloride was heated to 140° for a period of 1 hour and then at 180° for 3.5 hours. The dark solution was then poured into ice water and stirred for 2 hours. The crystals obtained were filtered, washed with water and dried at 50° under vacuum. The crude product (93.5 g.) was recrystallized from 235 ml. of ethanol to yield 61.5 g. (68.3%) of crystals (96% purity by gc). An analytical sample was obtained by crystallization from ethanol in the presence of decolorizing carbon, m.p. 134-135°; ir cm^{-1}: ν 1718 (ester), 1595, 1582, 1560, 1330, 1300, 1230, 1185; uv (methanol): λ max (ε) 258 (11,500), 268 (11,900), 298 (19,000), 305 (18,000); nmr (deuteriochloroform): δ 7.97 (d) H-4, 7.32 (d) H-5, J = 8.0 Hz, 7.47 (s) H-3 (furan ring), 4.42 (q) CH_2, and 1.40 (t) CH_3 both of the ethyl group.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 53.23; H, 3.57; Cl, 15.71; N, 6.20. Found: C, 53.06; H, 3.51; Cl, 15.70; N, 6.16.

6-Chlorofuro[2,3-*b*]pyridine-2-carboxylic Acid (**3**).

A suspension of 22.5 g. (0.1 mole) of **2** in 200 ml. of ethanol and 100 ml. of water containing 8.0 g. (0.2 mole) of sodium hydroxide was refluxed for a period of 1 hour. The solution was then evaporated to dryness and the solid residue dissolved in 600 ml. of water and filtered. The filtrate was acidified by addition of 25 ml. of concentrated hydrochloric acid yielding 16.4 g. (82.3%) of acid. An analytical sample was prepared by crystallization from

a 1:1 mixture of dimethylformamide-water, m.p. 300-301° dec.; ir cm^{-1}: ν 3050, 1683, 1585, 1563, 1555. No solvent was found which was suitable for recording the nmr-spectra.

Anal. Calcd. for $C_8H_4ClNO_3$: C, 48.63; H, 2.04; Cl, 17.94; N, 7.09. Found: C, 48.48; H, 2.04; Cl, 17.84; N, 7.19.

6-Chlorofuro[2,3-*b*]pyridine-2-carboxylic Acid Chloride (**4**).

A suspension of 39.4 g. (0.2 mole) of **3** in 500 ml. of benzene, 35.8 g. (0.3 mole) of thionyl chloride, and 1.2 ml. of dimethylformamide was heated to reflux for a period of 2 hours. Then a further 800 ml. of benzene and 5 g. of decolorizing carbon were added and refluxing continued for 10 minutes. The carbon was removed by filtration and washed with 100 ml. of benzene. The combined filtrates were evaporated to dryness and 60 ml. of benzene added to the solid residue yielding 38.0 g. (88%) of acid chloride. An analytical sample was prepared by crystallization from benzene, m.p. 165-166°; ir cm^{-1}: ν 1730, 1593, 1580, 1540; nmr (dimethylsulfoxide-d_6): δ 8.35 (d) H-4; 7.53 (d) H-5; 7.73 (s) H-3.

Anal. Calcd. for $C_8H_3Cl_2NO_2$: C, 44.48; H, 1.40; Cl, 32.82; N, 6.48. Found: C, 44.68; H, 1.60; Cl, 32.68; N, 6.42.

REFERENCES AND NOTES

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