Novel site-specific one-step bromination of substituted benzenes†

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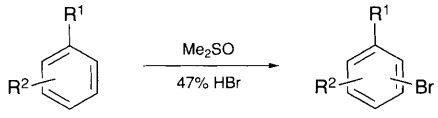
Regiospecific bromination of benzene derivatives has been carried out with Me_2SO–HBr; this method gives excellent yields of 2-bromobenzaldehyde and 2-bromonitrobenzene; strong *ortho*- and *para*-directing monosubstituted benzenes give *para*-bromo derivatives; a general discussion of the mechanism of these reactions is given.

Problems of site specificity during bromination of benzene derivatives arise because of the directing influence of the substituent already present in the aromatic substrates.[1–4] A single-step regiospecific bromination of substituted benzenes, irrespective of the nature of substituent is, therefore, not possible.[5–7] This makes simple benzene derivatives such as 2-bromobenzaldehyde and 2-bromonitrobenzene expensive commercial intermediates. Here we report the first single-step site-specific bromination of substituted benzenes, a reaction with obvious commercial value.

We have observed that monosubstituted benzene derivatives react with a mixture of dimethyl sulfoxide and aqueous hydrobromic acid (Scheme 1) to yield regiospecifically only the monobromo derivatives. It is interesting to note that electron-withdrawing groups such as NO_2, CHO yield *ortho*-bromo derivatives, while electron-donating groups such as NH_2, OH or Me give only *para*-bromo derivatives.

Preliminary studies on the bromination of disubstituted benzenes have also been carried out (Table 1). For example, the 1,2-disubstituted benzene derivative *o*-toluidine gave 4-bromo-2-methylaniline, the 1,3-disubstituted derivative *m*-chloroaniline yielded 6-bromo-3-chloroaniline and the 1,4-disubstituted derivatives *p*-nitroaniline and *p*-bromoaniline furnished 2-bromo-4-nitroaniline and 2,4-dibromoaniline, respectively.



Scheme 1

Table 1 Bromination of benzene derivatives using Me_2SO–HBr[a]

Entry	Substrate	Product[b]	Reaction time/h	Yield (%)
1	$PhNH_2$	$4\text{-}BrC_6H_4NH_2$	4	91
2	PhOH	$4\text{-}BrC_6H_4OH$	8	89
3	PhMe	$4\text{-}BrC_6H_4Me$	9.3	78
4	PhCHO	$2\text{-}BrC_6H_4CHO$	12	62
5	$PhNO_2$	$2\text{-}BrC_6H_4NO_2$	21	67
6	$2\text{-}MeC_6H_4NH_2$	$4\text{-Br-}2\text{-}MeC_6H_3NH_2$	16	50
7	$3\text{-}ClC_6H_4NH_2$	$6\text{-Br-}3\text{-}ClC_6H_3NH_2$	15	68
8	$4\text{-}O_2NC_6H_4NH_2$	$2\text{-Br-}4\text{-}O_2NC_6H_3NH_2$	24	36
9	$4\text{-}BrC_6H_4NH_2$	$2,4\text{-}Br_2C_6H_3NH_2$	10	82

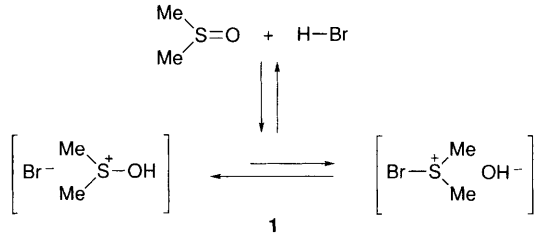
[a] *Typical procedure*: HBr was added to a stirred solution of the substrate in Me_2SO, and stirring was continued at room temperature. The reaction mixture was then neutralised with 10% aqueous Na_2CO_3. The product was either removed by filtration and recrystallised or extracted with EtOAc and dried and concentrated. [b] All compounds gave satisfactory spectroscopic data, and were identical to authentic samples. Single isomers were obtained for all compounds.

However, the bromination of all disubstituted benzenes has not been exhaustively studied.

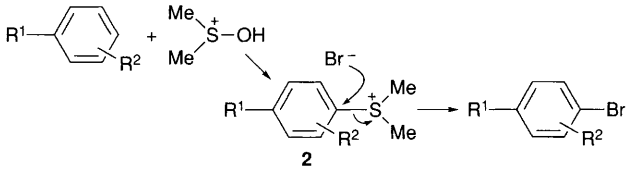
A plausible mechanism for this bromination has been proposed by us on the basis of products formed and spectral data. We suggest that the first intermediate along the reaction co-ordinate is the hydroxysulfonium bromide **1**, as shown in Scheme 2. The electrophile **1** then attacks preferentially at the *para*-position in the compounds having activating groups like R = NH_2, OH and Me, and gives the intermediate **2** which then facilitates the attack of Br^- and affords the *p*-bromo derivative as described in Scheme 3.

If the *para*-position is blocked, the electrophile attacks at the *ortho*-position, although this was found to be less favourable, probably due to the steric bulk of the electrophile.

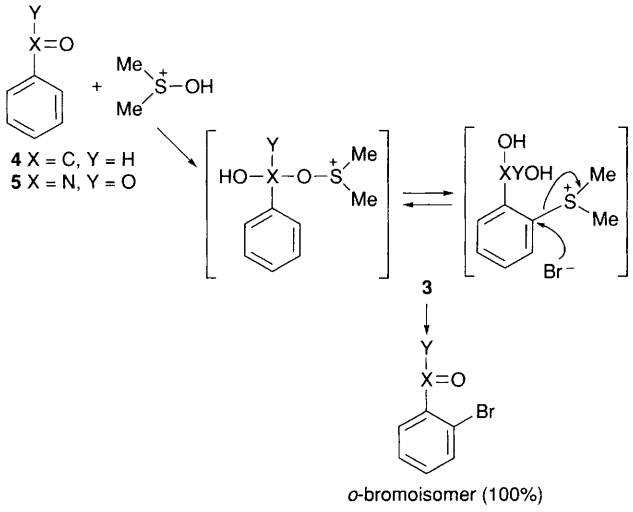
Formation of *o*-bromo derivatives from substrates possessing *meta*-directing groups such as NO_2 and CHO is explained *via* the formation of intermediate **3**, as discussed in Scheme 4. The



Scheme 2



Scheme 3



Scheme 4

non-existence of *meta* or *para* isomers for the products of **4** and **5** is possibly due to the formation of the intermediate **3**.

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Footnote

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