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Oxidative Bromination of Aromatic Amides using Sodium Perborate as Oxidant†

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Sodium perborate in glacial acetic acid–acetic anhydride with potassium bromide and sodium tungstate as a catalyst, provides a novel system for the bromination of aromatic amides.

The oxidative bromination of aromatic amides is an attractive, mild alternative to the more widely used bromine in glacial acetic acid.[1] Recently the oxidative bromination of aromatic compounds has been described using potassium bromide, hydrogen peroxide and various metal-oxo compounds as catalysts.[2–7] The use of vanadium(V) and molybdenum(VI) compounds as catalysts has been examined in the context of models for bio-halogenation. The tungsten(VI)-catalysed oxidation of bromide by hydrogen peroxide is fast. In a comparative study[8] utilizing sodium tungstate, ammonium molybdate and ammonium vanadate, there was some evidence that sodium tungstate was the more effective catalyst. Sodium perborate is a useful cheap oxidant whose applications are the subject of current interest.[9,10] We have examined its use as an alternative to hydrogen peroxide in the oxidative bromination of aromatic amines and amides. Some aromatic amines were examined because there is a possibility that they might be oxidized by this system rather than undergoing substitution.[9,10]

A representative range of aromatic amines and amides containing additional activating and deactivating substituents was examined using a standard bromination procedure. The results are given in Table 1. The sodium perborate was dissolved in a mixture of acetic acid and acetic anhydride to provide a solution which behaves as peracetic acid.[9,10] Indeed, bromination of acetanilide using peracetic acid as the oxidant gave *p*-bromoacetanilide in 76% yield. Sodium tungstate was used as a catalyst although this was not always necessary. For example, acetanilide was converted into *p*-bromoacetanilide in 60% yield in the absence of the catalyst. Some reactions proceeded at room temperature. However the most effective general procedure involved warming the solution to 75 °C. The yields of bromo compound refer to purified crystalline material. The bromo compounds were identified by their NMR spectra and by comparison of their melting points with literature data.

Most of the reactions were regioselective and in those examples where both *ortho* and *para* substitution was possible, the *para*-substituted product was the only isomer that was isolated. The conditions for the bromination of the simple anilines led to acetylation of the amine except in the case of the hindered 2,6-dichloroaniline and the *o*-nitroanilines. On occasions the yield with the *o*-nitroanilines was poor, possibly owing to benzofuroxan formation.

Phosphotungstic acid was a poorer catalyst (51% yield of

Table 1 Oxidative bromination of aromatic amides and amines using sodium perborate and sodium tungstate catalyst

Substrate	Product	% Yield	Mp (lit.[a])/°C
Acetanilide	4-bromoacetanilide	86	167 (167)
2-Methylacetanilide	4-bromo-2-methylacetanilide	85	171 (170)
3-Methylacetanilide	4-bromo-3-methylacetanilide	55	101 (102)
4-Methylacetanilide	2-bromo-4-methylacetanilide	86	117 (117)
2,3-Dimethylacetanilide	4-bromo-2,3-dimethylacetanilide	55	153 (154)
2,6-Dimethylacetanilide	4-bromo-2,6-dimethylacetanilide	47	189 (194)
2-Nitroacetanilide	4-bromo-2-nitroacetanilide	76	100 (104)
4-Nitroacetanilide	2-bromo-4-nitroacetanilide	22	125 (129)
Methyl *N*-acetylanthranilate	methyl *N*-acetyl-5-bromoanthranilate	87	134 (135)
2-Chloroacetanilide	4-bromo-2-chloroacetanilide	80	147 (151)
Aniline	4-bromoacetanilide	65	166 (167)
2,3-Dimethylaniline	4-bromo-2,3-dimethylacetanilide	70	153 (154)
2-Chloroaniline	4-bromo-2-chloroacetanilide	90	148 (151)
2,5-Dichloroaniline	4-bromo-2,5-dichloroacetanilide	80	140 (141)
2,6-Dichloroaniline	4-bromo-2,6-dichloroaniline	70	82–84 (86)
4-Methyl-2-nitroaniline	6-bromo-4-methyl-2-nitroaniline	87	64–65 (65)
2-Methyl-6-nitroaniline	4-bromo-2-methyl-6-nitroaniline	69	140 (139)

[a] Literature values taken from *Beilstein's Handbuch der Organischen Chemie*, Vierte Auflage, Springer, Berlin, vol. 12, 1929.

Table 2 Oxidative bromination of aromatic amides using sodium perborate and phosphomolybdic acid catalyst

Substrate	Product	% Yield
Acetanilide	4-bromoacetanilide	79
2-Methylacetanilide	4-bromo-2-methylacetanilide	74
3-Methylacetanilide	4-bromo-3-methylacetanilide	54
4-Methylacetanilide	2-bromo-4-methylacetanilide	66
2-Nitroacetanilide	4-bromo-2-nitroacetanilide	60
2-Chloroacetanilide	4-bromo-2-chloroacetanilide	62
Methyl *N*-acetylanthranilate	methyl *N*-acetyl-5-bromoanthranilate	59

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p-bromoacetanilide from acetanilide). Phosphomolybdic acid was also examined as a catalyst with a range of amides (see Table 2). However, the yields were not as satisfactory as those obtained with sodium tungstate as a catalyst.

In conclusion sodium perborate is a useful alternative to hydrogen peroxide as an oxidant for the oxidative bromination of aromatic amides. The yields are comparable to those obtained with the conventional procedure utilizing bromine in glacial acetic acid by which acetanilide is converted into *p*-bromoacetanilide in 84% yield.[11]

Experimental

General Experimental Procedure.—Sodium perborate (3 g) was dissolved in glacial acetic acid (50 cm^3) containing acetic anhydride (10 cm^3) and sulfuric acid (2.5 cm^3). A solution of sodium tungstate (300 mg) and potassium bromide (1 g) in water (10 cm^3) was prepared. This solution was added to a solution of the substrate (7.5 mmol) in glacial acetic acid (10 cm^3). The solution of sodium perborate was then added with stirring over 15 min and the temperature maintained at room temperature (or warmed to 75 °C) for 1 h. The solution was poured into water and the solution was neutralized with sodium hydrogen carbonate. The product was then filtered and recrystallized. If the product did not crystallize, the aqueous solution was extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate, sodium sulfite and water and dried. The solvent was evaporated and the residue was then purified by recrystallization. The yields quoted are for crystallized material. In the absence of the catalyst, bromination of acetanilide gave *p*-bromoacetanilide, 4-methylacetanilide gave 2-bromo-4-methylacetanilide and 2-methyl-6-nitroaniline gave 4-bromo-2-methyl-6-nitroaniline, each in 60% yield. The products were identified by their distinctive ^{1}H NMR aromatic substitution pattern and their mps.

When phosphomolybdic acid was the catalyst, 300 mg of this were used in place of the sodium tungstate and the reaction was carried out at 40 °C. The bromination was also carried out with hydrogen bromide (45%; 2.5 cm^3) in place of potassium bromide (acetanilide→4-bromoacetanilide, 87% yield).

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