The electrophilic substitution of some 2,4- and 2,6- dihaloacetanilides

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The orientation of electrophilic substitution of some 2,4- and 2,6-dihaloacetanilides has been examined by NMR methods. Mixed acid nitration of 2,6-dichloro and 2-chloro-6-methylacetanilides gave predominantly the 3-nitro derivatives.

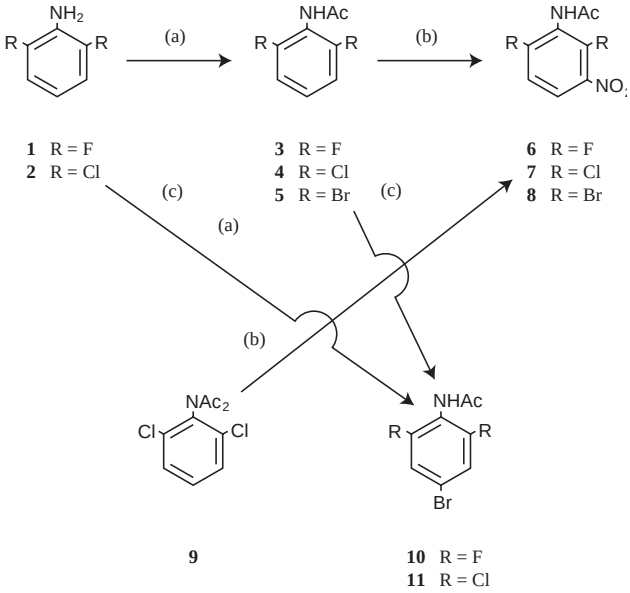
Keywords: 2,6-dihaloacetanilides, nitration, bromination

Many of the differences in the properties of 2,6-disubstituted anilines when compared to the unsubstituted compounds, have been ascribed to the steric inhibition of resonance.[1] In the case of 2,6-dimethylacetanilide this is reflected in the orientation of the substitution reactions of the aromatic ring.[2] A chlorine atom is a comparable size to a methyl group. In a study of the deacetylation of 4-nitroacetanilides by sodium methoxide, Wepster found[3] that the reaction of 4-nitro-2,5-dichloroacetanilide was considerably slower than that of 4-nitroacetanilide. He concluded that there was a strong steric inhibition by the chlorine atoms. The effect of the methyl groups on the orientation of substitution of xylidines is shown by 2,6- and to a lesser extent by 2,4-dimethylacetanilide.[2] We have therefore examined the orientation of substitution of the corresponding haloacetanilides.

Some substitution reactions of the 2,4- and the 2,6-dihaloanilines and acetanilides have been reported in the context of other studies. Nitration of 2,6-dichloroaniline has been reported[4] to give only oxidation products. 2,6-Dichloro-3-nitroaniline had to be prepared[4] by a lengthy route involving a Schmidt reaction on 2,6-dichloro-3-nitrobenzoic acid. The 4-nitro isomer was prepared by chlorinating 4-nitroacetanilide. A number of other 2,6-dihalogenated anilines have been prepared by selective hydrogenolysis of the *para* substituents in 2,4,6-trisubstituted anilines.[5] Bromination of 2,6-dichloroaniline with bromine in chloroform gave 4-bromo-2,6-dichloroaniline.[4] Chlorination of *p*-bromoaniline was unsatisfactory as a method for preparing this compound.[6] Nitration of 2,4-dichloro-6-nitroacetanilide has been reported[7] to give 2,4-dichloro-6-nitroacetanilide whilst bromination of 2,4-dichloroacetanilide in glacial acetic acid has been reported[8] to give 6-bromo-2,4-dichloroaniline with the loss of the acetyl group.

Acetylation of 2,6-difluoroaniline (**1**) and 2,6-dichloroaniline (**2**) in glacial acetic acid with acetic anhydride and a drop of sulfuric acid catalyst gave the monoacetyl derivatives. As observed previously[5,9] the diacetyl derivatives were very readily formed on more prolonged treatment with acetic anhydride and sulfuric acid catalyst.

We examined the influence of the 2,6-dihalogen substituents on the orientation of aromatic substitution in nitration by a nitric acid:sulfuric acid mixture. It had been reported[10] that nitration of 2,6-difluoroacetanilide (**3**) gave exclusively the 3-nitro derivative (**6**). We have confirmed this by examing the ^{1}H NMR spectrum of the product. The ^{1}H NMR signals for H-4 and H-5 (δ_H 8.07 and 7.11) showed vicinal couplings (J=8.0 Hz) and ^{1}H:^{19}F couplings of 5.0 and 9.3 Hz and 2.0 and 10.0 Hz, respectively. We obtained the 2,6-dichloro- and 2,6-dibromo-3-nitroacetanilides (**7** and **8**) from the corresponding 2,6-dichloro- and 2,6-dibromoacetanilides (**4** and **5**) under similar conditions and in satisfactory yield. The nitro compounds possessed aromatic ^{1}H NMR signals (2,6-dichloro- δ_H 7.80 and 7.45, doublets, J=8.5 Hz; 2,6-dibromo- δ_H 7.70 and 7.55, doublets, J=8.6 Hz) consistent with this substitution pattern. In our hands



Scheme 1 Reagents (a) Ac_2O, gl.AcOH, H_2SO_4; (b) c.HNO_3, H_2SO_4; (c) Br_2, gl.AcOH.

mixed acid nitration of the diacetyl derivative (**9**) of 2,6-dichloroaniline gave 2,6-dichloro-3-nitroacetanilide (**7**).

However, when we treated the 2,6-dichloro- and 2,6-difluoroacetanilides (**3** and **4**) with bromine in glacial acetic acid in the presence of hydrobromic acid we obtained the 4-bromo derivatives (**10** and **11**). The ^{1}H NMR spectra of the products contained aromatic signals at δ_H 7.44 (2H, doublet, $J_{H:F}$=7.3 Hz) (**10**) and δ_H 7.45 (2H, singlet) (**11**). We obtained the same compounds by bromination of the parent 2,6-difluoro- and 2,6-dichloroanilines (**1** and **2**) followed by careful acetylation in a glacial acetic acid:acetic anhydride mixture.

Nitration of 6-chloro-2-methylacetanilide (**12**) gave 6-chloro-2-methyl-3-nitroacetanilide (**13**) and 6-chloro-2-methyl-5-nitroacetanilide (**14**) in a 5:1 ratio based on the ^{1}H NMR spectrum of the mixture. The aromatic ^{1}H NMR signals of both isomers were doublets (3-nitro isomer, δ_H 7.33 and 7.69, J=8.8 Hz; 5-nitro isomer, δ_H 7.28 and 7.69, J=8.5 Hz). The isomers were distinguished by an nOe experiment. Irradiation of the aromatic methyl signal (δ_H 2.30) of the minor isomer (**14**) enhanced the minor aromatic doublet, δ_H 7.28 by 4.2%. Nitrosation:nitration[11,12] of the methanesulfonamide (**15**) gave the 4-nitro derivative (**16**). The aromatic ^{1}H NMR signals (δ_H 8.22 and 8.18) showed only meta coupling (J=2.5 Hz). A similar result had been obtained[13] in the nitrosation:nitration of the methanesulfonamide of 2,6-dimethylaniline.

Bearing in mind the electrophilic substitution reactions of 2,4-dimethylacetanilide,[2] we examined the nitration and bromination of 2,4-dichloroacetanilide (**17**). Nitration of (**17**) gave, as described previously,[7] 2,4-dichloro-6-nitroacetanilide (**18**) and not the 5-nitro isomer. The orientation of the 6-nitro compound was confirmed by the ^{1}H NMR spectrum.

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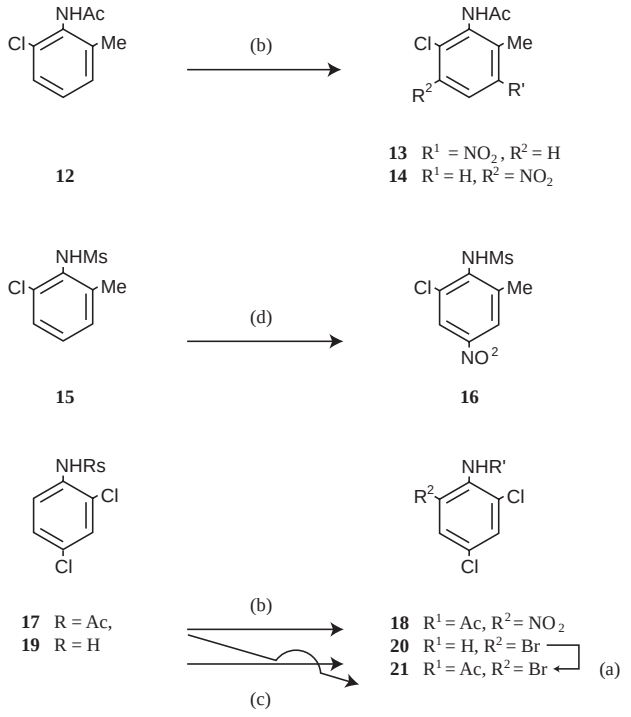

Scheme 2 Reagents (a) Ac_2O, gl.AcOH, H_2SO_4; (b) c.HNO_3, H_2SO_4; (c) Br_2, gl.AcOH; (d) $NaNO_2$, HNO_3, H_2O, AcOH.

The signal assigned to H-3 (δ_H 7.73) showed a *meta* coupling (J=2.7 Hz) to H-5 (δ_H 7.86). These was an nOe enhancement of the CH_3CO signal (δ_H 2.20, 3.6%) by irradiation of the N–H signal but there was no enhancement of the aromatic proton signals. Bromination of 2,4-dichloroaniline (**19**) with bromine in glacial acetic acid gave 6-bromo-2, 4-dichloroaniline (**20**). The aromatic ^{1}H NMR signals (δ_H 7.44 and 7.54) showed a *meta* coupling (J=1.5 Hz). The acetyl derivative (**21**) was identical to the product of bromination of 2,4-dichloroacetanilide (**17**). These results contrast with those of substitution of 2,4-dimethylacetanilide.[2]

The effect of a vicinal halogen on the orientation of substitution of the acetanilides appears to be restricted to the mixed acid nitration of 2,6-dihalogeno and 2-chloro-6-methylacetanilides. These gave products possessing a nitro group that is *meta* to the acetanilide. On the other hand, bromination gives the normal *para* substitution products.

Experimental

General experimental details: ^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform or at 500 MHz for nOe measurements. IR spectra were determined as nujol mulls. Mass spectra were determined on a Bruker Daltonics Apex III electrospray mass spectrometer. Extracts were dried over sodium sulfate. All experiments using fuming nitric acid and bromine in glacial acetic acid were carried out in an efficient fume cupboard.

Nitration experiments: The amide (1.9 g) was suspended in a cold mixture of concentrated sulfuric acid (8 cm^3), concentrated nitric acid (8 cm^3) and fuming nitric acid (4 cm^3). The nitrating mixture was prepared cautiously with ice-cooling. The mixture was left at room temperature for 24h. and then poured onto ice:water (150cm^3). The product was filtered and recrystallised from aqueous methanol.

2,6-Dichloro-3-nitroacetanilide (**7**) (1.7 g, 78%) crystallised as needles, m.p. 162–164°C decomp. (Found: M^+ 248.983 $C_8H_6Cl_2N_2O_3$+H^+ requires 248.983), ν_{max}/cm^{-1} 3232, 1674, 1570, 1522; δ_H 2.10 (3H, s, NHAc), 6.80 (1H, NH), 7.30 (1H, d, J=8 Hz), 7.60 (1H, d, J=8 Hz).

Under similar conditions 6-chloro-2-methylacetanilide (**12**) gave a crude product (1.8 g), the ^{1}H NMR spectrum of which showed that it contained 6-chloro-2-methyl-3-nitroacetanilide (**13**) (5 parts, c.1.5 g) to 6-chloro-2-methyl-5-nitroacetanilide (**14**) (1 part, c.0.3 g) (relative integrals of the Ar–H signals). After three recrystallisations from aqueous methanol a sample of 6-chloro-2-methyl-3-nitroacetanilide (**13**) was obtained as needles, m.p. 158–160°C, (Found: M^+ 251.0198 $C_9H_9ClN_2O_3$+Na^+ requires 251.0194), ν_{max}/cm^{-1} 3234, 1669, 1573, 1519; δ_H 2.19 (3H, s, NHAc), 2.33 (3H, s, Ar-Me) 7.19 (1H, NH), 7.33 (1H, d, J=8.8 Hz), 7.69 (1H, d, J=8.8 Hz). The minor product (**14**), which was not obtained pure, possessed ^{1}H NMR signals δ_H (CD_2Cl_2) 2.23 (3H, s, NHAc), 2.30 (3H, s, Ar–Me) 7.28 (1H, d, J=8.5 Hz), 7.29 (1H, NH), 7.69 (1H, d, J=8.5 Hz). Irradiation at δ_H 2.30 enhanced (4.2%) the signal at δ_H 7.28. There were no enhancements to the other signals.

Under similar conditions 2,6-difluoroacetanilide (**3**) (1.5 g) gave 2,6-difluoro-3-nitroacetanilide (**6**) (1.5 g, 79%) which crystallised from aqueous methanol as needles, m.p. 147–148°C (lit.,[10] 145–147°C), (Found M^+ 239.023 $C_8H_6F_2N_2O_3$+Na^+ requires 239.024), ν_{max}/cm^{-1} 3250, 1674, 1620, 1599, 1534; δ_H 2.27 (3H, s, NHAc), 7.01 (1H, NH), 7.11 (1H, ddd, J=10.1, 8.1, and 2.0 Hz 5-H), 8.07 (1H, ddd, J=9.3, 8.1 and 5.4 Hz 4-H).

Under similar conditions 2,6-dibromoacetanilide (**5**) gave 2,6-dibromo-3-nitroacetanilide (**8**) (1.8 g, 87%) which crystallised from aqueous methanol as needles, m.p. 178–180°C, (Found: M^+ 360.862 $C_8H_6Br_2N_2O_3$+Na^+ requires 360.862), ν_{max}/cm^{-1} 3199, 1642, 1556, 1528; δ_H 2.20 (3H, s, NHAc), 7.01 (1H, NH), 7.55 (1H, d, J=8.7 Hz), 7.70 (1H, d, J=8.7 Hz).

Under similar conditions 2,4-dichloroacetanilide (**17**) gave 2, 4-dichloro-6-nitroacetanilide (**18**) (1.6 g, 73%) which crystallised from aqueous methanol as needles, m.p. 188°C, (lit.,[7] 188°C), ν_{max}/cm^{-1} 3235, 1674, 1571, 1538, 1508; δ_H 2.20 (3H, s, NHAc), 7.69 (1H, NH), 7.73 (1H, d, J=2.4 Hz), 7.86 (1H, d, J=2.4 Hz).

Under similar conditions the diacetyl derivative (**9**) of 2, 6-dichloroaniline (1.8 g) gave 2,6-dichloro-3-nitroacetanilide (**7**) (1.4 g, 77%), identified by its IR spectrum.

The methanesulfonamide (**15**) of 2-chloro-6-methylaniline (2 g) in glacial acetic acid (15 cm^3) was added to a mixture of nitric acid (d. 1.5, 6 cm^3) in water (15 cm^3). A solution of sodium nitriate (1 g) in water (15 cm^3) was added and the solution was heated under reflux for 1 h. The solution was poured into water and the methanesulfonamide (**16**) of 2-chloro-6-methyl-4-nitroaniline (1.6 g, 66%) was collected and crystallised from aqueous methanol as needles, m.p. 172–174°C, (Found: M^+ 286.987 $C_8H_9ClN_2O_4S$+Na^+ requires 286.986), ν_{max}/cm^{-1} 3248, 1519; δ_H (DMSO-D_6) 3.20 (3H, s, SO_2Me), 8.18 (1H, d, J=2.5 Hz), 8.22 (1H, d, J=2.5 Hz), 9.72 (1H, s, NH).

Bromination experiments: The acetanilide (1.0 g) was dissolved in glacial acetic acid (12 cm^3) and treated with a solution of bromine in glacial acetic acid (25%, 8 cm^3) and hydrobromic acid (45%) in glacial acetic acid (1 cm^3). The mixture was heated under reflux for 30 min. and then poured into aqueous sodium sulfite (100 cm^3). The product was filtered and recrystallised from aqueous methanol.

4-Bromo-2,6-difluoroacetanilide (**10**) (1.0 g, 68%) had m.p. 188–190°C, (Found: M^+ 271.951 $C_8H_6BrF_2NO$+Na^+ requires 271.949), ν_{max}/cm^{-1} 3255, 1672, 1606; δ_H 1.99 (3H, s, NHAc), 7.46 (2H, d, $J_{H:F}$ 7.3 Hz), 9.69 (1H, s, NH).

4-Bromo-2,6-dichloroacetanilide (**11**) (0.95 g, 69%) had m.p. 214–216°C, (Found: M^+ 303.890 $C_8H_6BrCl_2NO$+Na^+ requires 303.890), ν_{max}/cm^{-1} 3225, 1673, 1568; δ_H 2.20 (3H, s, NHAc), 7.45 (2H, s,), 9.0 (1H, s, NH).

6-Bromo-2,4-dichloroacetanilide (**21**) (1.05 g, 76%) had m.p. 220–222°C, (Found: M^+ 303.890 $C_8H_6BrCl_2NO$+Na^+ requires 303.890), ν_{max}/cm^{-1} 3278, 1665, 1583; δ_H (DMSO-D_6) 2.20 (3H, s, NHAc), 6.93 (1H, s, NH), 7.44 (1H, d, J=1.5 Hz), 7.54 (1H, d, J=1.5 Hz).

Bromination of the amines: The amines [2,6-difluoroaniline (**1**), 2,6-dichloroaniline (**2**), and 2,4-dichloroaniline (**19**)] (1.0 g) were dissolved in glacial acetic acid (12 cm^3) and treated with bromine in glacial acetic acid (25%, 8 cm^3) at room temperature for 30 min. The semi-crystalline mass was poured into aqueous sodium sulfite and the product was filtered and dried. The products were then suspended in glacial acetic acid (10 cm^3) and treated with acetic anhydride (3 cm^3) and a few drops of conc. sulfuric acid for 1 h at room temperature. The mixture was poured into water and the product filtered and recrystallised from aqueous methanol. The products (0.5–0.6 g) were identified by their IR spectra and m.p.

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