Synthesis of some β-trichloromethyl-azines and -diazines

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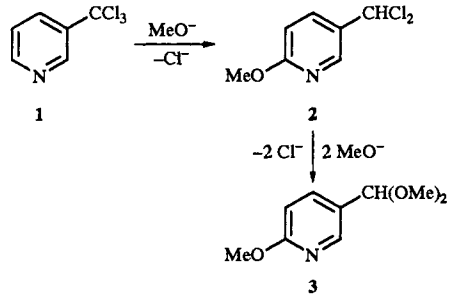
Syntheses of compounds required as substrates for reactions with nucleophiles are reported: 2-trichloromethylquinoxaline **5**, 3-trichloromethylquinoline **6**, 3,5-bis(trichloromethyl)pyridine **7**, 2,5-bis-(trichloromethyl)pyrazine **8** and 5-trichloromethylpyrimidine **9**.

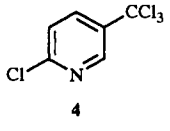
Introduction

We have reported that the reaction of methoxide with 3-trichloromethylpyridine **1** proceeds *via* attack at the 6-position, elimination of chloride ion, and migration of hydrogen, leading to 5-dichloromethyl-2-methoxypyridine **2** and thence to the acetal **3** as shown in Scheme 1.[1]



Scheme 1

Analogous reactions, in which the initial attack takes place adjacent to the trichloromethyl group, would clearly be potentially useful for one-pot syntheses of fused heterocycles. However, we did not observe any attack of methoxide adjacent to the trichloromethyl group in 3-trichloromethylpyridine **1**, and only a small amount in the case of 2-chloro-5-trichloromethylpyridine **4**.[1]



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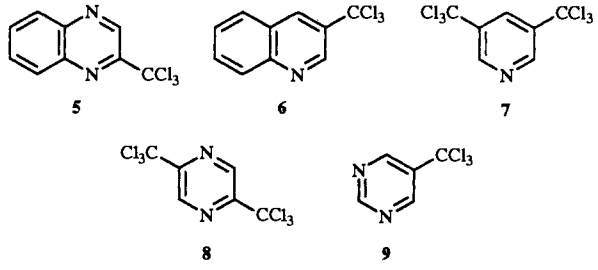
In order to enforce attack of nucleophiles adjacent to trichloromethyl groups, we required substrates such as 2-trichloromethylquinoxaline **5**, 3-trichloromethylquinoline **6**, 3,5-bis(trichloromethyl)pyridine **7** and 2,5-bis(trichloromethyl)-pyrazine **8**; 5-trichloromethylpyrimidine **9** was also of interest, since pyrimidines normally undergo attack by nucleophiles at the 4- and 6-positions rather than the 2-position.

Surprisingly, as in the case of 3-trichloromethylpyridine, whose isolation and characterisation had not been reported prior to our work,[1] none of these simple compounds was recorded in the literature. We regarded these compounds as desirable targets, not only for our own studies but also because of their relationship to compounds such as nicotinic acid and trifluorothymidine. We now report the synthesis of compounds

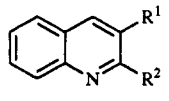


5 to **9**; although adaptations of existing methods were successful, selection of experimental conditions proved critical.

Results and discussion

Compounds **5** and **8**, with trichloromethyl groups α- to a ring nitrogen, were prepared by reaction of the corresponding methyl compounds with phosphorus pentachloride and phosphoryl chloride, by analogy with the syntheses of 2- and 4-trichloromethylpyridines, quinolines and pyrimidines reported by Kato and co-workers.[2] Under carefully controlled conditions they were obtained in acceptable yields, and could be purified as crystalline solids by flash chromatography and/or recrystallisation or sublimation, though in the case of the pyrazine **8** considerable losses during purification were experienced.

Initial attempts to prepare 3-trichloromethylquinoline by chlorination of 3-methylquinoline **10** or its hydrochloride led to



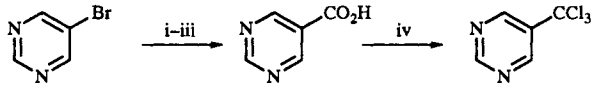
10 $R^1 = CH_3$, $R^2 = H$
11 $R^1 = CCl_3$, $R^2 = Cl$
12 $R^1 = CHCl_2$, $R^2 = Cl$

mixtures of unidentified products; presumably chlorination in the benzene ring and/or addition also occurred. Dechlorination of 2-chloro-3-trichloromethylquinoline **11**,[3] was also investigated, but was either unselective or occurred preferentially at the trichloromethyl group. For example, reduction with sodium boranuide gave 2-chloro-3-dichloromethylquinoline **12** in good yield. Success was eventually achieved by reaction of 3-methylquinoline **10** with phosphorus pentachloride in 1,2,4-trichlorobenzene,[3] which gave 3-trichloromethylquinoline **6** in good yield.

3,5-Bis(trichloromethyl)pyridine **7** was prepared in high yield by the reaction of pyridine-3,5-dicarboxylic acid with phenylphosphonic dichloride, which allows a higher reaction temperature than phosphorus pentachloride.[4] It was also a crystalline solid.

5-Trichloromethylpyrimidine **9** was prepared by photochlorination of 5-methylpyrimidinium chloride. This compound was very sensitive to moisture and although it was a crystalline solid it was difficult to handle and purify; for successful results it was necessary to use well-dried solvent and reagents, and to monitor the reaction closely to minimise underchlorination, giving 5-dichloromethylpyrimidine, or overchlorination, giving 4-chloro-5-trichloromethylpyrimidine. The identity of the ring-chlorinated product as the 4-chloro compound, rather than the 2-chloro isomer, was established by its ^{1}H NMR spectrum, which showed two signals. [Note that in the ^{1}H NMR spectrum of 5-trichloromethylpyrimidine the signals for 2-H and 4,6-H were coincident, but its structure was confirmed by its proton-coupled ^{13}C spectrum (see Experimental).] The use of sulfuryl chloride in place of chlorine in the photochlorination (*cf.* ref. 5) gave 5-trichloromethylpyrimidine with high selectivity, but in lower yield.

An alternative synthesis of 5-trichloromethylpyrimidine **9**, shown in Scheme 2, gave inferior results, as it proved impossible



Scheme 2 *Reagents and conditions:* i, BuLi; ii, CO_2; iii, pH 2.5;[7] iv, $PhP(O)Cl_2$ or PCl_5

to avoid hydrolysis of the product during work-up. Pyrimidines with electron-withdrawing 5-substituents are known to be very susceptible to covalent hydration.[6]

Experimental

Mps were recorded on an Electrothermal mp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FT instrument. NMR spectra were recorded at 90 MHz (Perkin-Elmer R-32) referenced to internal TMS, or 270 MHz (Bruker AC270), 300 MHz (Bruker AC300), or 400 MHz (Bruker AMX-400) referenced to deuteriochloroform. Mass spectra were obtained by use of Finnigan 4500 (low resolution) or Kratos Concept (high resolution or FAB) instruments, using chemical ionisation (NH_3); data are given for ions containing ^{35}Cl only: appropriate isotope patterns were observed. Gas chromatographs were run on a Perkin-Elmer 8320 Capillary Gas Chromatograph, using a BP1 column (0.25 mm × 25 m, hydrogen carrier gas). Combined GC–MS measurements were made using a Varian 3400 Capillary Gas Chromatograph coupled with a Finnigan 4500 mass spectrometer. Analytical TLC was carried out on Camlab Polygram SIL G/UV_{254} plates. Preparative 'flash' column chromatography was carried out using Merck 9385 silica gel.

Starting materials were commercial materials unless otherwise stated. 5-Methylpyrimidine was also prepared by a modification of published procedures.[8] Solvents were purified if necessary by conventional techniques. Light petroleum refers to the fraction with bp 40–60 °C, unless otherwise stated.

2-Trichloromethylquinoxaline 5

A mixture of phosphorus pentachloride (78 g, 0.375 mol) and phosphoryl chloride (100 cm^3) was cooled in ice–water and stirred rapidly as 2-methylquinoxaline (10.0 cm^3, 75 mmol) was added slowly. The mixture was stirred and heated under reflux for 1.5 h. Phosphoryl chloride and phosphorus trichloride were removed by rotary evaporation, and the residue was dissolved in chloroform (200 cm^3). The solution was poured onto ice (*ca.* 500 g), and the resulting mixture was neutralised with 4 mol dm^{-3} aqueous sodium hydroxide. The organic layer was separated and the solvent was evaporated under reduced pressure. Distillation of the residue gave the *title compound* (13.8 g, 74%), bp 120 °C/0.5 mmHg, mp 57 °C, δ 7.80–7.85 (2 H, m), 8.11–8.16 (2 H, m) and 9.46 (1 H, s, 3-H) (Found: C, 44.0; H, 1.9; N, 11.2. $C_9H_5Cl_3N_2$ requires C, 43.7; H, 2.0; N, 11.3%).

2,5-Bis(trichloromethyl)pyrazine 8

A mixture of phosphorus pentachloride (86 g, 0.42 mol) and phosphoryl chloride (75 cm^3) was cooled in ice–water and stirred rapidly as 2,5-dimethylpyrazine (3.0 cm^3, 28 mmol) was added slowly. The mixture was stirred and heated under reflux for 1.5 h. Phosphoryl chloride and phosphorus trichloride were removed by rotary evaporation, and the residue was dissolved in chloroform (200 cm^3). The solution was poured on to ice (*ca.* 500 g), and the resulting mixture was neutralised with 4 mol dm^{-3} aqueous sodium hydroxide and extracted with dichloromethane (3 × 200 cm^3). The combined extracts were dried, the solvent was evaporated, and the residue was redissolved in dichloromethane (10 cm^3). The solution was eluted through silica (20 g) with dichloromethane (20 cm^3), the solvent was evaporated, and the residue recrystallised from butan-2-one to give the *title compound* (2.30 g, 26%), mp 173–177 °C, δ_H 9.30 (s); δ_C 139.3 (C-3,6) and 154.5 (C-2,5) (Found: C, 23.1; H, 0.6; N, 8.7. $C_6H_2Cl_6N_2$ requires C, 22.9; H, 0.6; N, 8.9%).

3-Trichloromethylquinoline 6

A mixture of 3-methylquinoline (0.50 g, 3.5 mmol), phosphorus pentachloride (2.18 g, 10.5 mmol) and 1,2,4-trichlorobenzene (15 cm^3) was heated at 200 °C. After 3 h and again after 6 h further portions of phosphorus pentachloride (0.73 g, 3.5 mmol) were added, and heating was continued for a total of 15 h. Most of the solvent and phosphorus halides were distilled under reduced pressure. Flash chromatography of the residue (silica, 1:13 ethyl acetate–light petroleum) gave the *title compound* (0.69 g, 85%) as an oil, bp 83–85 °C/0.2 mmHg, δ_H 7.63 (1 H, td, *J* 7.0 and 1.0, 6-H), 7.81 (1 H, td, *J* 7.0 and 1.3, 7-H), 7.93 (1 H, dd, *J* 8.0 and 1.3, 5-H), 8.05 (1 H, d, *J* 8.4, 8-H), 8.74 (1 H, s, 4-H) and 9.53 (1 H, d, *J* 2.5, 2-H) [Found: *m/z* 262.9907 (M + 18). $C_{10}H_6Cl_3N$ requires 262.9910].

2-Chloro-3-dichloromethylquinoline

A solution of sodium boranuide (60 mg, 1.5 mmol) in dry ethanol (10 cm^3) was added to a stirred solution of 2-chloro-3-trichloromethylquinoline[3] (300 mg, 1.0 mmol) in dry tetrahydrofuran (10 cm^3). The mixture was heated under reflux for 24 h and then cooled. The solvents were removed under reduced pressure. Water (20 cm^3) was added to the residue and the mixture was extracted with dichloromethane. The extract was dried (Na_2SO_4), the solvent was evaporated, and the residue recrystallised (chloroform–hexane) to give the title compound (210 mg, 85%), mp 86–88 °C (lit.,[3] mp 88–90 °C), δ_H 7.19 (1 H, s, $CHCl_2$), 7.61 (1 H, dd, 6-H), 7.80 (1 H, m, 7-H), 7.91 (1 H, dd, 5-H), 8.00 (1 H, dd, 8-H) and 8.70 (1 H, s, 4-H).

3,5-Bis(trichloromethyl)pyridine 7

Phenylphosphonic dichloride (39 cm^3, 270 mmol) and pyridine-2,5-dicarboxylic acid (8.4 g, 50 mmol) were mixed thoroughly. The mixture was slowly heated to 60 °C with stirring and phosphorus pentachloride (65 g, 310 mmol) was added portionwise with care. When evolution of hydrogen chloride had slowed the remainder of the phosphorus pentachloride was added in one portion and the mixture was heated under reflux overnight. The flask was fitted with an anti-splash head and

heated with an oil bath (150 °C) until distillation of phosphoryl chloride into the head had ceased and then for a further 30 min. The mixture was poured onto ice (*ca.* 200 g), neutralised with conc. aqueous sodium hydroxide, and filtered. The solid was washed with water (3 × 100 cm^3) and dried (*ca.* 50 °C, water aspirator pressure) to give the *title compound* (14.9 g, 95%), mp 78–79 °C, δ_H 8.65 (1 H, t, *J* 2, 4-H) and 9.20 (2 H, d, *J* 2, 2,6-H) (Found: C, 27.0; H, 1.0; N, 4.2. $C_6H_3Cl_6N$ requires C, 26.8; H, 1.0; N, 4.5%).

Chlorination of 5-methylpyrimidinium chloride

(*a*) **With chlorine.** A rapid stream of dry hydrogen chloride was passed into a solution of 5-methylpyrimidine (4.7 cm^3, 50 mmol) in dry tetrachloromethane (350 cm^3) for 5 min. Chlorine was bubbled through the stirred suspension as it was heated and irradiated by an internal 125 W mercury lamp. The progress of the reaction was monitored by ^1H NMR spectroscopy. After 1 h 35 min the mixture was cooled and filtered, and the solvent was evaporated under reduced pressure. Chromatography of the residue [silica (300 g), 15:1 light petroleum–ethyl acetate] gave 5-*trichloromethylpyrimidine* (6.95 g, 70%), δ_H 9.22 (s); $\delta_{C(H)}$ 92.9 (s, CCl_3), 138.0 (t, *J* 4.5, C-5), 153.6 (ddd, *J* 186.5, 9.5 and 3.5, C-4 and C-6) and 159.5 (dt, *J* 206.5 and 10, C-2) [Found: *m/z* 196.9432 (M + 1). $C_5H_3Cl_3N_2$ requires 196.9440] and 4-*chloro*-5-*trichloromethylpyrimidine* (1.66 g, 14%), δ 9.03 (s, 1 H, 6-H) and 9.38 (s, 1 H, 2-H) [Found: *m/z* 230.9046 (M + 1). $C_5H_2Cl_4N_2$ requires 230.9050].

Another run, stopped at a slightly earlier stage, gave in addition to 5-trichloromethylpyrimidine traces of 5-dichloromethylpyrimidine, δ 6.72 (1 H, s, $CHCl_2$), 8.91 (2 H, s, 4,6-H) and 9.18 (1 H, s, 2-H); *m/z* 163 (M + 1); 4-chloro-5-dichloromethylpyrimidine, δ 6.95 (1 H, s, $CHCl_2$), 8.92 (1 H, s, 6-H), 9.11 (1 H, s, 2-H); *m/z* 197 (M + 1) and 4-chloro-5-trichloromethylpyrimidine.

(*b*) **With sulfuryl chloride.** A suspension of 5-methylpyridinium chloride (85 mmol) in dry tetrachloromethane (500 cm^3) was prepared as described above and degassed with a stream of argon for 30 min. Sulfuryl chloride (23 cm^3) was added and the mixture was irradiated under reflux with an internal 125 W lamp for 1.5 h. The reaction mixture was filtered through Celite and the solvent was evaporated. The residue was dissolved in dichloromethane (250 cm^3) and the solution was washed with water (100 cm^3) and saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated to give 5-trichloromethylpyridine (7.6 g, 45%).

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