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

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Regiospecific bromination of benzene derivatives has been carried out with Me₂SO-HBr; this method gives excellent yields of 2-bromobenzaldehyde and 2-bromonitrotoluene; among 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-bromonitrotoluene 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 NO₂, CHO yield ortho-bromo derivatives, while electron-donating groups such as NH₂, 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.

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 = NH₂, 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 NO₂ and CHO is explained via the formation of intermediate 3, as discussed in Scheme 4. The

![Scheme 1](image1)

![Scheme 2](image2)

![Scheme 3](image3)

![Scheme 4](image4)

Table 1 Bromination of benzene derivatives using Me₂SO-HBr

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product*</th>
<th>Reaction time/h</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhNH₂</td>
<td>4-BrC₆H₄NH₂</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>PhOH</td>
<td>4-BrC₆H₄OH</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>4-BrC₆H₄Me</td>
<td>9.3</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>PhCHO</td>
<td>2-BrC₆H₄CHO</td>
<td>12</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>PhNO₂</td>
<td>2-BrC₆H₄NO₂</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>2-BrC₆H₄NH₂</td>
<td>4-Br-2-BrC₆H₄NH₂</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>3-CIC₆H₄NH₂</td>
<td>6-Br-3-CIC₆H₄NH₂</td>
<td>15</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>4-O₂NC₆H₄NH₂</td>
<td>2-Br-4-O₂NC₆H₄NH₂</td>
<td>24</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>4-BrC₆H₄NH₂</td>
<td>2,4-BrC₆H₄NH₂</td>
<td>10</td>
<td>82</td>
</tr>
</tbody>
</table>

*Typical procedure: HBr was added to a stirred solution of the substrate in Me₂SO, and stirring was continued at room temperature. The reaction mixture was then neutralised with 10% aqueous Na₂CO₃. The product was either removed by filtration and recrystallised or extracted with EtOAc and dried and concentrated. All compounds gave satisfactory spectroscopic data, and were identical to authentic samples. Single isomers were obtained for all compounds.

Chem. Commun., 1996 2679
non-existence of meta or para isomers for the products of 4 and 5 is possibly due to the formation of the intermediate 3.

We wish to thank the RSIC, Lucknow, for providing spectroscopic and analytical data and one of us (S. K. S.) is indebted to WRAIR, USA for financial support.

Footnote
† CDRI Communication No. 5526.

References

2 L. Forlani, Synthesis, 1980, 6, 487.

Received, 21st August 1996: Com. 6/05819A