Halogenated 3-Pyridylketones

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The oxidation of 2,6-dichloro-3-benzylpyridines and bis(2,6-dichloro-3-pyridyl)methanes, respectively, was accomplished using chromic trioxide in a highly acidic medium. The synthesis of several phenyl-3-(2,6-dichloropyridyl)ketones and of bis(2,6-dichloro-3-pyridyl)ketone are reported.

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The oxidation of methylene groups situated between aromatic or heterocyclic substituents is one of the most renowned and extensively studied oxidation reactions. In connection with investigations directed towards the synthesis of phenyl-3-(pyridyl)ketones, we turned our attention to the oxidation of 2,6-dichloro-(3-benzyl)-pyridines and bis(2,6-dichloropyridyl)methanes, respectively.

The synthetic methodology for their preparation has recently been provided and offers a simple and efficient route leading to these compounds [1].

Previous experience with the difficulties to achieve oxidation of methyl- and chloromethyl groups at the carbon atom C-3 of the halogenated pyridine nucleus [2] lead us to investigate several approaches. Of the methods available to accomplish this objective (CrO_3/pyridine, CrO_3/sulfuric acid, MnO_2/dioxane, SeO_2/acetic acid) only the chromic trioxide procedure in a highly acidic medium has proven successful and thus constitutes an entirely practical synthesis of phenyl-3-(2,6-dichloropyridyl)ketones and of bis(2,6-dichloro-3-pyridyl)ketone.

Treatment of compounds **1** and **2**, respectively, in acetic acid with a two fold excess of chromic trioxide at 25° provided the corresponding ketones **6** and **7** in 83% and in 72% yield (Schemes I and II).

Scheme I

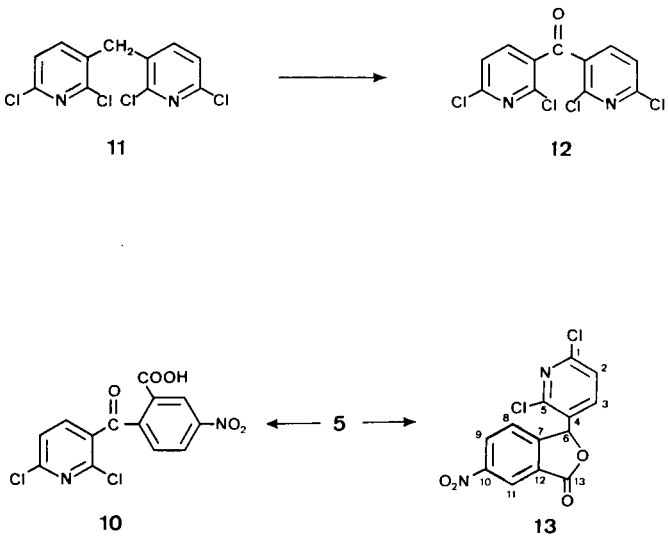
1 R = H
2 R = 4-Cl
3 R = 4-NO_2
4 R = 3-NO_2, 4-Cl
5 R = 2-CH_3, 4-NO_2

6 R = H
7 R = 4-Cl
8 R = 4-NO_2
9 R = 3-NO_2, 4-Cl
10 R = 2-COOH, 4-NO_2

Entries **3**, **4**, **5** and **11** indicate, however, that concentrated sulfuric acid was required as a solvent. It was recognized that 2,6-dichloropyridines form stable solutions in sulfuric acid [3] at room temperature and can be recovered unchanged on dilution with water.

Thus, submission of these compounds in a solution of concentrated sulfuric acid to oxidation with chromic trioxide at 25° produced the ketones **8-10** and **12** in fair yield. Oxidation of **5** with four parts of chromic trioxide allowed isolation of the lactone **13** albeit in small yield, while addition of 6.5 parts of the reagent furnished the ketocarboxylic acid **10**. Oxidation of **11** with two parts of chromic trioxide proceeded at room temperature over a period of 72 hours to form the ketone **12** in 94% yield. Attempts to accelerate the rate of oxidation at elevated temperature met with the formation of hydrolyzed derivatives.

Scheme II



EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The ^{13}C-nmr spectra were recorded on a Bruker HX-360 nmr spectrometer in the fourier transform mode. Samples for the infrared spectra were prepared in potassium bromide disks.

Compounds **1-5** and **11** were prepared according to the procedures detailed in [1].

Phenyl-3-(2,6-dichloropyridyl)ketone (**6**).

To a stirred solution of phenyl-3-(2,6-dichloropyridyl)methane (**1**) (7.14 g, 0.03 mole) in acetic acid (60 ml) was added chromic trioxide (6.6 g, 0.066 mole) in small portions at 55° over a period of 35 hours, and stirring was continued for an additional 10 hours. The resulting solution was added to 500 ml of water and extracted three times with 80 ml portions of ether. The combined extracts were washed neutral with an aqueous

solution of sodium carbonate and dried over sodium sulfate. Evaporation yielded 6.2 g (82%) of an oil which crystallized on standing. A sample was recrystallized from methanol, yielding white crystals, mp 67-68° [2]; ir: cm^{-1} 1665 (CO).

Anal. Calcd. for $C_{12}H_7Cl_2NO$: C, 57.17; H, 2.80; Cl, 28.13; N, 5.56. Found: C, 56.94; H, 2.81; Cl, 28.10; N, 5.51.

4-Chlorophenyl-3-(2,6-dichloropyridyl)ketone (**7**).

A stirred solution of 4-chlorophenyl-3-(2,6-dichloropyridyl)methane (**2**) (2.73 g, 0.011 mole) in acetic acid (50 ml) was heated to 55°, chromic trioxide (3 g, 0.03 mole) was added in small portions over a period of one hour and the temperature was maintained for an additional 1.5 hours. The solution was added to 250 ml of ice-water and extracted three times with 50 ml portions of chloroform. The combined extractions were washed with water (30 ml) and dried over sodium sulfate. Evaporation of the solvent furnished 3.07 g of an oil which was dissolved in 12 ml of hot methanol yielding 2.04 g of crystals, mp 94.5-96°; ir: cm^{-1} 1648 (CO).

Anal. Calcd. for $C_{12}H_6Cl_3NO$: C, 50.30; H, 2.11; Cl, 37.12; N, 4.89. Found: C, 50.32; H, 2.20; Cl, 37.06; N, 4.93.

4-Nitrophenyl-3-(2,6-dichloropyridyl)ketone (**8**).

A stirred solution of 4-nitrophenyl-3-(2,6-dichloropyridyl)methane (**3**) (11.32 g, 0.04 mole) in sulfuric acid (200 ml) was heated to 55° and chromic trioxide (7.2 g, 0.07 mole) was added in small portions over a period of four hours, and stirring was continued for an additional one hour. The solution was added to 800 g of ice and extracted five times with 250 ml portions of ether. The combined extracts were washed neutral with 100 ml of brine and dried over sodium sulfate. Evaporation of the solvent yielded 11.5 g (97%) of product which was recrystallized from 10 ml of ethanol and provided 6.7 g of **8**, mp 121-122°, ir: cm^{-1} 1680 (CO).

Anal. Calcd. for $C_{12}H_6Cl_2N_2O_3$: C, 48.51; H, 2.04; Cl, 23.87; N, 9.43. Found: C, 48.30; H, 2.01; Cl, 23.68; N, 9.34.

4-Chloro-3-nitrophenyl-3-(2,6-dichloropyridyl)ketone (**9**).

To a solution of 4-chloro-3-nitrophenyl-3-(2,6-dichloropyridyl)-methane (**4**) (0.635 g, 0.002 mole) in sulfuric acid (10 ml) was added chromic trioxide (0.36 g, 0.0036 mole) in small portions at 55° within three hours. Work-up followed the procedure detailed for the preparation of **8** yielding 0.78 g of an oil. Recrystallization from a mixture of 7 ml of methanol and 1.5 ml of acetonitrile gave 0.42 g (63%), mp 119-121°; ir: cm^{-1} 1650 (CO).

Anal. Calcd. for $C_{12}H_5Cl_3N_2O_3$: C, 43.48; H, 1.52; Cl, 32.08; N, 8.45. Found: C, 43.52; H, 1.66; Cl, 32.01; N, 8.51.

4-Nitro-2-carboxyphenyl-3-(2,6-dichloropyridyl)ketone (**10**).

To a stirred solution of 2-methyl-4-nitrophenyl-3-(2,6-dichloropyridyl)-methane (**5**) (2.97 g, 0.01 mole) in sulfuric acid (50 ml) was added chromic trioxide (6.4 g, 0.064 mole) over a period of seven hours and stirred overnight at ambient temperature. The solution was added to 400 g of ice, stirred for one hour and the crystals (2.15 g) filtered from the solution. They were suspended in 10 ml of water and 1 *N* sodium hydroxide was added (*p*H 10-11) to bring about dissolution. The solution was extracted three times with 20 ml portions of ether, the aqueous phase was filtered and acidified (*p*H 2) with concentrated hydrochloric acid. The crystals which precipitated were filtered and dried yielding 1.53 g (44%) of **10**, mp 211° dec; ir: cm^{-1} 1670 (COOH), 1660 (CO).

Anal. Calcd. for $C_{13}H_6Cl_2N_2O_5$: C, 45.78; H, 1.78; Cl, 20.79; N, 8.21. Found: C, 46.03; H, 1.95; Cl, 20.58; N, 8.13.

Bis(2,6-dichloro-3-pyridyl)ketone (**12**).

To a solution of 0.618 g (2 mmoles) of bis(2,6-dichloro-3-pyridyl)-methane (**11**) in 45 ml of sulfuric acid was added chromic trioxide (0.36 g, 3.6 mmoles), and the suspension was stirred at ambient temperature for 72 hours. Then the solution was added to an excess of ice and extracted four times with 50 ml portions of ether. The combined extracts were washed with 10 ml of aqueous sodium bicarbonate and dried over sodium sulfate. Evaporation of the the solvent afforded 0.60 g (93%) of **12**, mp 110-112° (methanol); ir: cm^{-1} 1675 (CO).

Anal. Calcd. for $C_{11}H_4Cl_4N_2O$: C, 41.04; H, 1.25; Cl, 44.05; N, 8.70. Found: C, 41.01; H, 1.44; Cl, 43.95; N, 8.59.

1-[3-(2,6-Dichloropyridyl)]-3(1*H*)-benzofuranone (**13**).

To a stirred solution of (2-methyl-4-nitrophenyl)-3-(2,6-dichloropyridyl)-methane (**5**) (5.94 g, 0.02 mole) in sulfuric acid (50 ml) was added chromic trioxide (8 g, 0.08 mole) in small portions over a period of four hours at 55°. The solution was added to 800 g of ice and stirred for one hour. The crystals which precipitated were filtered from the solution (5.1 g) and purified by chromatography (silica, Merck 7734, 8:2 toluene/acetone as the eluent) to afford 2.36 g as a yellow oil. Recrystallization from a mixture of methanol (20 ml) and acetonitrile (10 ml) gave 1.64 g, (24%) of crystals, mp 165-167°; ir: cm^{-1} 1750 (lactone); ^{13}C-nmr (deuteriochloroform): 167.11 (C-13), 153.03, 151.52, 149.56, 148.30, (C-1), (C-5), (C-7), (C-10), 129.00, 126.93, (C-4), (C-12), 138.60 (C-3), 129.72 (C-8), 124.30, 124.04, 121.62 (C-11), (C-9), (C-2), 77.77 (C-7).

Anal. Calcd. for $C_{13}H_6Cl_2N_2O_4$: C, 48.03; H, 1.86; Cl, 21.81, N, 8.62. Found: C, 47.89; H, 1.90; Cl, 21.89; N, 8.68.

REFERENCES AND NOTES

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[3] H. Fritz, C. D. Weis and T. Winkler, *Helv. Chim. Acta*, **59**, 179 (1976).