A Practical Synthesis of 1,4-Diiodo-2,5-bis(chloromethyl)benzene and 1,4-Diiodo-2,5-bis(bromomethyl)benzene

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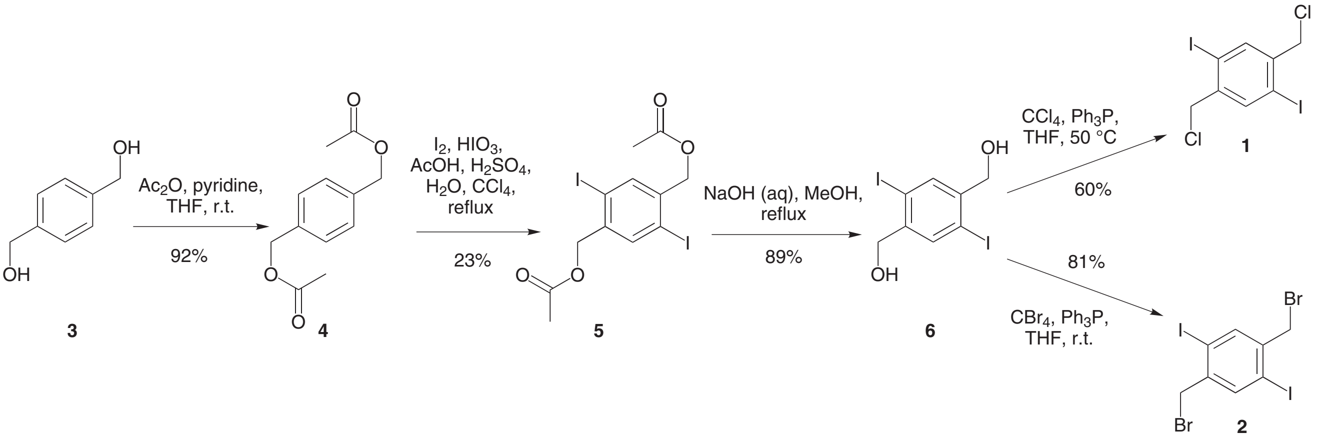
Abstract: Iodination of protected bis(hydroxymethyl)benzene, deprotection of the resulting diiodo aromatics, and subsequent transformation of the hydroxymethyl groups to benzyl halides provides an easy and reliable way to the pure title compounds.

Key words: halogenation, Appel reaction, substituted aromatic alkyl halides, arenes



Scheme 1

Organic compounds containing both aliphatic and aromatic halogens are valuable building blocks for the construction of complex molecular structures. The aliphatic halogens can be synthesized by nucleophilic substitution reactions while the aromatic position is able to undergo transition-metal-catalyzed (C–C) coupling reactions. For example, substitution of the benzyl halides by nitrogen or oxygen nucleophiles allows for the attachment of (solubilizing) side chains,[2,3] sulfur nucleophiles enable the synthesis of cyclophanes[4] and conjugated polymers,[5] and phosphorus nucleophiles allow the formation of phosphonium salts (ylides) for subsequent Wittig (Horner) reactions.[6] Additionally, benzyl halides are suitable initiators for controlled polymerization reactions.[7] The ease with which the aromatic halogen can be substituted decreases generally in the order I > Br >> Cl, allowing aryl iodides to react under very mild conditions and selectively in the presence of aryl bromides (chlorides).[8] Simple bromobenzyl bromides and iodobenzyl bromides as well as the corresponding benzyl chlorides can be synthesized in pure form and are also commercially available. They have been extensively used in different areas of synthetic organic chemistry. Although some compounds carrying more reactive centers are frequently used, as described in the examples given above, not all of them have been described in pure form. In particular, chloromethyl and bromomethyl aromatics carrying iodides at the aromatic core are rarely reported. For example, 1,5-dibromo-2,4-bis(bromomethyl)benzene is described, while the corresponding diiodobenzene is not. For the *para*-substituted compound the situation is similar; 1,4-dibromo-2,5-bis(chloromethyl)benzene is reported while 1,4-diiodo-2,5-bis(chloromethyl)benzene (**1**) is not described.[9] The same holds for the bromobenzyl derivatives; 1,4-dibromo-2,5-bis(bromomethyl)benzene is well described and frequently used,[10] while the 1,4-diiodo derivative **2** can only be obtained as a mixture with about 10% 1-bromo-4-iodo-2,5-bis(bromomethyl)benzene (**7**).[6b,11] This is a result of the synthesis of **2** which is usually performed by radical bromination of 2,5-diiodo-*p*-xylene (**8**) leading to partial halogen exchange under the reported conditions (Scheme 2).

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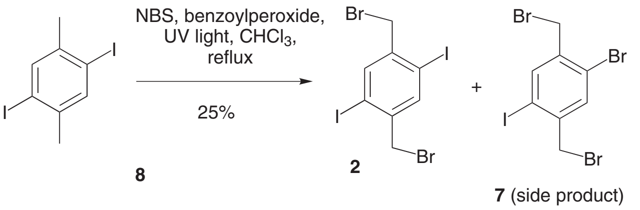

Scheme 2 Reported synthesis of **2**.

However, because the aryl iodo-position is much more reactive under the usual Pd-catalyzed coupling conditions it would be desirable to obtain **2** also in pure form.[2,8]

Here, we describe the easy synthesis and X-ray structure of **1** and **2** that are not contaminated with any by-products. The procedure allows the preparation of both compounds in reasonable quantities which can be used for further transformations and as a building block in materials chemistry.

In order to avoid any partial halogen exchange during the radical side chain halogenation, we decided to use 1,4-bis(hydroxymethyl)benzene (**3**) as the starting material for our synthesis. In this case, the side-chain carbon is already functionalized and should be transformable into the desired benzyl halides without problems. The hydroxy functions of **3** were protected as a diacetate and subsequently iodinated under acidic conditions using iodine/iodic acid.[12] Deprotection of the acetate groups of **5** under basic conditions gave the diol **6**. Initial attempts to obtain **1** by treating **6** with $SOCl_2$/DMF were not successful. However, **1** could be cleanly chlorinated and brominated under Appel conditions (CBr_4/PPh_3) to give **1** and **2**, respectively.[13] All intermediates described in this sequence are either already pure by NMR spectroscopy as crude products or can be easily purified by thoroughly washing with a non-solvating liquid. A chromatographic purification is in most cases not necessary, thus allowing easy scale-up.

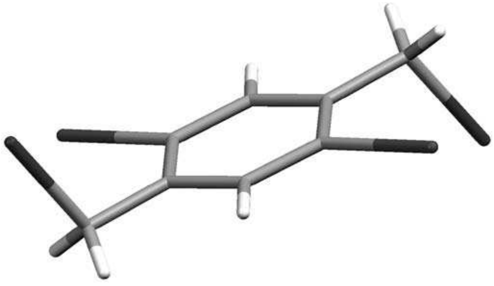

Figure 1 Solid state structure of **2**. Selected bond length: I1–C2: 2.098(3) Å; Br1–C4: 1.976(4) Å.

By recrystallization of **1** or **2** from chloroform, crystals suitable for X-ray analysis (Figure 1) could be obtained.[14,15] Both structures are isomorphous. In the solid state, the aromatics pack into columns with short intermolecular C–C contacts (**1**: C3-C3′: 3.390 Å; **2**: C3-C3′: 3.384 Å). The columns are organized into sheets that are separated by layers of halogens (Figure 2). Between halogens of different layers short Cl–I (Br–I) contacts can be observed which are less than the sum of the van der Waals radii (**1**: Cl1–I1: 3.537 Å; **2**: Br1–I1: 3.627 Å).

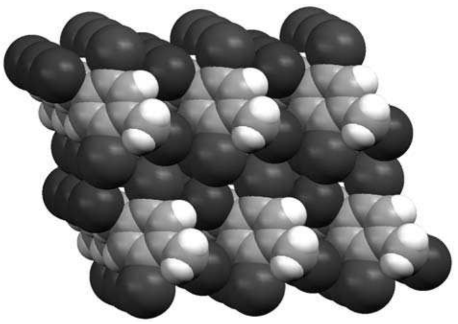

Figure 2 Packing of **2**.

In summary, we have presented a simple experimental procedure for obtaining 1,4-diiodo-2,5-bis(chloromethyl)benzene and 1,4-diiodo-2,5-bis(bromomethyl)benzene in pure form that should allow for an easy scale-up of the synthesis.

Commercially available chemicals were used as received, unless otherwise stated. THF was distilled from sodium and pyridine from CaH_2. Melting points were measured with a Leica DMLB microscope, equipped with a heating stage and a testo 925 digital thermometer. Microanalyses were performed on a Heraeus CHNO Rapid Analyzer. ^1H and ^{13}C NMR data were recorded on a Bruker AC 250 and a Bruker Avance 400 spectrometer, respectively. Chemical shifts are calibrated against the residual solvent resonance. EI mass spectra were accomplished at 70 eV using a Finnigan MAT 90 spectrometer. TLC was performed with Macherey-Nagel Alugram SIL G/UV 254 precoated aluminum sheets. Merck silica gel 60, 230–400 mesh ASTM was used for column chromatography.

Diffraction data were taken on a Nonius Kappa CCD diffractometer (Mo Kα radiation) at the Max Planck Institut für Polymerforschung. Crystal data have been deposited at the Cambridge Crystallographic Data Centre: **1** (CCDC 293038), **2** (CCDC 293039).

1,4-Bis(hydroxymethyl)benzene Diacetate (4)

Pyridine (25.8 g, 326 mmol) was added slowly to a suspension of 1,4-bis(hydroxymethyl)benzene (**3**, 15.0 g, 109 mmol) in Ac_2O (33.3 g, 326 mmol) and anhyd THF (20 mL). After stirring overnight, H_2O (30 mL) was added, the mixture was stirred for 1 h, and then poured into Et_2O (150 mL). The organic layer was separated, washed with H_2O (50 mL), aq HOAc (10%, 50 mL), H_2O (50 mL), aq NaOH (10%, 50 mL), brine (50 mL), and dried over $MgSO_4$. Evaporation of the solvent gave 22.3 g (92%) of **4** as a white solid; mp 48–49 °C.

^1H NMR (250 MHz, CD_2Cl_2): $\delta = 7.36$ (s, 4 H), 5.08 (s, 4 H), 2.07 (s, 6 H).

^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 171.1, 136.8, 128.8, 66.3, 21.3$.

MS (EI): *m*/*z* (%) = 222.1 (0.09) [M^+].

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.04; H, 6.26.

2,5-Diiodo-1,4-bis(hydroxymethyl)benzene Diacetate (5)

A suspension of **4** (20.0 g, 89.9 mmol), HIO_3 (7.0 g, 39.8 mmol), I_2 (18.5 g, 72.9 mmol) in AcOH (50 mL), H_2SO_4 (5 mL), H_2O (5 mL), and CCl_4 (7 mL) was refluxed for 15 h. After cooling to r.t. the mixture was slowly poured into a sat. solution of NaS_2O_3 (20 mL) and H_2O (80 mL). The yellow liquid was decanted and the residue suspended in MeOH (100 mL). The precipitate was isolated by filtration and washed with H_2O and MeOH. The precipitate was dried under vacuum to give 9.7 g (23%) of **5** as a pale brown solid, which was used in the next step without further purification. An analytical sample was obtained by recrystallization from $CHCl_3$ as a white solid; mp 202 °C.

^{1}H NMR (250 MHz, $C_2D_2Cl_4$): δ = 7.80 (s, 2 H), 5.04 (s, 4 H), 2.17 (s, 6 H).

^{13}C NMR (100 MHz, CD_2Cl_2): δ = 170.7, 140.7, 139.8, 97.9, 69.24, 21.2.

MS (EI): *m*/*z* (%) = 473.9 (11) [M$^+$].

Anal. Calcd for $C_{12}H_{12}I_2O_4$: C, 30.40; H, 2.55. Found: C, 30.43; H, 3.26.

2,5-Diiodo-1,4-bis(hydroxymethyl)benzene (6)

Diacteate **5** (9.0 g, 18.9 mmol) was suspended in MeOH (100 mL) and an aq solution of NaOH (10%, 15 mL) was added. The mixture was heated to reflux and stirred overnight. After cooling, the precipitate was collected by filtration and washed with MeOH. The precipitate was dried under vacuum to give 6.6 g (89%) of **6** as a white solid, that was used in the next step without further purification. An analytical sample was obtained by recrystallization from acetone; mp 211–212 °C.

^{1}H NMR (250 MHz, THF-d_8): δ = 7.91 (s, 2 H), 4.64 (t, *J* = 5.3 Hz, 2 H), 4.45 (d, *J* = 5.3 Hz, 4 H).

^{13}C NMR (100 MHz, THF-d_8): δ = 145.6, 138.2, 96.6, 68.4.

MS (EI): *m*/*z* (%) = 398.9 (23%) [M$^+$].

Anal. Calcd for $C_8H_8I_2O_2$: C, 24.64; H, 2.07. Found: C, 24.64; H, 2.71.

2,5-Diiodo-1,4-bis(chloromethyl)benzene (1)

Under an argon atmosphere, CCl_4 (492 mg, 3.20 mmol) and Ph_3P (839 mg, 3.20 mmol) were added to a suspension of **6** (500 mg, 1.28 mmol) in THF (2 mL). The mixture was heated to 50 °C and stirred overnight. After adding MeOH (5 mL), the white precipitate was collected by filtration. Filtration of the crude product through a short silica gel filled column (PE–CH_2Cl_2, 2:1) gave 330 mg (60%) of **1** as a white solid; mp 171 °C; R_f 0.8.

^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.95 (s, 2 H), 4.61 (s, 4 H).

^{13}C NMR (100 MHz, THF-d_8): δ = 143.5, 141.9, 100.1, 50.1.

MS (EI): *m*/*z* (%) = 425.8 (100) [M$^+$].

Anal. Calcd for $C_8H_6Cl_2I_2$: C, 22.51; H, 1.42. Found: C, 22.73; H, 1.71.

2,5-Diiodo-1,4-bis(bromomethyl)benzene (2)

Under an argon atmosphere, CBr_4 (2.12 g, 6.40 mmol) and PPh_3 (1.68 g, 6.39 mmol) were added to a solution of **6** (1.0 g, 2.56 mmol) in THF (20 mL). After stirring overnight, MeOH (10 mL) was added and the white precipitate was collected by filtration. The precipitate was dried under vacuum to give 1.07 g (81%) of **2** as a white solid. An analytical sample was obtained by recrystallization from $CHCl_3$; mp 221 °C.

^{1}H NMR (250 MHz, $C_2D_2Cl_4$): δ = 7.91 (s, 2 H), 4.50 (s, 4 H).

^{13}C NMR (100 MHz, $C_2D_2Cl_4$): δ = 141.9, 140.8, 99.7, 36.8.

MS (EI): *m*/*z* (%) = 515.5 (29) [M$^+$].

Anal. Calcd for $C_8H_6Br_2I_2$: C, 18.63; H, 1.17. Found: C, 18.53; H, 1.80.

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(14) Selected crystal data: **1** (T = 120 K): triclinic, P–1, a = 4.3575 (4), b = 7.2917 (4), c = 8.9994 (5) Å, α = 70.8917 (13), β = 83.3779 (12), γ = 84.9725 (12)°, V = 268.01 (3) Å^3, Z = 2, D_x = 2.645 gcm^{-3}, 5890 independent reflections, 1567 reflections observed, R = 0.0357, R_w = 0.0406. **2** (T = 120 K): triclinic, P–1, a = 4.3865 (4), b = 7.4454 (4), c = 9.0972 (5) Å, α = 71.7302 (13), β = 83.6831 (12), γ = 84.8666 (12)°, V = 279.94 (3) Å^3, Z = 1, D_x = 3.059 gcm^{-3}, 5457 independent reflections, 1454 reflections observed, R = 0.0313, R_w = 0.0345.

(15) Selected bond length for **1**: I1–C2: 2.096 (3) Å; Cl1–C4: 1.804 (4) Å.