

Regioselective Bromomethylation of 1,2-Dialkylbenzenes

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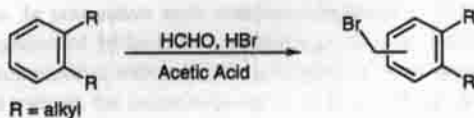
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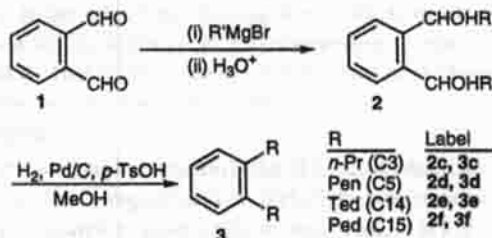
Abstract: This paper describes a systematic exploration of the regioselective bromomethylation of 1,2-dialkylbenzenes as a function of the reaction temperature and the chain length of the alkyl groups. At both 80 and 110 °C, bromomethyl groups can be introduced into the 4 and 5 positions of 1,2-dialkylbenzenes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

Halomethyl-substituted aromatics are versatile organic synthons whose preparative routes are well documented.¹⁻³ Among known halomethylation reactions, the chloromethylation of aromatic compounds has been the most widely studied.² 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-dialkylbenzene 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.⁴ Scheme 1 illustrates this approach.



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

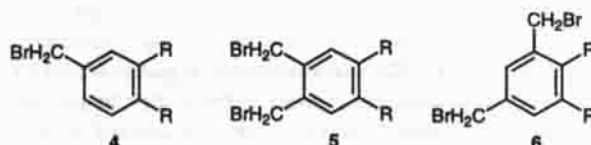
The starting 1,2-dialkylbenzene derivatives were either purchased (**3a** = Me; **3b** = Et) or synthesized as shown in Scheme 2 (**3c-f**).⁵ Addition of two equivalents of Grignard reagent to phthalaldehyde yielded the corresponding alcohol derivatives **2**, which upon hydrogenolysis provided the 1,2-dialkylbenzenes 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.⁶ **Caution:** The reagents used in the reaction are toxic and corrosive, and the bromomethylated 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**.⁷ In contrast, the bromomethylation of compounds **3b-f** proceeded with

high selectivity to give **4b-f** and only one bis-bromomethylated regioisomer.⁶



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**,⁷ 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% for 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

Entry	R	Time (days)	NMR data (ArCH ₂ Br in units of δ)	Mono:Bis
a	CH ₃	1	4.44 (2H, s), 4.52 (4H, s), 4.60 (4H, s)	86:2:12 ^W
		5	4.44 (2H, s), 4.52 (4H, s), 4.60 (4H, s)	70:18:12 ^W
		10	4.44 (2H, s), 4.52 (4H, s), 4.60 (4H, s)	52:26:22 ^W
b	C ₂ H ₅	1	4.48 (2H, s), 4.65 (4H, s)	98:2
		5	4.48 (2H, s), 4.65 (4H, s)	91:9
		10	4.48 (2H, s), 4.65 (4H, s)	90:10
c	C ₃ H ₇	1	4.48 (2H, s), 4.65 (4H, s)	98:2
		5	4.48 (2H, s), 4.65 (4H, s)	90:10
		10	4.48 (2H, s), 4.65 (4H, s)	88:12
d	C ₅ H ₁₁	1	4.48 (2H, s), 4.65 (4H, s)	100:0
		5	4.48 (2H, s), 4.65 (4H, s)	89:11
		10	4.48 (2H, s), 4.65 (4H, s)	80:20
e	C ₁₄ H ₂₉	1	4.48 (2H, s), 4.65 (4H, s)	100:0
		5	4.48 (2H, s), 4.65 (4H, s)	95:5
		10	4.48 (2H, s), 4.65 (4H, s)	86:14
f	C ₁₅ H ₃₁	1	4.48 (2H, s), 4.65 (4H, s)	100:0
		5	4.48 (2H, s), 4.65 (4H, s)	95:5
		10	4.48 (2H, s), 4.65 (4H, s)	89:11

^W Ratio of mono-/3,5-bis-/4,5-bis-bromomethylated products⁷

Table 2. Bromomethylation of **3** at 110 °C

Entry	R	Time (days)	NMR data (ArCH ₂ Br in units of δ)	Mono:Bis
a	CH ₃	1	4.44 (2H, s), 4.52 (4H, s), 4.60 (4H, s)	71:22:7 [¶]
		5	3.0-4.0	---
		10	3.0-4.0	---
b	C ₂ H ₅	1	4.48 (2H, s), 4.65 (4H, s)	85:15
		5	4.48 (2H, s), 4.65 (4H, s)	58:42
		10	3.0-4.0	---
c	C ₃ H ₇	1	4.48 (2H, s), 4.65 (4H, s)	95:5
		5	4.48 (2H, s), 4.65 (4H, s)	87:13
		10	4.48 (2H, s), 4.65 (4H, s)	69:31
d [†]	C ₅ H ₁₁	1	4.48 (2H, s), 4.65 (4H, s)	90:10
		5	4.48 (2H, s), 4.65 (4H, s)	46:54
		10	4.48 (2H, s), 4.65 (4H, s)	---
e [†]	C ₁₄ H ₂₉	1	4.48 (2H, s), 4.65 (4H, s)	100:0
		5	4.48 (2H, s), 4.65 (4H, s)	84:16
		10	4.48 (2H, s), 4.65 (4H, s)	62:38
f [†]	C ₁₅ H ₃₁	1	4.48 (2H, s), 4.65 (4H, s)	98:2
		5	4.48 (2H, s), 4.65 (4H, s)	88:12
		10	4.48 (2H, s), 4.65 (4H, s)	74:26

[¶] Ratio of mono-/3,5-bis-/4,5-bis-bromomethylated products.⁷

[†] The data for the indicated intervals of time were extracted from a plot of ratio vs.

time for experiments conducted over a period of approximately three weeks

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.^{3,8}

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.

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References and Notes

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- (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*-pentadecylmagnesium bromide (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 satd 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 (R_f = 0.5 in hexanes) was separated, and the eluant was adjusted to a 3:1 ratio of hexanes/Et₂O. A fraction (R_f = 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**. ¹H NMR (300 MHz, CDCl₃): δ 0.88 (t, 6 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, *J*_{1,2} = 7.5 Hz, *J*_{1,3} = 2.8 Hz, Ar-H), 7.43 (d of "d", 2 H, *J*_{1,2} = 7.5 Hz, *J*_{1,3} = 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*-toluenesulfonic 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 ¹H 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. ¹H NMR (300 MHz, CDCl₃): δ 0.88 (t, 6 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.
- (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 ^1H NMR spectroscopy. Formation of the mono-bromomethylated **4d** (δ 4.48, 2 H, s, ArCH_2Br) was initially observed. The peak corresponding to the bis-bromomethylated **5d** (δ 4.65, 4 H, s, ArCH_2Br) 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_2O . 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 $\mu\text{Bondpack C}_{18}$ column (7.8 X 300 mm) using a mixture of THF/ H_2O (60/40) at a flow rate of 4 mL/min. Mixtures derived from the other substrates could also be efficiently separated.

Analytical data for **4d**: ^1H 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_2Ar), 4.48 (s, 2 H, CH_2Br), 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%, $\text{M}^+ - \text{Br}$). HRMS calcd for $\text{C}_{17}\text{H}_{27}^{81}\text{Br}$ (M^+): 312.1278. Found: 312.1277.

Analytical data for **5d**: ^1H 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_2Ar), 4.65 (s, 4H, CH_2Br), 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%; $\text{M}^+ - \text{Br}$), 244 (31%; $\text{M}^+ - 2\text{Br}$), 91 (12%; C_7H_7^+). HRMS calcd for $\text{C}_{18}\text{H}_{28}^{81}\text{Br}_2$ (M^+): 406.0521. Found: 406.0525.

- (7) The bromomethylated products generated from **3a** were characterized by ^1H NMR (300 MHz, CDCl_3) and GC/MS (70 eV, EI) of fractions separated by chromatography on silica gel. **4a** (ArCH_2Br at δ 4.44): m/z (rel. intensity; ion) 198, 200 (5%, 5%; M^+), 119 (100%; $\text{M}^+ - \text{Br}$), 91 (31%; C_7H_7^+). **5a** (ArCH_2Br at δ 4.52): 290, 292, 294 (9%, 18%, 9%; M^+), 211, 213 (95%, 92%; $\text{M}^+ - \text{Br}$), 132 (100%; $\text{M}^+ - 2\text{Br}$), 91 (16%; C_7H_7^+). **6a** (ArCH_2Br at δ 4.60): 290, 292, 294 (13%, 27%, 13%; M^+), 211, 213 (100%, 99%; $\text{M}^+ - \text{Br}$), 132 (75%; $\text{M}^+ - 2\text{Br}$), 91 (20%; C_7H_7^+). The broad resonances observed by ^1H NMR spectroscopy within the region of δ 3.0-4.0 could not be identified.
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