

The Chlorination of Thiophene-2-aldehyde and Ethyl Thiophene-2-carboxylate in the Presence of Excess Aluminum Chloride (1)

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The profound influence of a large excess of aluminum chloride on the orientation of electrophilic substitution reactions in aromatic systems has been termed (2) the "swamping catalyst effect". This concept, which is largely due to Pearson (3), has been extensively applied to the highly selective synthesis of 4-bromothiophenes (4), pyrroles (5) and furans (6) substituted at C-2 with an electron attracting (-R, -I) group. These compounds, in general, are not readily available by direct bromination in the absence of aluminum chloride.

In principle, it should be possible to synthesise the 4-chloro analogues of the above compounds by a similar process (7), but the chlorination of 5-membered aromatic mono hetero atomic systems under "swamping catalyst" conditions has not been reported. The work described herein shows that the above technique can be applied to the synthesis of certain 4-chloro-2-substituted thiophenes. For example, the addition, at room temperature, of a solution of chlorine in carbon tetrachloride (8), to an equimolar quantity of thiophene-2-aldehyde dissolved in chloroform, containing aluminum chloride (2.3 molar equivalents), gave, after 20 hours, a 74% yield of 4-chlorothiophene-2-aldehyde. The chlorination of ethyl thiophene-2-carboxylate under similar conditions gave the corresponding 4-chloro derivative which was converted into crystalline 4-chlorothiophene-2-carboxylic acid by alkaline hydrolysis. This latter compound was also available, in much higher overall yield, by the silver oxide oxidation of 4-chlorothiophene-2-aldehyde. Finally, it is worthy of note that none of the 2-substituted-4-chlorothiophenes described in this work has been reported previously.

EXPERIMENTAL (9)

4-Chlorothiophene-2-aldehyde.

To a vigorously stirred (mechanical) solution of thiophene-2-aldehyde (24.3 g., 0.217 mole) in distilled chloroform (150 ml.) was added anhydrous aluminum chloride (65 g., 0.487 mole). A solution of chlorine (250 ml. of a 0.86 M solution;

0.215 mole) in carbon tetrachloride was added in a dropwise manner, and then stirring was continued at room temperature for 20 hours. The solution was poured into ice-water, the organic phase was separated and combined with a chloroform extract of the aqueous phase. The organic phase was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residual oil was purified by column chromatography on Florisil (1.5 kg.) using hexane as the eluting solvent. The aldehyde (23.2 g., 73.6%) was obtained as a pale yellow oil which was sufficiently pure for most purposes. For analysis, a small portion of this oil was rechromatographed on silica gel (hexane) and then distilled, b.p. 45-47°/0.025 mm. Spectra: uv (methanol): 255.5 (9230) and 296 (4270) nm; ir (neat): 2840, 2810, 2775, 2740, 1680, 1520 cm^{-1} ; nmr (deuteriochloroform): 7.45 (d, 1H, J = 1.1 Hz), 7.51 (d, 1H, J = 1.1 Hz), 9.67, 9.71 (2 singlets, 1H total).

Anal. Calcd. for $\text{C}_5\text{H}_3\text{ClOS}$: C, 40.97; H, 2.05; Cl, 24.18. Found: C, 40.77; H, 2.12; Cl, 24.07.

Ethyl 4-Chlorothiophene-2-carboxylate.

To a vigorously stirred solution of ethyl thiophene-2-carboxylate (12.0 g., 0.077 mole) in chloroform (200 ml.) was added aluminum chloride (60.0 g., 0.45 mole). A solution of chlorine (180 ml. of a 0.89 M solution, 0.16 mole) in carbon tetrachloride was then added at room temperature and after stirring for 20 hours, the reaction was worked up in the manner described above. The crude product was passed over a column of Florisil (hexane) and then fractionally distilled *in vacuo*. The fraction (7.0 g., 47.7%) b.p. 60-62°/0.025 mm was collected. Spectra: uv (methanol): 244 (8910), 280 (5130) nm; ir (chloroform): 1715, 1525 cm^{-1} ; nmr (deuteriochloroform): 1.35 (t, 3H, J = 7.0 Hz), 4.30 (q, 2H, J = 7.0 Hz), 7.21 (d, 1H, J = 1.5 Hz), 7.57 (d, 1H, J = 1.5 Hz).

Anal. Calcd. for $\text{C}_7\text{H}_7\text{ClO}_2\text{S}$: C, 44.11; H, 3.70; Cl, 18.60. Found: C, 44.12; H, 3.60; Cl, 18.72.

4-Chlorothiophene-2-carboxylic Acid.

(A) Silver Oxide Oxidation of 4-Chlorothiophene-2-aldehyde.

To a vigorously stirred suspension of silver oxide [from silver nitrate (65 g.) and sodium hydroxide (30 g.)] in water (250 ml.), cooled in an ice bath, was added the aldehyde (20.5 g., 0.14 mole). After 20 minutes the mixture was filtered, the precipitate was washed with hot water, and the cooled aqueous filtrate was acidified with concentrated hydrochloric acid. The solid was collected by filtration and dried. The crude acid, m.p. 124-126°, was obtained in quantitative yield, and was sufficiently pure for most purposes. After repeated crystallization from methanol or dichloromethane it had m.p. 131-132°.

Spectra: uv (methanol): 243 (8510), 277 (4360) nm; ir (potassium bromide): 2660, 2550, 1697, 1530 cm^{-1} ; nmr (deuteriochloroform): 7.32 (d, 1H, $J = 1.3$ Hz), 7.63 (d, 1H, $J = 1.3$ Hz), 10.45 (s, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $\text{C}_5\text{H}_3\text{ClO}_2\text{S}$: C, 36.92; H, 1.88; Cl, 21.80. Found: C, 36.77; H, 1.94; Cl, 21.76.

(B) Saponification of Ethyl 4-Chlorothiophene-2-carboxylate.

To a 50% aqueous methanol solution (50 ml.), which was 1% in potassium hydroxide, was added the ester (1.0 g.), and the resultant was heated at reflux temperature for 2 hours. The solution was poured into water and extracted with ether. The aqueous phase was acidified, the solid was collected by filtration and dried. This material had m.p. 125-126° and was identical to the carboxylic acid obtained in the above experiment.

REFERENCES AND NOTES

(1) Contribution No. 464 from the Syntex Institute of Organic Chemistry.

(2) D. E. Pearson and H. W. Pope, *J. Org. Chem.*, **21**, 381 (1956).

(3) For a brief summary of Pearson's studies see reference 4, p. 522.

(4) J. L. Goldfarb, J. B. Volkenstein and L. I. Belenkij, *Angew. Chem. Int. Ed. Engl.*, **7**, 519 (1968).

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(6) B. Roques, M. C. Zaluski and M. Dutheil, *Bull. Soc. Chim. France*, 238 (1971).

(7) D. E. Pearson, W. W. Hargrove, J. K. T. Chow and B. R. Suthers, *J. Org. Chem.*, **26**, 789 (1961).

(8) A solution of chlorine in chloroform can also be used. The reaction cannot, however, be carried out in pure carbon tetrachloride because of the insolubility of the aluminum chloride complex in this solvent.

(9) The melting points were determined in a Mel-Temp apparatus and are not corrected. The infrared spectra were measured with a Perkin-Elmer model 237 grating infrared spectrophotometer. The ultraviolet spectra were recorded with a Perkin-Elmer model 402 ultraviolet-visible spectrophotometer. The nmr spectra were measured with a Varian T-60 spectrometer. The chemical shifts are expressed as ppm (δ) from internal tetramethylsilane.