Regioselective Bromomethylation of 1,2-Dialkylbenzenes

Nupur Garg and T. Randall Lee
Department of Chemistry, University of Houston, Houston, TX 77204-5641, USA
FAX: (713)-743-2725; E-mail: trlee@uh.edu
Received 5 November 1997.

Abstract: This paper describes a systematic exploration of the regioselective bromomethylation of 1,2-dialkylbenzenes as a function of the reaction temperature and the chain length of the alkyl groups. At both 80 and 110 °C, bromomethyl groups can be introduced into the 4 and 5 positions of 1,2-dialkylbenzenes with high selectivity when the alkyl chains consist of two or more carbon atoms.

Halomethyl-substituted aromatics are versatile organic synths whose preparative routes are well documented. Among known halomethylation reactions, the chloromethylation of aromatic compounds has been the most widely studied. Although bromomethyl derivatives are synthetically more versatile than their chloromethyl analogs, relatively few studies have explored the bromomethylation of benzene and alkylbenzenes. The focus of the present study was to examine the influence of reaction time, temperature and reagents on the rate, yield and regioselectivity of the bromomethylation of 1,2-dialkylbenzenes. We wished to develop a synthetic method that would yield 1,2-bis(bromomethyl)-4,5-dialkylbenzenes derivatives of high purity and in synthetically useful quantities. Of the various strategies examined in our laboratories, the most satisfactory procedure for generating these derivatives involved the bromomethylation of 1,2-dialkylbenzenes using the method of van der Made. Scheme 1 illustrates this approach.

Scheme 1. Conditions: 80-110 °C; sealed vessel.

The starting 1,2-dialkylbenzene derivatives were either purchased (3a = Me; 3b = Et) or synthesized as shown in Scheme 2 (3c-f). Addition of two equivalents of Grignard reagent to phthalaldehyde yielded the corresponding alcohol derivatives 2, which upon hydrogenolysis provided the 1,2-dialkylbenzenes in approximately 75% overall yield.

Scheme 2. Two-step synthesis of 1,2-dialkylbenzenes 3c-f.

We conducted the bromomethylation of 1,2-dialkylbenzenes 3a-f at both 80 and 110 °C. Caution: The reagents used in the reaction are toxic and corrosive, and the bromomethylation products are likely to be lachrymators. Tables 1 and 2 show the relative ratios of mono- and bis-bromomethylated products, which were measured by 1H NMR spectroscopy by integrating the indicated ArCH2Br resonances. Treatment of o-xylene (3a) with paraformaldehyde and hydrobromic acid yielded 4a and two bis-bromomethylated regioisomers 5a and 6a. In contrast, the bromomethylation of compounds 3b-f proceeded with high selectivity to give 4b-f and only one bis-bromomethylated regioisomer.

To establish the configuration of the bis-bromomethylated products, we conducted several 1D NOE (Nuclear Overhauser Effect) and 1H-1H COSY experiments. Together with GC/MS analyses, these experiments confirm that the bis-bromomethylation of 3a generates both 5a and 6a, while the bis-bromomethylation of 3b-f generates only 5b-f, respectively. The formation of other distinguishable multiply bromomethylated isomers was less than 3-4% in all substrates except 3a, where substantial formation of 6a was observed. Also, the bromomethylation of 3a and 3b at 110 °C ultimately forms tar-like substances with 1H NMR resonances in the range of δ 3.0-4.0 ppm. The relatively high temperature apparently leads to polymerization and/or decomposition for these substrates.

Since alkyl groups are known to be both ortho and para directors, the bromomethylation of 1,2-dialkylbenzenes 3 can potentially occur at all four vacant sites on the aromatic ring. Our results show, however, that the bromomethylation takes place exclusively at the 4 and 5 positions when the alkyl chains are two or more carbons long (see Tables 1 and 2). The origin of this high selectivity is probably steric in nature: sufficiently large alkyl groups are likely to hinder substitution of the bromomethyl groups at the ortho positions of 1,2-dialkylbenzenes.

Table 1. Bromomethylation of 3 at 80 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (days)</th>
<th>NMR data (ArCH2Br in units of δ)</th>
<th>Mono/Bis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>CH3</td>
<td>1</td>
<td>4.44 (2H, s), 4.52 (4H, s), 4.60 (4H, s)</td>
<td>86:2:12f</td>
</tr>
<tr>
<td>b</td>
<td>CH3</td>
<td>10</td>
<td>4.44 (2H, s), 4.52 (4H, s), 4.60 (4H, s)</td>
<td>52:26:22f</td>
</tr>
<tr>
<td>c</td>
<td>C2H5</td>
<td>1</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>98:2</td>
</tr>
<tr>
<td>d</td>
<td>C2H5</td>
<td>10</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>90:10</td>
</tr>
<tr>
<td>e</td>
<td>C3H7</td>
<td>1</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>90:10</td>
</tr>
<tr>
<td>f</td>
<td>C3H7</td>
<td>10</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>88:12</td>
</tr>
<tr>
<td>g</td>
<td>C3H11</td>
<td>1</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>100:0</td>
</tr>
<tr>
<td>h</td>
<td>C4H9</td>
<td>1</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>95:5</td>
</tr>
<tr>
<td>i</td>
<td>C5H13</td>
<td>1</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>86:14</td>
</tr>
<tr>
<td>j</td>
<td>C6H15</td>
<td>1</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>100:0</td>
</tr>
<tr>
<td>k</td>
<td>C7H15</td>
<td>1</td>
<td>4.48 (2H, s), 4.65 (4H, s)</td>
<td>95:5</td>
</tr>
</tbody>
</table>

f Ratio of mono-3,5,5-bis-4,5-bis-bromomethylated products

In contrast, the bromomethylation of compounds 3b-f proceeded with high selectivity to give 4b-f and only one bis-bromomethylated regioisomer. 
Tables 1 and 2 show a progressive decrease in the rate of formation of bis-bromomethylated products as the length of the substituent R increases. Substantially slower rates of reaction were observed for the substrates 3e and 3f when compared to the derivatives having shorter alkyl chains. In preparative scale reactions conducted at 110 °C, the bromomethylation of 3d for 6 days yielded a product ratio of 30:70 of mono:bis-bromomethyl with a 45% overall yield of bromomethylated products. In contrast, the bromomethylation of 3e and 3f for 19 and 24 days, respectively, yielded product ratios of 25:75 and 29:71 with overall yields of 51% and 38%, respectively.

Increasing the temperature from 80 to 110 °C increased the rate of bromomethylation for all substrates. For longer chain derivatives, a brief study exploring the use of the co-solvents carbon tetrachloride, chloroform and 1,4-dioxane found no substantial increase in the rate of the reaction. Also, the addition of a phase transfer catalyst (hexadecyltrimethylammonium bromide) or a Lewis acid catalyst (ZnBr₂) showed no increase in the rate of the reaction. We found, however, that the reaction was highly sensitive to the experimental conditions (e.g., freshness of the HBr solution; rate of stirring). These latter observations are consistent with the results of halomethylation reactions reported by other researchers.²,³

As a synthetic tool, the bromomethylation of 1,2-dialkylbenzenes shows great promise for its regioselectivity. Relatively long reaction times, however, are required to generate the desired products in high yields. We are currently attempting to optimize the yields of bis-bromomethylated products as a function of the reaction time.

Acknowledgments. The National Science Foundation (CAREER Award to TRL; CHE-9625003), the Robert A. Welch Foundation (Grant No. E-1320) and the Camille and Henry Dreyfus Foundation (New Faculty Award to TRL; NF-93-040) provided generous support for this research. We thank our colleagues Jonathan Friedman and Randy Thummel for helpful advice.

References and Notes

(5) Compounds 3a and 3b were commercially available from Aldrich; compounds 2c-f and 3c-f were synthesized using typical procedures described here for 2f and 3f, respectively. 1,2-Di(1-hydroxypentadecyl)benzene (2f). A dropping funnel was capped with a rubber septum, and attached to a 200 mL Schlenk flask equipped with a magnetic stirring bar. The assembly was flame dried under Ar. In a separate dry 200 mL round-bottomed flask, 4.23 g (31.5 mmol) of phthalaldehyde was introduced. The flask was capped with a rubber septum, and purged with Ar. Dry and degassed toluene (60 mL) was added, and the solution was transferred to the Schlenk flask via cannula. The flask was placed in a -20 °C salt/ice bath, and n-pentadecylnium chloride (0.090 mol in Et₂O) was added dropwise via the dropping funnel. The stirred solution was allowed to warm to rt over a period of 20 h. After addition of said NH₄Cl, the mixture was filtered through a medium glass frit, and the filtrate was concentrated by rotary evaporation, and chromatographed on silica gel using hexanes. A fast eluting fraction (RF = 0.5 in hexanes) was separated, and the eluant was adjusted to a 3:1 ratio of hexanes/Et₂O. A fraction (RF = 0.65 using the solvent mixture as eluant) was then collected. Removal of the solvent in vacuo gave 16.7 g (31.5 mmol, 76%) of 2f.¹ H NMR (300 MHz, CDCl₃): δ 8.08 (t, 2 H, J = 8 Hz, CH₃), 1.25-1.50 (m, 52 H), 4.97 (t, 2 H, J = 5.7 Hz, CHOH), 7.27 (d of d, 2 H, J₁₋₂ = 7.5 Hz, J₁₋₃ = 2.8 Hz, Ar-H), 7.43 (d of d, 2 H, J₂₋₃ = 7.5 Hz, J₁₋₃ = 2.8 Hz, Ar-H).¹³C NMR (75 MHz, CDCl₃): δ 14.1, 22.7, 26.4, 29.4, 29.7, 31.9, 38.6, 71.1, 126.2, 127.7, 141.6.

1,2-Dipentadecylbenzene (3f). A dry 250 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 10% palladium on carbon (100 mg) and p-toluene sulfonic acid (100 mg). The flask was capped with a rubber septum, and purged with Ar. Degassed methanol (40 mL) was added via cannula, and the suspension was stirred under H₂ for 25-30 min. Separately, a 250 mL round-bottomed flask was charged with 2.00 g (37.8 mmol) of 2f and methanol (40 mL). The flask was capped with a rubber septum and purged with Ar. The methanolic solution was then added via cannula to the catalyst. The mixture was stirred under H₂ for 24 h at rt, after which no olefinic peaks of the starting material could be observed by H¹ NMR spectroscopy. The solution was concentrated under vacuum, and passed through a plug of silica gel using hexanes. The filtrate was concentrated by rotary evaporation to give 1.85 g (39.2 mmol, 98%) of 3f as a colorless liquid.¹¹H NMR (300 MHz, CDCl₃): δ 8.08 (t, 2 H, J = 8 Hz, CH₃), 1.25-1.50 (m, 52 H), 2.58 (t, 4 H, J = 8 Hz, CH₂Ar), 7.09-7.11 (m, 4 H, Ar-H).¹³C NMR (75 MHz, CDCl₃): δ 14.1, 22.7, 29.4, 29.6, 29.7, 29.8, 31.4, 31.9, 32.7, 125.6, 129.1, 140.6.

The synthesis of 5d from 3d illustrates a typical bromomethylation procedure: A 100 mL cylindrical high pressure glass vessel equipped with a magnetic stirring bar was charged with 0.50 g (2.3 mmol) of 3d, 10 mL of acetic acid, 0.25 g (8.3 mmol) of paraformaldehyde and 1 mL of 33 wt% hydrobromic acid in acetic acid.⁴ The resulting mixture was heated with stirring at 110 °C for 6 days. Hydrobromic acid solution (~1 mL) and paraformaldehyde (~0.25 g) were added twice during the course
of the reaction. Aliquots of the reaction mixture were removed via pipet, and analyzed by $^1$H NMR spectroscopy. Formation of the mono-bromomethylated 4d (δ 4.48, 2 H, s, ArCH$_2$Br) was initially observed. The peak corresponding to the bis-bromomethylated 5d (δ 4.65, 4 H, s, ArCH$_2$Br) increased while that of 4d decreased. Water (10 mL) was added, and the mixture was transferred to a 500 mL separatory funnel using hexanes and Et$_2$O. The organic phase was washed with satd NaHCO$_3$ (3 X 50 mL) and satd brine (1 X 50 mL), and dried (MgSO$_4$). Removal of the solvent by rotary evaporation gave an oil that was chromatographed on silica gel using hexanes to yield 0.49 g (1.2 mmol, 45%) of a pale yellow oil, which consisted of a mixture of mono- and bis-bromomethylated products in a 3:7 ratio, respectively. The products were cleanly separated by reversed-phase chromatography on a Waters μBondpack C$_{18}$ column (7.8 X 300 mm) using a mixture of THF/H$_2$O (60/40) at a flow rate of 4 mL/min. Mixtures derived from other substrates could also be efficiently separated.

Analytical data for 4d: $^1$H NMR (300 MHz, CDCl$_3$): δ 0.89 (t, 6 H, J = 8 Hz, CH$_3$), 1.25-1.50 (m, 12 H), 2.54 (t, 4 H, J = 8 Hz, CH$_2$Ar), 4.48 (s, 2 H, CH$_2$Br), 7.10-7.15 (m, 3 H, Ar-H). GC/MS data for 4d: m/z (rel. intensity; ion) 310, 312 (5%, 5%; M$^+$), 231 (100%, M$^+$ - Br). HRMS calc'd for C$_{17}$H$_{27}$Br$_2$ (M$^+$): 312.1278. Found: 312.1277. 

Analytical data for 5d: $^1$H NMR (300 MHz, CDCl$_3$): δ 0.89 (t, 6 H, J = 8 Hz, CH$_3$), 1.25-1.50 (m, 12 H), 2.54 (t, 4 H, J = 8 Hz, CH$_2$Ar), 4.65 (s, 4 H, CH$_2$Br), 7.11 (s, 2 H, Ar-H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 14.0, 22.5, 30.6, 30.7, 31.9, 32.3, 131.8, 131.9, 133.6, 142.3. GC/MS (70 eV, EI): m/z (rel. intensity; ion) 402, 404, 406 (1.2%, 2.5%, 1.1%; M$^+$), 323, 325 (100%, 99%; M$^+$ - Br), 244 (31%; M$^+$ - 2Br), 91 (12%; C$_7$H$_7$$^+$). HRMS calc'd for C$_{18}$H$_{26}$Br$_2$ (M$^+$): 406.0521. Found: 406.0525.

(7) The bromomethylated products generated from 3a were characterized by $^1$H NMR (300 MHz, CDCl$_3$) and GC/MS (70 eV, EI) of fractions separated by chromatography on silica gel. 4a (ArCH$_2$Br at δ 4.44): m/z (rel. intensity; ion) 198, 200 (5%, 5%; M$^+$), 119 (100%; M$^+$ - Br). 5a (ArCH$_2$Br at δ 4.52): 290, 292, 294 (9%, 18%, 9%; M$^+$), 211, 213 (95%, 92%; M$^+$ - Br), 132 (100%; M$^+$ - 2Br), 91 (16%; C$_7$H$_7$$^+$). 6a (ArCH$_2$Br at δ 4.60): 290, 292, 294 (13%, 27%, 13%; M$^+$), 211, 213 (100%, 99%; M$^+$ - Br), 132 (75%; M$^+$ - 2Br), 91 (20%; C$_7$H$_7$$^+$). The broad resonances observed by $^1$H NMR spectroscopy within the region of δ 3.0-4.0 could not be identified.