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Oxidative Iodination of Aromatic Amides Using Sodium Perborate or Hydrogen Peroxide with Sodium Tungstate†

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Hydrogen peroxide or sodium perborate in the presence of a sodium tungstate catalyst are shown to be cheap oxidants for the iodination of aromatic amides using potassium iodide as the source of the iodine.

Recently there has been some interest in developing novel methods for the bromination of aromatic compounds based on the catalytic oxidation of the bromide ion to an electrophilic species.[1] Aromatic iodination[2] using iodine also requires an oxidant although the reactive electrophile may be an acetylhypiodite or some similar oxyiodo species rather than the simple iodonium ion.[3,4] A variety of reagents have been used[2] in the oxidative iodination of aromatic compounds using both elemental iodine and the iodide ion. Recent examples of oxidants include lead tetraacetate[5] and mercuric oxide.[6] We have shown that both hydrogen peroxide and sodium perborate, in the presence of sodium tungstate as a catalyst, are effective systems for the oxidation of the bromide ion in the bromination of aromatic amides[7] and phenyl ethers.[8] Here we describe the application of these oxidants with the iodide ion to the iodination of aromatic amides.

The iodination of a limited number of aromatic compounds using peroxyacetic acid and iodine has been reported previously.[3,9] The uncatalysed iodination of aniline using hydrogen peroxide has also been described previously.[10] Sodium perborate in glacial acetic acid has been used[11] as a reagent for the oxidation of aromatic iodo compounds to iodoso derivatives and hence there was the possibility of over-oxidation of the iodo derivatives formed in the substitution reaction. Sodium perborate will also oxidize aromatic amines to azobenzenes and nitroarenes.

Potassium iodide was oxidized with either sodium perborate or hydrogen peroxide in the presence of sodium tungstate catalyst in glacial acetic acid solution. The iodinations were then carried out in glacial acetic acid in the presence of some sulfuric acid. The latter has been found previously[2] to facilitate aromatic iodination. The results of the iodination of a representative range of aromatic amides are given in Table 1. The products were identified by their mp and ^{1}H NMR spectra. In general the reactions using hydrogen peroxide as the oxidant proceeded in better yield to give the mono-iodo compound without further oxidation.

The iodination of 2,6-dimethylacetanilide, unlike the bromination which gives the 4-substituent, gave 2,6-dimethyl-3-iodoacetanilide. The substitution pattern was clear from the ^{1}H NMR spectrum which showed two aromatic doublets (δ_H 6.80 and 7.67, J 8.1 Hz). The abnormal aromatic substitution of 2,6-dimethylacetanilide has been noted previously[12] and rationalized[13] in terms of the steric inhibition of resonance. The difference between the bromination and iodination may reflect a difference in mechanism. Thus the oxidative bromination might be proceeding through an Orton mechanism involving prior *N*-bromination whilst the iodination is a direct electrophilic aromatic substitution. The iodination of *N*-acetyl-2-anisidine gave a 1:3 mixture of 4- and 5-iodo-*N*-acetyl-2-anisidine in 90% yield using hydrogen peroxide as the oxidant. The ratio of the products was established by ^{1}H NMR using an NOE effect from the NHCOMe and OMe signals to identify the relevant aromatic signals [*N*-acetyl-4-iodo-2-methoxyaniline, δ_H (DMSO) 7.24 and 7.76 (each 1 H, d, J 8.6 Hz), 7.31 (1 H, s); *N*-acetyl-5-iodo-2-methoxyaniline, δ_H (DMSO) 6.86 and 7.37 (each 1 H, d, J 8.5 Hz), 8.31 (1 H, s)]. The iodination of the nitroacetanilides with sodium perborate was accompanied by hydrolysis of the *N*-acetyl group to form the amine. The iodination was faster with the hydrogen peroxide and hydrolysis did not occur.

In conclusion we have shown that the iodination of aromatic amides can be achieved using potassium iodide as the source of the iodine and a cheap oxidant such as hydrogen peroxide or sodium perborate with sodium tungstate as the catalyst.

Experimental

General Experimental Details.—Melting points are uncorrected. ^{1}H NMR spectra were recorded in [^{2}H$_6$]DMSO at 300 MHz.

Iodination Using Sodium Perborate.—Sodium perborate (3 g) was dissolved in a mixture of glacial acetic acid (15 cm^3) and acetic anhydride (10 cm^3). A solution of potassium iodide (1.4 g) and sodium tungstate (300 mg) in water (10 cm^3) was added together with conc. sulfuric acid (5 cm^3). The substrate (7.5 mmol) in glacial acetic acid (10 cm^3) was added and the solution was warmed to 50 °C over 1 h. The mixture was poured into water (100 cm^3) and the excess iodine was destroyed with sodium thiosulfate and the solution was neutralized with sodium hydroxide. The product was filtered and recrystallized from ethanol. The products (see Table 1) were identified by their ^{1}H NMR spectra and melting point data. Occasionally it was necessary to extract the product with chloroform in this last step. The extract was then washed with water, dried over sodium sulfate and the solvent evaporated to give the product.

Iodination Using Hydrogen Peroxide.—Hydrogen peroxide (30%, 3 cm^3) was dissolved in glacial acetic acid (20 cm^3), cooled in ice and treated with conc. sulfuric acid (1 cm^3). A solution of potassium iodide (1.6 g) and sodium tungstate (300 mg) in water (10 cm^3) was added. After 15 min a solution of the substrate (10 mmol) in glacial acetic acid (10 cm^3) was added and the mixture was warmed to 50 °C for 1 h. The mixture was poured into water (100 cm^3) and the excess iodine was destroyed with sodium sulfite. The solution was neutralized with sodium hydroxide and the iodo derivative filtered and recrystallized. The products (see Table 1) were identified by their ^{1}H NMR spectra and mp data.

2,3-*Dimethyl*-4-*iodoacetanilide*. Mp 158 °C (Found: C, 41.7; H, 4.2; N, 4.7. $C_{10}H_{12}NOI$ requires C, 41.5; H, 4.2; N, 4.8%) δ_H (DMSO) 2.02, 2.14, 2.38 (each 3 H, s), 6.92 and 7.62 (each 1 H, d, J 8.5 Hz), 9.43 (1 H, s, NH).

2,6-*Dimethyl*-3-*iodoacetanilide*. Mp 190 °C (Found: C, 41.4; H, 4.2; N, 4.7. $C_{10}H_{12}NOI$ requires C, 41.5; H, 4.2; N, 4.8%) δ_H (DMSO) 2.15, 2.20, 2.35 (each 3 H, s), 6.98 and 7.79 (each 1 H, d, J 8.2 Hz), 9.95 (1 H, s, NH).

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Table 1 Iodination of aromatic amides

Substrate	Product	Sodium perborate		Hydrogen peroxide		
		Yield (%)	Mp/°C	Yield (%)	Mp/°C	Lit. mp[a]
Acetanilide	4-Iodoacetanilide	83	180	96	175	180
2-Methylacetanilide	4-Iodo-2-methylacetanilide	51	165	87	165	162
3-Methylacetanilide	4-Iodo-3-methylacetanilide	71	138	87	135	134
4-Methylacetanilide	2-Iodo-4-methylacetanilide	35	130	40	125	131
2,3-Dimethylacetanilide	2,3-Dimethyl-4-iodoacetanilide	43	155	69	158	
2,4-Dimethylacetanilide	2,4-Dimethyl-6-iodoacetanilide	30	86	56	85	85
2,6-Dimethylacetanilide	2,6-Dimethyl-3-iodoacetanilide	51	190	72	190	
2-Nitroacetanilide	4-Iodo-2-nitroaniline	45	121	—	—	123
4-Nitroacetanilide	2-Iodo-4-nitroaniline	38	114	—	—	115
	2-Iodo-4-nitroacetanilide			77	200	202
Methyl *N*-acetylanthranilate	Methyl 2-acetylamino-5-iodobenzoate	31	110	37	110	

[a] *Dictionary of Organic Compounds*, ed. J. Buckingham and F. Macdonald, Chapman and Hall, London, 6th edn., 1996.

Methyl 2-acetylamino-5-iodobenzoate. Mp 110 °C (Found: C, 37.1; H, 3.1; N, 4.4. $C_{10}H_{10}NO_3I$ requires C, 37.6; H, 3.2; H, 4.4%) δ_H (DMSO) 2.09 and 3.83 (each 3 H, s), 7.89 (1 H, d, *J* 8.8 Hz), 7.97 (1 H, dd, *J* 2.1 and 8.8 Hz), 8.12 (1 H, d, *J* 2.1 Hz), 10.45 (1 H, s, NH).

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