SHORT PAPER

The oxidative bromination and iodination of dimethylacetanilides[†]

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The oxidative bromination and iodination of the six dimethylacetanilides have been examined; whereas bromination of 2,4-dimethyl- and 2,6-dimethylacetanilides using potassium bromide, sodium tungstate and peracetic acid gave predominantly the 6- and 4-bromo compounds respectively, the 5- and 3-iodo compounds were obtained using hydrogen iodide and peracetic acid.

The oxidative halogenation of aromatic amides has been explored recently in the context of models for bio-halogenation and in the development of new preparative methods.[1] For bromination these methods provide a mild alternative to the more widely used bromine in glacial acetic acid. The iodination of aromatic compounds with elemental iodine often requires an oxidant to generate the reactive iodinating species.[2,3]

Although the bromination of acetanilide takes place predominantly in the *para* position, bromination of 2,6-dimethylacetanilide occurs in either the 3- or the 4-positions.[4] Bromination with bromine in chloroform takes place predominantly in the 4-position whilst bromination with bromine in hydrobromic acid or sulfuric acid takes place at the 3-position. Steric inhibition of the amide resonance by the adjacent methyl groups reduces its influence on the orientation of substitution. On the other hand the twisting of the amide out of conjugation with the aromatic ring, may favour the initial attack of a bromonium ion on the amide lone pair and hence lead to an *N*-bromo compound. A subsequent Orton rearrangement may then lead to aromatic substitution *para* to the amide.[5,6] It is also possible that the oxidative conditions might favour initial substitution on the nitrogen. It was therefore of interest to identify the regioisomers that were formed on bromination and iodination of various dimethylacetanilides using oxidative methods to generate the reactive species.

In previous work we have used[7,8] either sodium perborate or hydrogen peroxide with sodium tungstate as a catalyst as the oxidant. In the present work we used peracetic acid as the oxidant. In the case of bromination the dimethylacetanilide was treated with a mixture of potassium bromide, sodium tungstate, sulfuric acid and peracetic acid in glacial acetic acid. Iodination was carried out using a mixture of hydrogen iodide and peracetic acid in glacial acetic acid with sulfuric acid as a catalyst. The results are given in Tables 1 and 2.

The orientation of substitution was established from the multiplicity of the aromatic ^{1}H NMR signals and from nuclear Overhauser effect (nOe) experiments based on irradiation of the aromatic methyl, acetyl and amide N–H signals. The spectra were determined in dimethylsulfoxide to reduce the rate of exchange and facilitate the use of the N–H signal in these experiments.

There were interesting differences between the bromination and iodination of 2,4-dimethylacetanilide and 2,6-dimethylacetanilide. Bromination of 2,4-dimethylacetanilide

Table 1 Bromination of dimethylacetanilides

Substrate	Product	Yield/%
2,3-Dimethylacetanilide	4-Bromo-2,3-dimethyl-acetanilide	86
2,4-Dimethylacetanilide	6-Bromo-2,4-dimethyl-acetanilide	50
	5-Bromo-2,4-dimethyl-acetanilide	10*
2,5-Dimethylacetanilide	4-Bromo-2,5-dimethyl-acetanilide	97
2,6-Dimethylacetanilide	4-Bromu-2,6-dimethyl-acetanilide	44
	3-Bromo-2,6-dimethyl-acetanilide	11*
3,4-Dimethylacetanilide	2-Bromo-4,5-dimethyl-acetanilide	67
3,5-Dimethylacetanilide	4-Bromo-3,5-dimethyl-acetanilide	72
	2,4-Dibromo-3,5-dimethyl-acetanilide	17

*Estimated from the ^{1}H NMR spectrum of the crude product.

Table 2 Iodination of dimethylacetanilides

Substrate	Product	Yield/%
2,3-Dimethylacetanilide	2,3-Dimethyl-4-iodo-acetanilide	60
2,4-Dimethylacetanilide	2,4-Dimethyl-5-iodo-acetanilide	70
	2,4-Dimethyl-3-iodo-acetanilide	2
2,5-DimethylacetaMlide	2,5-Dimethyl-4-iodo-acetanilide	42
2,6-Dimethylacetanilide	2,6-Dimethyl-3-iodo-acetanilide	90
	2,6-Diethyl-3-iodo-acetanilide	60
3,4=Dimethylacetanilide	4,5-Dimethyl-2-iudo-acetanilide	50
3,5-Dimethylacetanilide	3,5-Dimethyl-4-iodo-acetanilide	51
	2,4-Diiodu-3,5-dimethyl-acetanilide	20

gave predominantly 6-bromo-2,4-dimethyl-acetanilide.[4] The orientation of substitution was confirmed by irradiation of the aromatic methyl signal, δ_H 2.23, which gave an nOe enhancement to both aromatic proton resonances [δ_H 7.04 (9.1%), 7.28 (9.1%)] whilst irradiation of the other aromatic methyl signal, δ_H 2.11, only produced an enhancement of the signal at δ_H 7.04 (7.8%). Irradiation of the acetyl methyl signal (δ_H 2.00) only enhanced the N–H signal [δ_H 9.45 (7.5%)]. On the other hand iodination of 2,4-dimethylacetanilide gave 2,4-dimethyl-5-iodoacetanilide. Irradiation of the N–H signal (δ_H 9.31) gave an nOe enhancement of the aromatic proton resonance at δ_H 7.84 (4.4%). Bromination of 2,6-dimethylacetanilide gave predominantly the 4-bromo compound [δ_H 2.01 (3H), 2.09 (6H), 7.25 (2H,singlet), 9.30 (1H)] together with a small amount of the 3-isomer which was detected by the presence of aromatic ^{1}H NMR signals at δ_H 7.01 and 7.38 (doublets, *J* 8.2 Hz). On the other hand iodination gave almost exclusively the 3-iodo compound [^{1}H NMR signals at δ_H 6.85 and 7.62 (doublets, *J* 8.1 Hz)]. Similarly iodination of 2,6-diethylacetanilide gave the 3-isomer (60% yield) [^{1}H NMR signals at δ_H 6.87 and 7.67 (doublets, *J* 8.1 Hz)]. The methylene of the 2-ethyl group in this compound was a broad signal at 20°C but was resolved into a quartet at 60°C. This was presumably due to steric hindrance to rotation by the

adjacent iodine and amide groups. Although some of the halogenations of the other dimethylacetanilides have not been reported previously, the results are unexceptional. The confirmatory nOe enhancements are given in the experimental section.

The increased proportion of the 4-bromo-2,6-dimethylacetanilide formed under these oxidative conditions, compared to the reaction with bromine in the presence of hydrobromic acid or sulfuric acid, suggests that the oxidative conditions may favour an alternative mechanism. The results of the iodination experiments parallel those of nitration.[4]

Experimental

General experimental details: Light petroleum refers to the fraction b.p. 60–80°C ^{1}H NMR spectra were recorded in [^{2}H$_6$]dimethylsulfoxide at 300 MHz and nOe enhancements were measured at 500 MHz. IR spectra were determined as nujol mulls. Extracts were dried over sodium sulfate.

Bromination of dimethylacetanilides: The substrate (7.5 mmol) was dissolved in a mixture of glacial acetic acid (15 cm^3) and acetic anhydride (10 cm^3). Potassium bromide (1 g) and sodium tungstate (300 mg) were dissolved in water (10 cm^3). The solutions were mixed and conc. sulfuric acid (1 cm^3) was added. A solution of peracetic acid (35%) in acetic acid (3 cm^3) was then added over a period of 45 minutes. The solution was left to stand for 1 hour (2,6-dimethylacetanilide, overnight). The mixture was then poured into water and the product filtered and recrystallised from ethanol. If the product did not crystallise the aqueous solution was extracted with chloroform. The extract was washed with aqueous sodium thiosulfate, brine and dried. The solvent was then evaporated to give the product.

Iodination of dimethylacetanilides: The substrate (7.5 mmol) was dissolved in a mixture of glacial acetic acid (15 cm^3) and acetic anhydride (10 cm^3). 40% Hydrogen iodide (2 cm^3) and conc. sulfuric acid (1 cm^3) were added followed by the dropwise addition of peracetic acid (35%) in acetic acid (3 cm^3). The mixture was stirred for 1 – 4 days and then poured into aqueous sodium sulfite. The products were filtered and recrystallised from ethanol. If the product did not crystallise the aqueous solution was extracted with chloroform. The extract was washed with aqueous sodium sulfite, brine and dried. The solvent was then evaporated to give the product.

The results are given in Tables 1 and 2

4-Bromo-2,3-dimethylacetanilide had m.p.157°C (lit.,[10] 161–2°C)
6-Bromo-2,4-dimethylacetanilide had m.p.194°C (lit.,[11] 194–6°C)
4-Bromo-2,5-dimethylacetanilide had m.p.188°C (lit.,[12] 187°C)
4-Bromo-2,6-dimethylacetanilide had m.p.195–196°C (lit.,[4] 194°C)
2-Bromo-4,5-dimethylacetanilide had m.p.160–165°C (lit.,[13] 164°C)
4-Bromo-3,5-dimethylacetanilide had m.p.l70–175°C (lit.[14] l70–174°C)

2,4-Dibromo-3,5-dimethylacetanilide had m.p. 155–160°C (Found: C, 38.0; H, 3.6; N, 4.2. C$_{10}$H$_{11}$Br$_2$ON requires C, 37.4; H, 3.45, N,4.4%), v_{max}/cm^{-1} 3270, 1659; δ_H 2.05 (3H, s, AC), 2.32 (3H, s, Me-5), 2.58 (3H, s, Me-3), 7.42 (1H, s, H-6), 9.51 (1H, s, NH).

2,3-Dimethyl-4-iodoacetanilide had m.p.156°C (lit.,[6] 158°C)
2,6-Dimethyl-3-iodoacetanilide had m.p.185–190°C (lit.,[6] 190°C)
2,4-Dimethyl-5-iodoacetanilide had m.p. 170°C (Found: C, 41.0; H,4.1; N,4.5. C$_{10}$H$_{12}$INO requires C, 41.5; H, 4.2, N, 4.8%), v_{max}/cm^{-1} 3274, 1650; δ_H 2.02 (3H, s, AC), 2.10 (3H, s, Me-2), 2.28 (3H, s, Me-4), 7.15 (1H, s, H-3), 7.84 (1H, s, H-6), 9.31 (1H, s, NHAc). Irradiation at δ_H 2.02 enhanced the signals at δ_H 9.31 (5.5%) and 7.84 (1%).

Irradiation at δ_H 9.31 enhanced the signals at δ_H 7.84 (4.4%), 2.10 (1.8%) and 2.02 (2.8%). Irradiation at δ_H 2.27 enhanced the signal at δ_H 7.15 (10.1%) whilst irradiation at δ_H 2.10 enhanced the signals at δ_H 9.31 (4.1%) and 7.15 (10.3%).

2,4-Dimethyl-3-iodoacetanilide had m.p. 170°C (Found: M$^+$ 288.995. C$_{10}$H$_{12}$INO requires M$^+$ 288.996),v_{max}/cm^{-1} 3281, 1651; δ_H 2.05 (3H; s, Ac), 2.30 (3H, s, Me-2), 2.38 (3H, s, Me-4), 7.14 (1H, d, *J* 7.9 Hz, H-5), 5.16 (1H, d, *J* 7.9 Hz, H-6), 9.55 (1H, s, NH). Irradiation at δ_H 2.05 enhanced the signal at δ_H 9.55 by 9.6%.

Irradiation at δ_H 9.55 enhanced the signal at δ_H 7.16 (4.7%), 2.30 (1.8%) and 2.05 (2.0%). Irradiation at δ_H 2.38 enhanced the signal at δ_H 7.13 by 10.3% whilst irradiation at δ_H 2.30 enhanced only δ_H 9.55 by 3.0%.

2,5-Dimethyl-4-iodoacetanilide had m.p.195–200°C (Found: M$^+$ 288.995; C$_{10}$H$_{12}$INO requires M$^+$ 288.996),v_{max}/cm^{-1} 3275, 1653; δ_H 2.02 (3H, s, Ac), 2.10 (3H, s, Me-2), 2.27 (3H, s, Me-5), 7.37 (1H, s, H-6), 7.63 (1H, s, H-3), 9.27 (1H, s, NH). Irradiation at δ_H 2.02 enhanced the signal at δ_H 9.27 (9.4%). Irradiation at δ_H 9.27 enhanced the signal at δ_H 7.37 (3.4%), 2.10 (2.1%) and 2.02 (3.0%). Irradiation at δ_H 2.27 enhanced the signal at δ_H 7.37 (11.7%) and irradiation at δ_H 2.10 enhanced the signal at δ_H 7.63 (10.5%).

2,6-Diethyl-3-iodoacetanilide had m.p. 165–170°C (Found: C, 45.2; H, 5.1; N, 4.3. C$_{12}$H$_{16}$INO requires C, 45.4; H, 5.1; N, 4.4%), v_{max}/cm^{-1} 3281, 1654; δ_H 0.98 and 1.06 (each 3H, t, *J* 7.5 Hz, Et-2 and 6 respectively), 2.03 (3H, s, AC), 2.40 and 2.67 (each 2H, q, *J* 7.5 Hz, Et-6 and 2 respectively) (the signal at δ_H 2.67 was broad at 25°C but resolved at 60°C), 6.87 (1H, d, *J* 8.1 Hz, H-5), 7.67 (1H, d, *J* 8.1 Hz,H-4), 9.41 (1H, s, NH). Irradiation at δ_H 2.40 enhanced the signals at δ_H 6.87 (5.8%) and 1.05 (3.6%). Irradiation at δ_H 2.63 enhanced the signal at δ_H 0.98 (4.2%). Irradiation at δ_H 2.03 enhanced the signal at δ_H 9.41 (7.9%).

4,5-Dimethyl-2-iodoacetanilide had m.p.145–150°C (Found: C, 41.4; H, 4.3; N, 4.3. C$_{10}$H$_{12}$INO requires C, 41.5; H, 4.2; N, 4.8%), v_{max}/cm^{-1} 3270, 1660; δ_H 2.00 (3H, s, Ac), 2.14 and 2.15 (each 3H, s, Ar–Me), 7.12 (1H, **s**, H-6), 7.60 (1H, s, H-3), 9.34 (1H, s, NH), Irradiation at δ_H 9.34 enhanced the signals at δ_H 7.12 (2.9%) and 2.00 (3.3%).

3,5-Dimethyl-4-iodoacetanilide had m.p.163–165°C (Found: C, 41.8; H, 4.2; N, 4.5. C$_{10}$H$_{12}$INO requires C, 41.5; H, 4.2; N, 4.8%), v_{max}/cm^{-1} 3270, 1655; δ_H 2.00 (3H, s, Ac), 2.34 (6H, s, Ar–Me), 7.37 (2H, s, H-2 and H-6), 9.91 (1H, s, NH).

2,4-Diiodo-3,5-dimethylacetanilide had m.p. 188–190°C (Found: M$^+$ 414.895. C$_{10}$H$_{11}$I$_2$NO requires M$^+$ 414.893), v_{max}/cm^{-1} 3278, 1660; δ_H 2.02 (3H, s, Ac), 2.37 (3H, s, Me-5), 2.84 (3H, s, Me-3), 7.17 (1H, s, H-6), 9.52 (1H, s, NH).

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