Short Communication

Activation of Phosphorus Oxychloride for Hydroxy to Chlorine Displacement Reactions. Preparation of 3-Chloro- and 3-Ethylthio-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine

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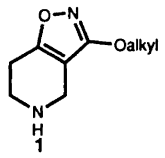
In our research program for the development of cholinergic agents, we attempted to prepare a series of 3-alkylthio-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridines as analogs to the known 3-alkoxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridines (**1**), which exhibit interesting central cholinergic activity.[1]



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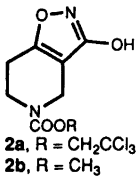
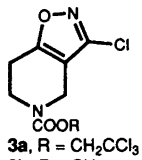
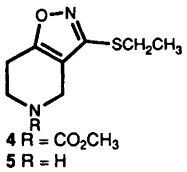


2a, R = CH_2CCl_3
2b, R = CH_3



3a, R = CH_2CCl_3
3b, R = CH_3



4 R = CO_2CH_3
5 R = H

Reaction of methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-5-carboxylate (**2b**) with an old sample of phosphorus oxychloride and pyridine provided the 3-chloro-compound **3b**. The old sample of phosphorus oxychloride had been in use for several years. Surprisingly, **3b** was not formed when freshly distilled phosphorus oxychloride was employed. The hydroxy compound (**2b**) remained unchanged, even under forcing conditions. When, however, pyridine hydrochloride was added, **3b** was formed in low yield. The yield increased to 51 % if phosphoric acid was also added.† ^{13}C NMR spectra recorded during the reaction with freshly distilled phosphorus oxychloride alone showed that the signals from the hydroxy-substituted carbon and the adjacent carbon were both split into a doublet immediately after mixing of the reagents at 20 °C. The spectrum then remained almost unchanged even when the temperature of the reaction was raised to 90 °C for 5 h. The magnitude of the signal splittings corresponds to that of a ^{31}P–^{13}C coupling in an intermediate with a phosphorylated hydroxy group.[2] Subsequent work-up comprising washing with water leads to hydrolysis of the phosphorylated intermediate to give unchanged starting material. When pure phosphorus oxychloride is applied the subsequent substitution of the phosphoryloxy group with chloride ion liberated in the phosphorylation step fails. The reason may be that the chloride ion needed for the second step is lost by evaporation of hydrogen chloride. Addition of pyridine hydrochloride may provide a supplementary and more reliable source of chloride ion needed for the substitution. The role of the phosphoric acid may be to protonate the dichlorophosphoryloxy group, thereby improving its leaving-group ability.

Another possibility is that the phosphoric acid phosphorylates the phosphoryloxy group providing a polyphosphate group with improved leaving-group ability.

According to the literature, substitution of a hydroxy group with chlorine by the use of phosphorus oxychloride frequently produces low or unreliable yield. In such cases the present modification may lead to improved and reproducible yields.

The method described for the conversion of a 3-hydroxyisoxazole into the corresponding 3-chloroisoxazole is superior to known approaches which comprise dealkylation of 2-alkyl-3-chloroisoxazoles.[3,4]

Reaction of the chloro compound **3b** with sodium ethanethiolate in *N*,*N*-dimethylformamide (DMF) gave the corresponding ethylthio compound **4** which was readily depro-

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†An even higher yield (68 %) was obtained if the hydroxy compound was protected at the nitrogen atom by trichloroethylcarbamoylation rather than by methylcarbamoylation.

tected by standard procedures[1] to provide the target compound **5**.

Experimental

N,N-Dimethylformamide was dried over molecular sieves (4 Å) for two days. Melting points (uncorrected) were determined on a Büchi SMP-20 apparatus. The NMR spectra were recorded on a Bruker AC-250 instrument. ^{1}H NMR spectra were obtained at 250.133 MHz and the positions of signals are given in ppm relative to tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 62.93 MHz and the positions of signals are given in ppm relative to the deuteriochloroform signal at 76.90 ppm. Microanalyses were performed by Lundbeck Analytical Department and by Preben Hansen Microanalytical Laboratory.

NMR Experiment. Methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-5-carboxylate (**2b**) exhibits the following characteristics in the ^{13}C NMR spectrum ($CDCl_3$): 167.6 (C-3), 167.2 (C-7a), 101.9 (C-3a). Compound **2b** (0.40 g) was dissolved in freshly distilled phosphorus oxychloride (2.0 ml). Aliquots of 0.5 ml were diluted with deuteriochloroform (0.5 ml) and ^{13}C NMR spectra were recorded immediately after mixing, after heating at 90 °C for 1 h, and after heating at 90 °C for 5 h. Apart from a small contamination in the last spectrum, a single compound was present showing the following characteristics: 170.2 (s, C-7a), 160.7 (d, $J_{^{13}C-^{31}P} = 10.7$, C-3), 102.6 (d, $J_{^{13}C-^{31}P} = 4.9$, C-3a).

Substitution of OH with Cl. (a) A mixture of 2,2,2-trichloroethyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]-pyridine-5-carboxylate (**2a**) (7.9 g, 25 mmol) (prepared according to Ref. 5), pyridinium hydrochloride (9.5 g), phosphoric acid (1.6 g) and phosphorus oxychloride (19 ml) was heated at 85–90 °C for 5 h. After the volatile products had been removed *in vacuo*, ethyl acetate (100 ml) was added. The mixture was cooled to 0 °C and saturated sodium hydrogencarbonate (100 ml) was added slowly. After 15 min of stirring the phases were separated and the organic phase was washed with sodium hydrogencarbonate (100 ml) and dried (Na_2SO_4). Removal of the solvents afforded 2,2,2-trichloroethyl 3-chloro-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]-pyridine-5-carboxylate (**3a**) as an oil which was purified by column chromatography (ethyl acetate–heptane [1:1]) and crystallization from ethyl acetate to produce 5.7 g (68%), m.p. 60–62 °C, ^{1}H NMR ($CDCl_3$) 4.80 (2 H, s), 4.47 (2 H, br s), 3.82–3.95 (2 H, m), 2.95 (2 H, t, $J = 5.7$ Hz); ^{13}C NMR[‡] ($CDCl_3$): 168.5, 153.8 (br), 150.4, 110.0+109.9, 95.1, 75.2, 40.7, 39.1+38.7, 23.8+23.3. MS [*m/z* (% rel. int.)]: 332 (19, *M*) and 331 (18, *M*−H) complicated pattern indicating four chlorine atoms. Anal. $C_9H_8Cl_4N_2O_3$: C, H, N.

(b) Similarly, methyl 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-5-carboxylate (**2b**) produced 51 % of methyl 3-chloro-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-5-carboxylate (**3b**) as an oil. ^{1}H NMR ($CDCl_3$): 4.38 (2 H, br s), 3.82 (2 H, br t, $J = 5.7$ Hz), 3.76 (3 H, s), 2.84 (2 H, t, $J = 5.7$ Hz); ^{13}C NMR ($CDCl_3$): 168.5, 155.7, 150.5, 110.0, 52.9, 40.2, 38.5, 23.5. MS [*m/z* (% rel. int.)]: 216, pattern characteristic of one chlorine atom (2, *M*), 215 (2, *M*−H), 181 (100, *M*−Cl). Anal. $C_8H_9ClN_2O_3$: C, H, N.

Substitution of Cl with SCH_2CH_3. A 60 % suspension of sodium hydride in mineral oil (0.44 g, 1 mmol) was extracted twice with heptane (10 ml) and dry DMF (10 ml) was added. The mixture thus formed was cooled to 0 °C and ethanethiol (1.0 ml, 13.5 mmol) was added over 5 min. After 0.5 h of stirring, a solution of methyl 3-chloro-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-5-carboxylate (**3b**) (1.2 g, 5.5 mmol) in dry DMF (10 ml) was added over 10 min. The reaction was continued for 3 h at 0 °C. The reaction mixture was poured onto ice and water (50 ml), and the aqueous phase was extracted twice with ethyl acetate (100 ml). The combined organic phases were washed with brine and dried (Na_2SO_4). Removal of the solvents gave an oil which was purified by column chromatography (ethyl acetate–heptane [1:1]). Crystallization from ethyl acetate afforded 0.91 g (68 %) of methyl-3-ethylthio-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-5-carboxylate (**4**), m.p. 80–82 °C, ^{1}H NMR ($CDCl_3$): 4.26 (2 H, br s), 3.78 (2 H, br t), 3.72 (3 H, s), 3.15 (2 H, q, $J = 7.3$ Hz), 2.78 (2 H, t, $J = 5.6$ Hz), 1.41 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): 165.7, 156.2, 155.7, 109.8, 52.7, 40.2, 38.8, 25.1, 23.2, 14.4; MS [*m/z* (% rel. int.)]: 242 (6, *M*), 181 (100, *M*−SCH_2CH_3). Anal. $C_{10}H_{14}N_2O_3S$: C, H, N.

Deprotection of the pyridine nitrogen. A solution of methyl 3-ethylthio-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-5-carboxylate (**4**) (2.7 g, 11.2 mmol) in 65 ml of a 1:1 mixture of 0.85 M aqueous potassium hydroxide and methanol was heated to 80 °C for 18 h. The solvents were removed *in vacuo* and water (50 ml) was added. Extraction with ethyl acetate (3×100 ml), drying (Na_2SO_4) and evaporation of the ethyl acetate afforded 1.91 g of 3-ethylthio-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine (**5**) as an oil, which was precipitated as its maleate from acetone. Yield 2.5 g (75 %), ^{1}H NMR (DMSO-d_6): 6.0 (2 H, s), 4.0 (2 H, s), 3.4 (2 H, t, $J = 6.1$ Hz), 3.1 (2 H, q, $J = 7.3$ Hz), 3.0 (2 H, t, $J = 6.1$ Hz), 1.3 (3 H, t, $J = 7.3$ Hz). Anal. $C_8H_{12}N_2OS$, $C_4H_4O_4$: C, H, N.

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‡Some signals were duplicated or broad owing to the presence of two conformers as the result of hindered rotation at the amide nitrogen–carbon bond.

References

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