An Efficient Method for the Preparation of Benzylic Bromides

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Abstract: Substituted benzylic compounds are brominated with an excess of \( \text{N-bromosuccinimide (NBS)} \) in \( \text{CCl}_4 \) to the corresponding polybrominated mixtures which are then debrominated with diethyl phosphate and \( \text{N,N-diisopropylethylamine (i-Pr}_2\text{NEt)} \) in satisfactory yields and high purity.

Key words: debromination, benzylic bromides, diethyl phosphate, \( \text{N,N-diisopropylethylamine} \)

The benzylic bromides, especially the poly(monobromomethyl)arenes are very useful intermediates in organic synthesis. They are used widely in the synthesis of the dendrimers,1 caged compounds,2 cappedophanes,3 etc. Generally, the preparation of such compounds is carried out by converting benzylic alcohols to benzylic bromides, however, the alcohols are commonly very expensive or have to be synthesized following a cumbersome route.1,3–5 Although the benzylic bromination with \( \text{N-bromosuccinimide (NBS)} \)6 is an important method and the reaction gives 67% yield of benzyl bromide from toluene, it is not satisfactory for three reasons. First, in multiple brominations, e.g., of xylenes or mesitylene, yields are reduced significantly because of the inevitable dibromination or even polybromination. Secondly, the byproducts, polybromides and monobromides have the same \( R_f \) values in TLC, which causes the purification very difficult. Finally, the electron-withdrawing substituents and heteroatoms make the yields worse. For example, 2,6-lutidine was brominated in only 2% yield to 2,6-bis(bromomethyl)pyridine in \( \text{CCl}_4 \).7,8

Many reports have demonstrated that diethyl phosphate–triethylamine system is a good choice for debromination of \( \alpha,\alpha\)-dibromomethyl arylketones, \( \text{gem-dibromoalkenes and gem-dibromocyclopropanes} \)9–12 to the corresponding monobromo compounds in good yields. In the present work we report a convenient two-step procedure for the preparation of benzylic bromides from methyl benzenes which are brominated first with an excess of NBS in \( \text{CCl}_4 \) and then debrominated selectively to the monobromides with diethyl phosphate and \( \text{N,N-diisopropylethylamine (i-Pr}_2\text{NEt)} \) in satisfactory yields and high purity.

Initially, compound \( 1\text{a} \) was reacted with 2 equivalents of NBS in \( \text{CCl}_4 \) at reflux temperature in the presence of a catalytic amount of benzoyl peroxide, but the subsequent debromination of the mixture of the bromides with diethyl phosphate and triethylamine gave the corresponding quaternary ammonium halide. The debromination of dibromo product in the reaction mixture to the monobromide \( 2\text{a} \) could be successfully achieved by treating with 2 equivalents diethyl phosphate and a non-nucleophilic base, such as \( \text{i-Pr}_2\text{NEt} \) in \( \text{THF} \) at room temperature in 75% yield (Table 1). Under these reaction conditions, polymethylated benzenes \( 1\text{b–d},\text{2,6-lutidine (1e) and 4-methylbenzonitrile (1f)} \) were also brominated with 2 equivalents of NBS and then debrominated with diethyl phosphate and \( \text{i-Pr}_2\text{NEt} \) to give the monobromides \( 2\text{b–f} \) in satisfactory yields and high purity (Scheme, Tables 1 and 2). Further debromination of the monobromide was not observed by TLC or \( ^1\text{H NMR} \) analysis, except for \( 2\text{e} \).

In contrast to the reaction with the substrates carrying an electron-withdrawing group (1a,b), the debromination of polybrominated \( m\)-xylene could not be carried out completely with 4 equivalents of reagents even in 5 days with portionwise addition of the reagents. When the reaction temperature was increased to 60 °C, the conversion of polybromide to monobromide took place completely in 40 hours, but the yield (7%) fell greatly. Finally, we increased the quantities of reagents to 8 equivalents and the reaction progressed smoothly at room temperature. For mesitylene (1d), 4 equivalents of reagents were needed.
Preparation of Benzylic Bromides

for complete debromination. However, the debromination of polybromides of \( \text{o} \)- and \( \text{p} \)-dimethylarenes was unsuccessful. For example, \( \text{o} \)-xylene and 3,4-dimethylphenyl acetate gave complicated mixtures and an undetectable gum was obtained from the debromination of \( \text{p} \)-xylene and 1,2,4,5-tetramethylbenzene, respectively.

Although the polybromides of 2,6-lutidine (1e) were completely debrominated with 2 equivalents of reagents at 60 °C, higher yield (76% vs. 50%) was obtained when 4 equivalents of reagents were used (Table 1). Because the polybromides are separable on TLC (silica gel), 1e was subjected to further investigations to study the influence of reaction conditions. The results showed that the inorganic base \( \text{K}_2 \text{CO}_3 \) also accelerated the debromination reaction, but the debromination could not be carried out when pyridine, 2,6-lutidine, 2,4,6-trimethylpyridine, N-methylmorpholine or proton sponge was used as the base with diethyl phosphite. Moreover, pyridine and N-methyl-

**Table 1** Preparation of Benzylic Bromides 2a–f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (h)</th>
<th>HPO(OEt)_2/ ( i-\text{Pr}_2\text{NEt} ) (equiv)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>found</th>
<th>reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{OAc} )</td>
<td>24</td>
<td>2:2</td>
<td>2a</td>
<td>75</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>( \text{CO}_2\text{Me} )</td>
<td>24</td>
<td>2:2</td>
<td>2b</td>
<td>79</td>
<td>28(^{14})</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>72</td>
<td>8:8</td>
<td>2c</td>
<td>54</td>
<td>31(^{15})</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>29</td>
<td>4:4</td>
<td>2d</td>
<td>52</td>
<td>23(^{16})</td>
<td></td>
</tr>
<tr>
<td>5(^c)</td>
<td></td>
<td>5</td>
<td>4:4</td>
<td>2e</td>
<td>76</td>
<td>2(^{7})</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>15</td>
<td>4:4</td>
<td>2f</td>
<td>82</td>
<td>38(^{15})</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) All reactions were carried out in THF at 25 °C under argon with 3 mmol of the substrate.

\(^b\) All compounds prepared showed physical and spectral data in accordance with their expected structures (see Table 2).

\(^c\) The debromination of this substrate could be monitored by TLC.

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. \(^1\)H NMR spectra were measured using Bruker 300 MHz and 400 MHz spectrometers. IR spectra were recorded on a Nicolet Mx-1 spectrometer. Mass spectra were recorded on a VG7070E, GC/MS/DS instrument. Elemental analyses were carried out on a Carlo Erba-1160 instrument. All
Table 2  Melting Points and Spectral Data of Benzylic Bromides 2a–f

<table>
<thead>
<tr>
<th>Product</th>
<th>Mp (°C)</th>
<th>$^1$H NMR (CDCl$_3$) $\delta$, $J$ (Hz)</th>
<th>MS (70 eV, EI) $M^+$ (%)</th>
<th>IR (KBr) cm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a$^a$</td>
<td>84–85</td>
<td>2.26 (s, 3 H), 4.40 (s, 4 H), 7.04 (d, 2 H, $J = 1.6$), 7.23 (t, 1 H, $J = 1.6$)</td>
<td>322 (M + 2, 5), 280 (37), 241 (16), 199 (56), 120 (32), 91 (29), 43 (100)</td>
<td>1764 (C=O), 1614, 1589, 1451, 1369, 1296, 1203, 1141, 1022, 982, 913, 693</td>
</tr>
<tr>
<td>2b</td>
<td>95–97</td>
<td>3.93 (s, 3 H), 4.49 (s, 4 H), 7.61 (br s, 1 H), 7.99 (d, 2 H, $J = 1.6$)</td>
<td>322 (M + 2, 6), 291 (8), 241 (100), 162 (43), 103 (24)</td>
<td>1728 (C=O), 1604, 1436, 1318, 1231, 1108, 996, 902, 771, 698, 600</td>
</tr>
<tr>
<td>2c</td>
<td>75–77</td>
<td>4.50 (s, 4 H), 7.32 (m, 3 H), 7.44 (m, 1 H)</td>
<td>264 (M + 2, 10), 185 (89), 104 (100)</td>
<td>1485, 1439, 1263, 1209, 897, 798, 698, 583, 532</td>
</tr>
<tr>
<td>2d</td>
<td>94–95$^b$</td>
<td>4.45 (s, 6 H), 7.35 (s, 3 H)</td>
<td>355 (M + 1, 17), 275 (100), 233 (10), 196 (54), 115 (54), 91 (28)</td>
<td>1824, 1800, 1610, 1460, 1440, 1218, 1171, 1128, 986, 900, 862, 708</td>
</tr>
<tr>
<td>2e</td>
<td>87–88$^c$</td>
<td>4.55 (s, 4 H), 7.39 (d, 2 H, $J = 7.8$), 7.72 (t, 1 H, $J = 7.8$)</td>
<td>265 (M + 2, 16), 184 (100), 105 (35), 78 (20)</td>
<td>1595, 1578, 1460, 1220, 1210, 1169, 1090, 1000, 962, 872, 820, 749</td>
</tr>
<tr>
<td>2f</td>
<td>116–118</td>
<td>4.49 (s, 2 H), 7.53 (m, 2 H), 7.67 (dd, 2 H, $J = 2.1, 6.6$)</td>
<td>197 (M + 2, 4), 116 (100), 89 (18)</td>
<td>2225 (C=O), 1605, 1504, 1411, 1289, 1230, 1097, 847, 743, 604</td>
</tr>
</tbody>
</table>

$^a$ Anal. Calc'd for C$_{10}$H$_{10}$Br$_2$O$_2$: C, 37.31; H, 3.11; Br, 49.64. Found: C, 37.53; H, 3.23; Br, 50.00.

$^b$ Lit.$^{15}$ mp 94 °C.

$^c$ Lit.$^{14}$ mp 85–89 °C.

Acknowledgement

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References


7. Barnes, R. A.; Fale, H. M. J. Org. Chem. 1979, 44, 710; and Ref.$^{13,14}$


13. Two equivalents of NBS were necessary for the complete bromination of the methyl groups; see also Ref.$^{13,14,15}$

