meta-Bromination of Phenols in Superacids

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Summary In SbF_5–HF, *para*-alkylated or 2,6-dialkylated phenols (and their ethers) react with bromine to give the corresponding *meta*-bromo-substituted compounds; the mechanism implies bromination of the *O*-protonated substrate.

IT is generally held that halogenation of phenols (and their ethers) occurs in the *ortho* and *para* position to the OR group, the reaction eventually leading to cyclohexadienones.[1,2] Because of the *ortho*, *para*-directing effect of the functional group, *meta*-substitution is expected to be difficult.[2,3a]

We report here our results on the bromination of substituted phenols in the superacid HF–SbF_5 (see Table).

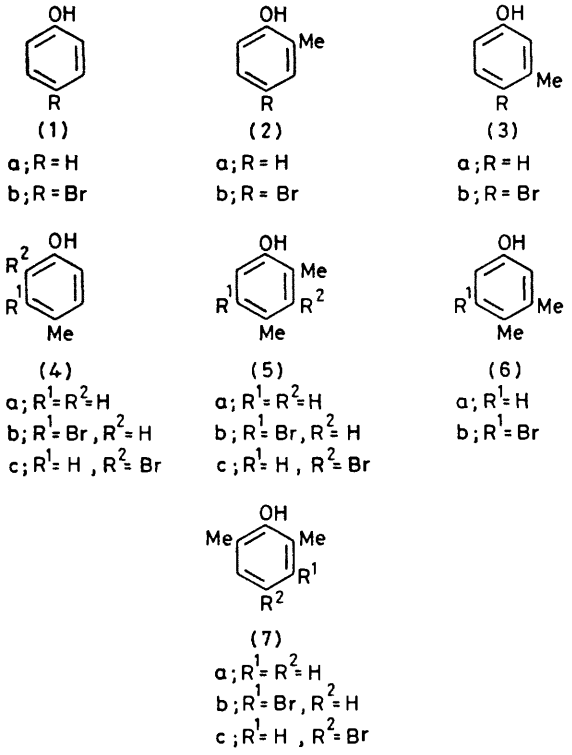


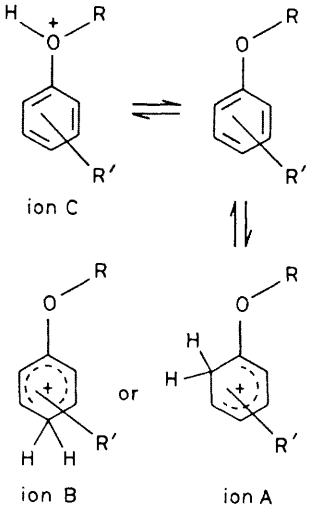
TABLE [a]

Starting material	Product (% yield)[b]
(**1a**)	(**1b**) (45) + (**1a**) (45)
(**2a**)	(**2b**) (56) + (**2a**) (35)
(**3a**)	(**3b**) (51) + (**3a**) (40)
(**4a**)	(**4b**) (85)
(**5a**)	(**5b**) (47) + (**5c**) (38)
(**6a**)	(**6b**) (83)
(**7a**)	(**7b**) (85)

[a] Reactions were performed as previously described; *i.e.* at 45 °C; bromine was added to the solution of the starting material in HF–SbF_5. Reaction time: 1 h for the phenols and 15 min for the ethers. Molar ratio SbF_5 : substrate 6 : 1; SbF_5 : HF 0·04 : 1; Br_2 : substrate 0·7 : 1 (HBr formed in the reaction is oxidized by the medium). [b] Yields are for isolated products after purification by column chromatography over SiO_2.

It appears that, although the phenols (**1a**—**3a**) gave the expected compounds, all other substrates gave the corresponding *meta*-bromo compounds in good yield. The methyl ethers of the phenols (**1a**—**7a**) gave similar results under the same conditions but exhibited higher reactivity (reaction time < 15 min). The *m*-bromo compounds do not arise from isomerisation of *o*- or *p*-bromo compounds since, for example, the phenols (**4c**) and (**7c**) (or their ethers) are recovered unchanged when treated with HF–SbF_5.

These results can be accounted for by considering the equilibrium between the neutral substrate and its protonated forms (Scheme).[4] Ring protonation would give



SCHEME.

either ion A or B, both of which are unreactive towards electrophiles. Therefore bromination of either the neutral or the oxygen-protonated form (ion C) has to occur. The reaction course will be governed by the relative concentrations and reactivities of these species; the ion C is expected to be less reactive than the neutral compound, whose concentration should, however, be small under these highly acidic conditions. Yet, in the case where the *O*-protonation (leading to ion C, the stability of which depends on the ring substitution) is disfavoured,[5] reaction of the neutral substrate will occur, leading to the *o*- or *p*-bromo derivative [bromination of (**1a**—**3a**) and their ethers]. With the other substrates, bromination of the corresponding ions C, formation of which is favoured by the ring substitution,[4,5] is directed by the co-operative effect of the alkyl group(s) and the protonated function leading to *meta*-substitution.

This is in agreement with the results of Olah[4] on the protonation of phenolic compounds in superacids, and with our own studies on the rearrangement of alkyl aryl ethers.[6] It is substantiated by molecular orbital studies on methylanisoles showing that oxygen protonation is a competing reaction only for the *para* isomer; the fact that this trend for oxygen protonation is less pronounced with methyl-

phenols might explain their lower reactivity.[5] Finally *O*-protonation might account for the high percentage of *meta*-substitution observed previously in 2,6-dialkylphenols or their ethers.[3b]

Whatever the electrophilic species is (Br^+, Br_2^+, Br_3^+, or HBr_2^+)[7] under these conditions, this reaction appears to be a very attractive method of preparation of *meta*-substituted phenols from the corresponding bromo compounds.

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