The Bromination of Phenolic Methyl Ethers with Hydrogen Bromide using Sodium Tungstate and Hydrogen Peroxide as Oxidant†

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Sodium tungstate has been found to be an effective catalyst for the nuclear bromination of some aromatic methyl ethers using hydrogen bromide in glacial acetic acid and hydrogen peroxide as the oxidant.

Mild environmentally acceptable methods for the bromination of aromatic compounds are attracting interest.[1] Recently the oxidative bromination of aromatic compounds has been examined[2,3] with hydrogen peroxide and a metal–oxo catalyst as the oxidant to convert a bromide ion into the bromonium ion. Catalytic systems based on vanadium(V)–peroxo complexes have been examined as models for biological halogenation. Ammonium molybdate has also been examined in this context.[4–7] The tungsten(VI)-catalysed oxidation of bromide by hydrogen peroxide has been reported to be faster than the catalysis by either molybdenum(VI) or vanadium(V).[8] A study of the oxidative bromination of aromatic amides has revealed that sodium tungstate is an effective catalyst compared to ammonium molybdate and ammonium vanadate.[9] In this paper we report the use of sodium tungstate as a catalyst for the nuclear oxidative bromination of aromatic methyl ethers. *N*-Bromosuccinimide in acetonitrile has also been recommended recently[10] as a mild brominating agent for methoxybenzenes.

The compounds that were successfully brominated are listed in Table 1. The products were identified by their ^{1}H NMR spectra and by comparison with literature data. In each case it was possible to control the reaction so that monobromination took place. For example, with anisole it was possible to obtain *p*-bromoanisole and in a second reaction, bromination of *p*-bromoanisole gave 2,4-dibromoanisole. Alternatively 2,4-dibromoanisole was obtained directly by the use of twice the amount of reagent. When the position *para* to the methoxy group was free, it was this position that was brominated cleanly and we did not isolate any *ortho* isomer. The aldehydes were successfully brominated under these conditions and there was no oxidative loss of the formyl group in a Dakin reaction. However, the bromination was not successful with free phenols (*e.g.*, 2,5-, 3,4- and 2,3-dimethylphenol) which gave intractable quinonoid products.[11] Low yields (13 and 22% respectively) of 4-bromo-2,3-dimethylphenol and 4-bromo-2,5-dimethylphenol were obtained using ammonium molybdate as a catalyst.[12] Nitrophenyl ethers (*e.g.*, 4-nitroveratrole and 1,2-methylenedioxy-4-nitrobenzene) were recovered unchanged. Acetylation of the phenolic hydroxy group also reduced the reactivity of the aromatic ring and the majority of phenyl acetates were not brominated in the time-scale of these conditions. Thus bromination of phenyl acetate (*cf.* anisole), acetylsalicylic acid (*cf.* *o*-anisic acid), 1,2-diacetoxybenzene (*cf.* veratrole and acetoxyguaiacol) and acetoxyvanillin (*cf.* vanillin) did not take place under these conditions whilst the bromination of 2-acetoxynaphthalene was slow.

In conclusion, oxidative bromination using hydrogen peroxide and sodium tungstate catalysis affords a mild and selective method for the mono-bromination of reactive aromatic methyl ethers and may provide an alternative to the more conventional use of bromine in acetic acid.[13] It avoids the use of the hazardous elemental bromine.

Table 1 Oxidative bromination of phenyl methyl ethers using hydrogen peroxide and sodium tungstate

Substrate	Product	% Yield[a]
Anisole	4-bromoanisole	80
4-Bromoanisole	2,4-dibromoanisole	56 (40)[b]
4-Iodoanisole	2-bromo-4-iodoanisole	90
o-Anisic acid	5-bromo-2-methoxybenzoic acid	70
m-Anisic acid	6-bromo-3-methoxybenzoic acid	66
2,4-Dimethoxy-acetophenone	5-bromo-2,4-dimethoxy-acetophenone	70
2,4-Dimethoxy-benzaldehyde	5-bromo-2,4-dimethoxy-benzaldehyde	96
3,4-Dimethoxy-benzaldehyde	6-bromo-3,4-dimethoxy-benzaldehyde	68
Vanillin	5-bromovanillin	73
Piperonal	2-bromopiperonal	74
Veratrole	4-bromoveratrole	70
Acetoxyguaiacol	1-acetoxy-5-bromo-2-methoxy-benzene	62
2-Methoxy-naphthalene	1-bromo-2-methoxy-naphthalene	93
2-Acetoxy-naphthalene	2-acetoxy-1-bromo-naphthalene	44[c]

[a]Isolated yield. [b]Direct from anisole. [c]Overnight at room temperature.

Experimental

General Bromination Method.—The phenol methyl ether (1 g) was dissolved in glacial acetic acid (25 cm^3). 48% Hydrogen bromide (7 cm^3) and a solution of sodium tungstate (0.3 g) in the minimum of water were added. The mixture was warmed to 40–45 °C. In some instances this warming was not required. Hydrogen peroxide (30%; 2 cm^3) was added dropwise over 30 min and the reaction mixture was then stirred for a further 30 min. The product was isolated by dilution with water, filtration and recrystallization. Alternatively the mixture was treated with saturated aqueous sodium hydrogen carbonate and extracted with diethyl ether. The extract was rinsed with aqueous sodium sulfite, water and dried over sodium sulfate. The solvent was evaporated to yield the bromo compound. The products were identified by their mp (except *p*-bromoanisole and 4-bromoveratrole which were distilled) and by their ^{1}H NMR spectra.

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13 See, *e.g.*, A. S. Hussey and I. J. Wilk, *J. Am. Chem. Soc.*, 1950, **72**, 830, for the bromination of anisole with bromine in glacial acetic acid.