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POLYHALOGENOAROMATIC COMPOUNDS

XXX*. THE METAL—HALOGEN EXCHANGE REACTION BETWEEN n-BUTYLLITHIUM AND 2,3,4,5,6-PENTACHLORO-*N*,*N*-DIMETHYLBENZYLAMINE

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Summary

The reaction of n-butyllithium with 2,3,4,5,6-pentachloro-*N*,*N*-dimethylbenzylamine proceeds by metal—halogen exchange at the positions *meta* and *para* to the dimethylaminomethyl group, but not at the *ortho* position. Coordination by the substituent thus plays little or no part in determining which position undergoes reaction.

Introduction

Our earlier studies have shown that, whereas *N*,*N*-dimethylaniline undergoes metallation*** by organolithium compounds *ortho* to the substituent [2,3], 2,3,4,5,6-pentachloro-*N*,*N*-dimethylaniline undergoes metal—halogen exchange only *meta* and *para* to the dimethylamino-group [4]. In the case of the metallation reaction, the *ortho*-directing effect of substituents such as dimethylamino is generally attributed to the fact that the lone pair on the nitrogen atom can interact with the electron-deficient organolithium reagent. We have suggested [4] that the lack of an analogous effect in the metal—halogen exchange reaction can be attributed to the electron-withdrawing nature of the pentachlorophenyl group. This lowers the Lewis basicity of the amine to such an extent that it does not interact strongly with the organolithium compound (particularly when it is in competition with an electron-donating solvent).

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* For Part XXIX see ref. 1.

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*** We prefer to restrict the term 'metallation' to metal—hydrogen exchange reactions, as opposed to other reactions which result in the introduction of a metal.

Results and discussion

In our search for a system which might provide evidence for an *ortho*-directing influence on the metal—halogen exchange reaction we have investigated the reactions of 2,3,4,5,6-pentachloro-*N,N*-dimethylbenzylamine (I). In this compound, the lone pair on nitrogen cannot be delocalised into the aromatic ring. [The (dimethylamino)methyl group is evidently a more effective *ortho*-directing substituent than the dimethylamino group in the metallation reaction [5], presumably for a similar reason.] Furthermore, inspection of a model suggests that coordination with the organolithium compound by compound (I) should be less subject to steric hindrance than in the case of pentachloro-*N,N*-dimethylaniline (cf. ref. 6).

Compound (I) was conveniently prepared from 2,3,4,5,6-pentachlorotoluene (II) [7] by benzylic bromination with *N*-bromosuccinimide followed by reaction with dimethylamine. On treatment with one molar equivalent of n-butyllithium in diethyl ether at —50°, followed by hydrolysis with water, it gave a product whose elemental analysis and mass spectrum (M^+ 271, with four chlorine isotope pattern) were appropriate for tetrachloro-*N,N*-dimethylbenzylamines. The ^{1}H NMR spectrum of the product, summarized in Table 1, indicated that at least two isomers were present, and the syntheses described below show that the mixture contained 2,3,5,6-tetrachloro-*N,N*-dimethylbenzylamine (III) and 2,3,4,6-tetrachloro-*N,N*-dimethylbenzylamine (IV), but not 2,3,4,5-tetrachloro-*N,N*-dimethylbenzylamine (V).

Haiduc and Gilman have reported that the reaction of 1,2,3,4-tetrachlorobenzene with phenyllithium in tetrahydrofuran at —70°, followed by chlorotrimethylsilane, gives trimethyl(2,3,4,5-tetrachlorophenyl)silane as the major product, via 2,3,4,5-tetrachlorophenyllithium (VI) [8]. Our attempts to prepare 2,3,4,5-tetrachlorotoluene (VII) by an analogous reaction, with dimethyl sulphate in place of chlorotrimethylsilane, were unsuccessful; the desired product (VII) was accompanied by a roughly equal amount of 2,3,6-trichlorotoluene. However, the commercially available 1,2,3,4-tetrachloronitrobenzene was readily converted into 1,2,3,4-tetrachloroiodobenzene (VIII) by reduction,

TABLE 1

^{1}H NMR SPECTRA OF TETRACHLORO-*N,N*-DIMETHYLBENZYLAMINES [a]

Compound	τ	Number of protons	Assignment
(III) + (IV) [b]	2.46 2.55	1 [c]	Aromatic H
	6.30 6.39	2	CH_2NMe_2
	7.72	6	$N(CH_3)_2$
(V)	2.38	1	Aromatic H
	6.50	2	CH_2NMe_2
	7.70	6	$N(CH_3)_2$
(III)	2.48	1	Aromatic H
	6.30	2	CH_2NMe_2
	7.72	6	$N(CH_3)_2$

[a] In CCl_4. All signals were singlets. [b] Mixture from hydrolysis of the product of metal—halogen exchange of compound (II). [c] The ratio of the integrals of the signals at τ 2.46 and 2.55 was 2/1.

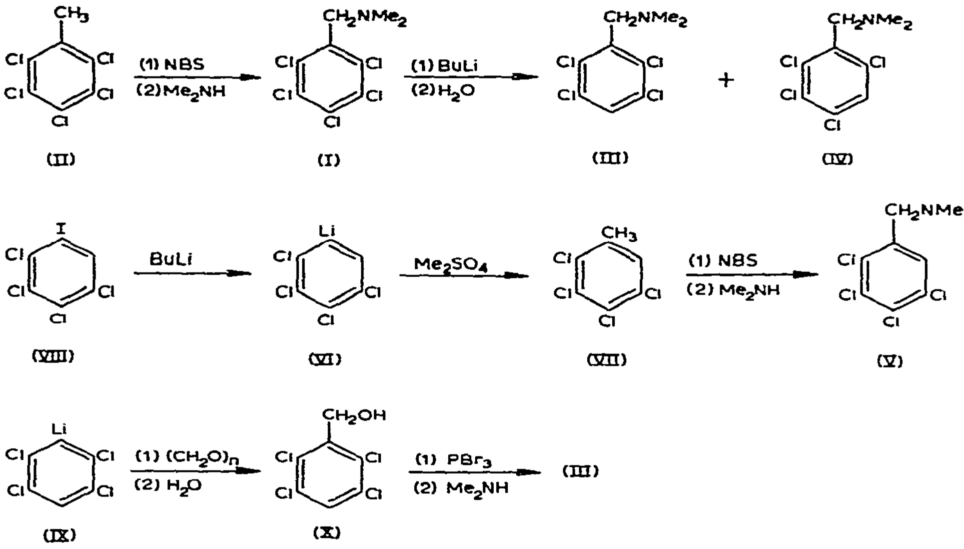
diazotisation and reaction with potassium iodide (cf. ref. 9). Metal—halogen exchange with n-butyllithium, followed by reaction with dimethyl sulphate, then gave 2,3,4,5-tetrachlorotoluene (VII)*, which was converted into 2,3,4,5-tetrachloro-*N*,*N*-dimethylbenzylamine (V) by benzylic bromination, followed by reaction with dimethylamine. The ^{1}H NMR spectrum of compound (V) (see Table 1) showed that it was not one of the products derived from the metal—halogen exchange reaction of 2,3,4,5,6-pentachloro-*N*,*N*-dimethylbenzylamine (I).

Metallation of 1,2,4,5-tetrachlorobenzene by n-butyllithium gave a solution of 2,3,5,6-tetrachlorophenyllithium (IX) [8,11] which on treatment with paraformaldehyde followed by hydrolysis gave 2,3,5,6-tetrachlorobenzyl alcohol (X). Compound (X) was readily converted into 2,3,5,6-tetrachloro-*N*,*N*-dimethylbenzylamine (III) by treatment with phosphorus tribromide, followed by dimethylamine. The ^{1}H NMR spectrum of compound (III) (see Table 1) corresponded to one of the components of the mixture derived from the metal—halogen exchange reaction of pentachloro-*N*,*N*-dimethylbenzylamine. The other component of the mixture was therefore 2,3,4,6-tetrachloro-*N*,*N*-dimethylbenzylamine (IV).

Our experiments demonstrate that metal—halogen exchange between n-butyllithium and 2,3,4,5,6-pentachloro-*N*,*N*-dimethylbenzylamine occurs at the positions *meta* and *para* to the dimethylaminomethyl group, but not at the *ortho*-position. Thus, even in this relatively favourable case, coordination by the substituent plays little or no part in determining which position undergoes reaction.

The reactions are summarised in Scheme 1.

SCHEME 1



(NBS = *N*-Bromosuccinimide)

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* Preliminary experiments were carried out on a sample of compound (VII) prepared by another route [10].

Experimental

All experiments involving organolithium compounds were carried out in dried apparatus and solvents, under dry, oxygen-free nitrogen. n-Butyllithium was used as a commercial 2.3 *M* solution in hexane. ^{1}H NMR spectra were measured at 60 MHz, with tetramethylsilane as internal standard. Calculated *m/e* values for molecular ions are based on ^{35}Cl.

2,3,4,5,6-Pentachloro-N,N-dimethylbenzylamine

2,3,4,5,6-Pentachlorotoluene [7] (3.0 g), *N*-bromosuccinimide (1.7 g) and a trace of dibenzoyl peroxide were heated under reflux in carbon tetrachloride (100 ml) during 1 h. Conventional work-up followed by chromatography on silica, gave α-bromo-2,3,4,5,6-pentachlorotoluene (eluted with chloroform) (2.0 g, 53%), m.p. 112—114° (lit. [12] m.p. 116°). (Found: C, 24.75; H, 0.7; Br, 23.7; Cl, 52.4, $C_7H_2BrCl_5$ calcd.; C, 24.45; H, 0.6; Br, 23.3; Cl, 51.7%.)

A solution of α-bromo-2,3,4,5,6-pentachlorotoluene (4.5 g) in ethanol (20 ml) was added to a solution of dimethylamine (1.5 g) in ethanol (30 ml) and the mixture was stirred during 2 h. Conventional work-up gave 2,3,4,5,6-pentachloro-*N,N*-dimethylbenzylamine (nc) (2.8 g, 64%), m.p. 57° (from light petroleum and chloroform) τ (CCl_4) 6.18 (s, 2H), 7.61 (s, 6H). (Found: C, 34.8; H, 2.1; N, 4.1; M^+ 305. $C_9H_8Cl_5N$ calcd.: C, 35.1; H, 2.5; N, 4.55%, M^+ 305.)

Metal—halogen exchange of 2,3,4,5,6-pentachloro-N,N-dimethylbenzylamine

A solution of n-butyllithium (12 mmole) was added to a stirred solution of pentachloro-*N,N*-dimethylbenzylamine (3.7 g; 12 mmole) in diethyl ether (200 ml) at —70°. The solution was stirred at —50° during 45 min and water (50 ml) was added. Conventional work-up gave the product as an oil, which was freed from small amounts of unidentified materials by chromatography on silica. (The aromatic region of the NMR spectrum of the crude product was unaffected by this procedure). The purified product was a mixture (1.8 g, 62%) of 2,3,4,6-tetrachloro-*N,N*-dimethylbenzylamine and 2,3,5,6-tetrachloro-*N,N*-dimethylbenzylamine, b.p. 98°/0.2 mm. (Found: C, 40.1; H, 3.4, M^+ 271. $C_9H_9Cl_4N$ calcd.: C, 39.6; H, 3.3%, M^+ 271.)

2,3,4,5-Tetrachloro-N,N-dimethylbenzylamine

A cold solution of 2,3,4,5-tetrachloroaniline (3.7 g) in glacial acetic acid (15 ml) was added dropwise to a stirred solution of sodium nitrite (1.2 g) in concentrated sulphuric acid (20 ml) at 0° during 30 min. The mixture was stirred at 0° during 30 min and added dropwise to cold 1.5 *M* aqueous potassium iodide (40 ml). The mixture was stirred at room temperature during 30 min and extracted with chloroform. The chloroform layer was washed with sodium thiosulphate solution, dried and evaporated. Chromatography of the residue (silica, light petroleum) gave 2,3,4,5-tetrachloroiodobenzene (3.5 g, 65%), m.p. 85° (lit. [9] m.p. 89—90°), τ (CCl_4) 2.60.

A solution of n-butyllithium (14 mmole) was added to a solution of 2,3,4,5-tetrachloroiodobenzene (4.8 g; 14 mmole) in diethyl ether at —70°. The solution was stirred at —70° during 15 min and at —20° during 30 min. Dimethyl sulphate (4.0 ml), was added, and the mixture was stirred at room temperature during 2 h.

Hydrolysis with concentrated aqueous ammonia, followed by conventional work-up and chromatography on silica gave 2,3,4,5-tetrachlorotoluene (eluted with 20% benzene/light petroleum) (1.8 g, 59%), τ (CCl_4) 2.70 (s, 1H), 7.59 (s, 3H) (cf. ref. 10), contaminated by a little 2,3,4,5-tetrachlorobenzene (τ 2.67).

The crude 2,3,4,5-tetrachlorotoluene (3.45 g) was brominated and then treated with dimethylamine as described above for 2,3,4,5,6-pentachlorotoluene, to give successively α-bromo-2,3,4,5-tetrachlorotoluene [12] (2.0 g, 44%), τ (CCl_4) 2.47 (s, 1H), 5.49 (s, 2H) and 2,3,4,5-tetrachloro-*N*,*N*-dimethylbenzylamine (nc) (0.5 g, 20%), b.p. 94°/0.2 mm, m.p. 54° (Found: C, 39.6; H, 3.4; N, 5.0. M^+ 271. $C_9H_9Cl_4N$ calcd.: C, 39.6; H, 3.3; N, 5.1%. M^+ 271.) The non-identity of this compound with the components of the mixture of tetrachloro-*N*,*N*-dimethylbenzylamines, described above, was checked by an NMR spectrum of a mixture of the two products.

2,3,5,6-Tetrachloro-N,N-dimethylbenzylamine

n-Butyllithium (14 mmole) was added to a solution of 1,2,4,5-tetrachlorobenzene (6.48 g; 30 mmole) in diethyl ether (250 ml) at —70°. The solution was stirred at —70° during 15 min, allowed to warm to —10° during 45 min and re-cooled to —30°. Paraformaldehyde (30 mmole) was added and the mixture was stirred at room temperature during 3 h and under reflux during 90 min. Hydrolysis with water, followed by conventional work-up and chromatography on silica gave a mixture of tri- and tetrachlorobenzenes (eluted with light petroleum) (1.9 g) and 2,3,5,6-tetrachlorobenzyl alcohol (eluted with chloroform) (2.6 g, 41%), m.p. 97° *, τ (CCl_4) 2.36 (s, 1H), 4.95 (s, 2H), 7.73 (s, 1H, exchangeable), M^+ 244.

Phosphorus tribromide (2.7 g; 10 mmole) was added dropwise to a stirred solution of 2,3,5,6-tetrachlorobenzyl alcohol (2.46 g; 10 mmole) in dry toluene (80 ml) at 0°. The mixture was heated under reflux for 24 h. Conventional work-up followed by chromatography on silica (light petroleum) gave α-bromo-2,3,5,6-tetrachlorotoluene (2.0 g, 65%), m.p. 84—85°, τ (CCl_4) 2.36 (s, 1H), 5.20 (s, 2H). Further reaction with dimethylamine, as described above for α-bromo-2,3,4,5,6-pentachlorotoluene, gave 2,3,5,6-tetrachloro-*N*,*N*-dimethylbenzylamine (nc) (0.30 g, 31%), b.p. 115°/2 mm, m.p. 38—39° (Found: C, 39.5; H, 2.9; N, 4.75. M^+ 271. $C_9H_9Cl_4N$ calcd.: C, 39.6; H, 3.3; N, 5.1%. M^+ 271.)

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* On account of the difference in melting points, the 2,3,x,y-tetrachlorobenzyl alcohol, m.p. 128 - 130°, described in ref. 13a (and originally reported in 13b) was probably the 2,3,4,6-isomer.

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