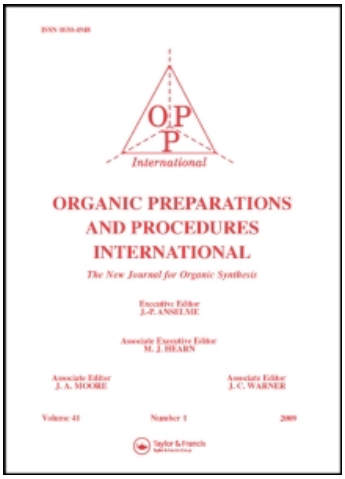

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SYNTHESIS OF 3- AND 4-CHLORO-1H-PYRROLO[3, 2-c]PYRIDIN-4(5H)-ONE

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SYNTHESIS OF 3- AND 4-CHLORO-1H-PYRROLO[3,2-c]PYRIDIN-4(5H)-ONE

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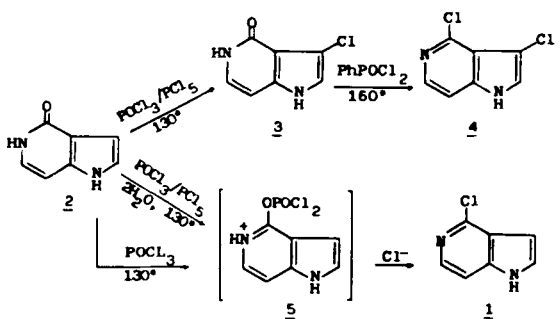
As part of our investigation into the preparation of dideaza analogues of adenosine of biological interest,[1] we had a need for 4-chloro-1H-pyrrolo[3,2-c]pyridine (1). The method of Ducrocq and coworkers,[2] involving chlorination of the dihydrate of 1H-pyrrolo[3,2-c]pyridin-4(5H)-one (2) by a mixture of phosphorus oxychloride/phosphorus pentachloride was considered. We were unable to obtain the required hydrate of 2 through the debenzylation of 1-benzylpyrrolo[3,2-c]pyridin-4(5H)-one with



sodium in liquid ammonia.[2] In spite of several attempts only white crystals of 2 containing varying amounts of water could be isolated. Drying of the wet product under vacuum at room temperature gave 2, identical to the product obtained by sublimation.[1] Thus, we attempted to chlorinate this form under conditions identical to those used by Ducrocq

and coworkers; surprisingly, however, we only isolated 3-chloro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (3). The structure of 3 was supported by the ^1H nmr spectrum which showed signals of H-6 and H-7 as doublets at δ7.08 and 6.40 with a coupling constant (6 Hz) similar to that reported for the same protons in the case of 1.[2] The structure of 3 was confirmed by conversion into 3,4-dichloro-1H-pyrrolo[3,2-c]pyridine (4), by phenylphosphonic dichloride at 160° for 2 hrs (Scheme 1). Compound 4 was shown to be different from a sample of the isomeric 4,6-dichloro-1H-pyrrolo[3,2-c]pyridine.[3]

The conversion of 1H-pyrrolo[3,2-c]pyridin-4(5H)-one (2) into 3-chloro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (3) in the absence of water presumably involves an electrophilic substitution at the carbon 3 by chlorine generated by thermal dissociation from PCl_5.[4] The addition of water to the reaction mixture promoted formation of hydrogen chloride which catalyzed the conversion of the proposed intermediate 5 to 1 by attack of the chloride ion at the carbon 4. Thus the presence of water in the reaction mixture shifts the reaction pathway towards 1 rather than 3.

EXPERIMENTAL SECTION

All melting points were taken on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrofotometer model 257. EM-390 and FT-80 Spectrometers (all Varian) were used to obtain nmr spectra and chemical shifts are reported on the δ scale relative to TMS as an internal standard. The elemental analyses were performed on a Carlo-Erba 1106 elemental analyzer.

1H-Pyrrolo[3,2-c]pyridin-4(5H)-one (2).- This compound was prepared starting from 1-benzylpyrrolo[3,2-c]pyridin-4(5H)-one as described in the literature.[2] After crystallization from water, 2 was obtained as white needles which, after drying under vacuum at room temperature, melted at 242-244°, lit.[2] 245-247°; ^{13}C nmr (DMSO-d_6): ppm 159.83 (C=O), 138.67 (C-8), 127.01 (C-6), 121.60 (C-2), 115.28 (C-9), 103.73 (C-3), 95.04 (C-7).

4-Chloro-1H-pyrrolo[3,2-c]pyridine (1).- To a stirred mixture of anhydrous 2 (1 g, 7.45 mmoles) and water (0.268 ml, 14.9 mmoles) cooled to 0°, were added phosphorus oxychloride (23.4 ml) and phosphorus pentachloride (3.55 g). The reaction mixture was heated at 130° for 1.5 hr. After concentration under vacuum and cooling, the residue was neutralized with ammonia (20%) and extracted several times with ethyl acetate. The combined extracts were dried (sodium sulfate) and evaporated to a solid residue which was purified by flash column chromatography on silica gel (chloroform-methanol, 95:5) to give a solid. Recrystallization from acetonitrile gave 0.33 g (37%) of 1, mp. 189-192°, lit.[2] 190-193°; ^{13}C nmr (DMSO-d_6): ppm 140.62 (C-4 or C-8), 140.07 (C-8 or C-4), 139.19 (C-6), 127.71 (C-2), 122.75 (C-9), 107.90 (C-3), 100.0 (C-7).

The title compound was also obtained by heating a mixture of 2 (1 g, 7.4 mmoles) and phosphorus oxychloride (20 ml) in a sealed tube at 130° for 1.5 hr. After cooling, the phosphorus oxychloride was evaporated in vacuo, and the residue was neutralized with 2 N ammonia and extracted several times with ethyl acetate. The combined extracts were dried (sodium sulfate) and evaporated to a solid which was purified as described above to give 1 (0.36 g, 40%).

3-Chloro-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (3).- A suspension of 2 (1 g, 7.45 mmoles) and phosphorus oxychloride (12 ml) was added with stirring to a cooled mixture of phosphorus pentachloride (16 g) and phosphorus oxychloride (12 ml). The reaction mixture was stirred and heated at 130° fo4 1.5 hr. After evaporation under vacuum and cooling, the residual oil was neutralized with aqueous ammonia and the precipitate which formed was collected by filtration, taken up with water and extracted several times with ethyl acetate. The extract was dried over sodium sulfate and evaporated to dryness in vacuo. The residue was crystallized from dimethylformamide to give 0.42 g (33%) of 3, mp. 261-263°.

IR (nujol): 3175, 3120 (NH), 1620 (C=O), 1307, 1222, 1072, 1021, 930, 870, 775, 760, 635 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.40 (d, $J_{7,6}$ = 6 Hz, 1 H, H-7), 7.08 (d, $J_{6,7}$ = 6 Hz, 1 H, H-6), 7.23 (d, $J_{2,1}$ = 2 Hz, 1 H, H-2); after addition of deuterium oxide, the doublet was converted in a singlet), 10.84 (broad, 1 H, amide NH), 11.63 (broad, 1 H, pyrrole NH); ^{13}C nmr (DMSO-d_6): ppm 158.81 (C=O), 138.60 (C-8), 128.42 (C-6), 119.44 (C-2), 110.91 (C-9), 107.42 (C-3), 95.02 (C-7).

Anal. Calcd. for $C_7H_5ClN_2O$: C, 49.86; H, 2.98; N, 16.60

Found: C, 49.59; H, 2.93; N, 16.38

3,4-Dichloro-1H-pyrrolo[3,2-c]pyridine (4).- A mixture of 3 (1 g, 5.93 mmoles) and phenylphosphonic dichloride (2.48 ml, 17.79 mmoles) was heated at 160° for 2.5 hrs. After cooling, the reaction mixture was poured onto 100 ml of ice water. After neutralization with 2 N sodium hydroxide, the semisolid which separated was extracted several times with ethyl acetate. The combined extracts were dried (sodium sulfate) and evaporated to yield a solid which was chromatographed on a silica gel column [eluting with chloroform-methanol (85:15)] to yield a solid which, on crystallization from methanol, gave 0.56 g (51%) of 4, mp. 234-236°.

IR (nujol): 3095 (NH), 1610 (C=C), 1568, 1510, 1322, 1260, 1220, 1200, 1110, 1068, 1002, 952, 826, 792, 670, 595 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.50 (d, $J_{7,6}$ = 5.5 Hz, 1 H, H-7), 7.75 (s, 1H, H-2), 8.03 (d, $J_{6,7}$ = 5.5 Hz, 1H, H-6), 12.19 (broad, 1 H, NH); ^{13}C nmr (DMSO-d_6): ppm 141.01 (C-8 or C-4), 140.06 (C-4 or C-8), 140.07 (C-6), 125.80 (C-2), 117.82 (C-9), 107.91 (C-7), 102.51 (C-3).

Anal. Calcd. for $C_7H_4Cl_2N_2$: C, 44.95; H, 2.15; N, 14.97

Found: C, 44.73; H, 2.07; N, 14.86

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PREPARATION OF 2,6-DIMETHYL-4-PHENYLPYRYLIUM SULFOACETATE

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Although pyrylium salts are valuable intermediates in the synthesis of various carbocyclic and heterocyclic compounds,[1] only a few preparative methods are described in detail and these are limited to the commercially available 2,4,6-trimethylpyrylium[2,3] and 2,4,6-triphenylpyrylium[4] salts. Some of these methods are based on the diacylation of alkenes or of alkene precursors[5] and all except the ones described in the present Journal,[3,4]