The Synthesis of 5-Substituted 2,3-Dihydrobenzofurans

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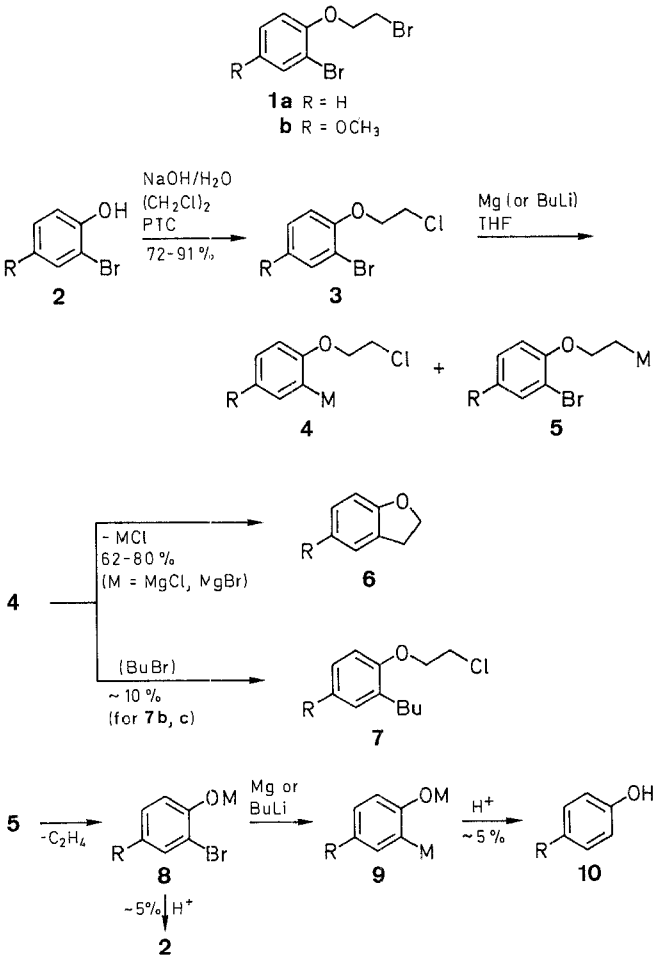
The preparation of 2,3-dihydrobenzofurans **6** from 2-(2-bromophenoxy)ethyl chlorides **3** by reaction with magnesium in a development of the Parham cyclialkylation reaction is described. A high yielding procedure using phase-transfer catalysis has also been developed for the preparation of the intermediate chloroethyl ethers **3** from bromophenols **2**. The 5-hydroxy derivative **15** may be obtained from 2,3-dihydrobenzofuran **(6a)** by reaction with electrophilic reagents followed by oxidation.

2,3-Dihydrobenzofurans have generally been prepared by reduction of benzofurans[1] or benzofuran-3-ones.[2–6] Low yields of 2,3-dihydrobenzofurans may be obtained directly from bromoethyl and hydroxyethyl ethers of phenols by acid-catalysed cyclization at high temperatures,[7,8] and sodium in a Wurtz–Fittig reaction has also been used to cyclise bromoethyl ethers of 2-bromophenols to dihydrobenzofurans.[9]

Our interest in a method for the large scale preparation of 5-substituted 2,3-dihydrobenzofurans led us to investigate the Parham cyclialkylation reaction as a route to these compounds. The Parham reaction is well documented[10] and has been extended to the synthesis of oxygen heterocycles including 2,3-dihydrobenzofurans[11] from 2-(2-bromophenoxy)ethyl bromides, e.g. **1a** and **1b** by treatment with *n*-butyllithium at −100 °C.

The ease of halogen-metal exchange has been found to be ArBr > $ArOCH_2CH_2Br$ > $ArOCH_2CH_2Cl$, and it is essential that conditions are used, which favour formation of the organometal derivatives **4** leading to cyclization and **6**, rather than the alkyl-metal derivatives **5**, which result in dealkylation and generation of the phenoxides **8**. In order to minimize this side reaction, we reasoned that utilization of the chloroethyl ethers would allow selective arylbromide-lithium exchange to occur at temperatures higher than −100 °C and render the reaction more suitable for large scale plant. Bromoethyl ethers **1a** and **1b** were obtained from phenols **2** in only moderate yields,[11] due to formation of diphenoxyethanes. However, the chloroethyl ethers **3a–e** have been prepared in high yield (72–91 %) by alkylation of the bromophenols **2** in a mixture of aqueous sodium hydroxide solution and 1,2-dichloroethane with phase-transfer catalysis[12] (Table 1).



2–10	R	2–10	R
a	H	**d**	Cl
b	OCH_3	**e**	Ph
c	OCH_2Ph		

Selective aryl bromide–lithium exchange was achieved by treatment of the chloroethyl ethers **3b** and **3c** in tetrahydrofuran with *n*-butyllithium at 20 °C, to give the crude dihydrobenzofurans **6b** and **6c** in 90% yields. Unfortunately the products were contaminated with the butylated compounds **7b** and **7c**, which were difficult to remove from the dihydrobenzofurans. Due to the lower reactivity of the chloroethyl group, some intermolecular coupling of the aryllithium with the by-product bromobutane had occurred, and even at −70 °C the butyl derivative **7c** was still generated (~10%).

In order to avoid the formation of the by-products, the cyclization of the Grignard reagents of 2-(2-bromophenoxy)ethyl chlorides **3** was investigated. Reaction of the chloroethyl ethers **3a–e** with magnesium and dibromoethane (10 mol %) in tetrahydrofuran at 30 °C gave a mixture of the 2,3-dihydrobenzofurans **6a–e** with small amounts (~5%) of the phenols **2** and **10**. The latter are easily removed by extraction with 2 N aqueous sodium hydroxide solution to give the pure dihydrobenzofurans **6a–e** in 62–80% yield (Table 2). Thus, the magnesium mediated cyclization of 2-(2-bromophenoxy)ethyl chlorides provides a convenient and economic process for the preparation of 2,3-dihydrobenzofurans and offers scope for extension to other ring systems.

The 5-hydroxy **15** and other derivatives were prepared from 2,3-dihydrobenzofuran **6a** by taking advantage of the selective attack at the 5-position of the ring system by electrophilic

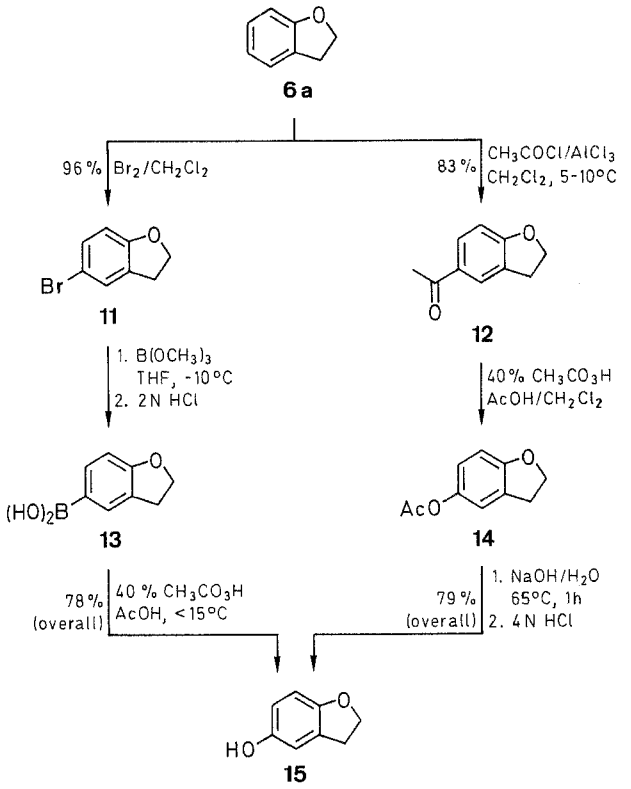


Table 1. Chloroethyl Ethers **3** Prepared

Product	Yield (%)	mp (°C)[a] (solvent) or bp (°C)/mbar[b]	Molecular Formula[c]	^{1}H-NMR (acetone-d_6/TMS)[d] δ, J(Hz)	MS (70 eV)[e] m/z (%)[f]
3a	90	66/0.3	C_8H_8BrClO (235.4)	3.95 (t, 2H, J = 6, CH_2Cl); 4.42 (t, 2H, J = 6, CH_2O); 6.87–7.52 (m, 4H_{arom})	234 (M^+, 36); 172 (100)
3b	91	69–71 (EtOAc/*n*-hexane)	$C_9H_{10}BrClO_2$ (265.5)	3.58 (s, 3H, OCH_3); 3.93 (t, 2H, J = 6, CH_2Cl); 4.30 (t, 2H, J = 6, CH_2O); 6.87–7.19 (m, 3H_{arom})	264 (M^+, 77); 266 (100)
3c	72	66–68 (CH_3OH)	$C_{15}H_{14}BrClO_2$ (341.6)	3.80 (t, 2H, J = 5.5, CH_2Cl); 4.51 (t, 2H, J = 5.5, CH_2O); 5.12 (s, 2H, CH_2Ph); 6.8–7.5 (m, 8H_{arom})	340 (M^+, 15); 91 (100)
3d	87	95/0.07	$C_8H_7BrCl_2O$ (269.9)	3.89 (t, 2H, J = 5.5, CH_2Cl); 4.41 (t, 2H, J = 5.5, CH_2O); 7.11–7.5 (m, 3H_{arom})	268 (M^+, 54); 63 (100)
3e	87	68–69 (*n*-hexane)	$C_{14}H_{12}BrClO$ (311.6)	3.95 (t, 2H, J = 6.5, CH_2Cl); 4.36 (t, 2H, J = 6.5, CH_2O); 7.1–7.9 (m, 8H_{arom})	310 (M^+, 59); 139 (100)

[a] Uncorrected, measured with a Büchi apparatus.
[b] Kugelrohr distillation, bath temperature is given.
[c] Satisfactory microanalyses obtained: C ±0.24, H ±0.07.
[d] Recorded on a Bruker FT 250 MHz spectrometer.
[e] Recorded on a Finnegan MAT TSQ70 spectrometer.
[f] M^+ for ^{35}Cl, ^{79}Br ions quoted.

Table 2. Dihydrobenzofurans **6** Prepared

Product	Yield (%)	mp (°C)[a] (solvent) or bp (°C)/mbar[b]	Molecular Formula[c] or Lit. bp (°C)/mbar	^{1}H-NMR (acetone-d_6/TMS)[d] δ, J(Hz)	MS (70 eV)[e] m/z (%)
6a	76	50/0.4	67–70/11[11]	3.15 (t, 2H, J = 9, CH_2); 4.49 (t, 2H, J = 9, CH_2O); 6.87–7.52 (m, 4H_{arom})	120 (M^+, 70); 91 (100)
6b	74	58/0.013	90–91/3.3[11]	3.61 (s, 3H, OCH_3); 3.15 (t, 2H, J = 9, CH_2); 4.47 (t, 2H, J = 9, CH_2O); 6.6–6.82 (m, 3H_{arom})	150 (M^+, 84); 135 (100)
6c	75	68–60 (CH_3OH)	$C_{15}H_{14}O_2$ (226.2)	3.14 (t, 2H, J = 9, CH_2); 4.49 (t, 2H, J = 9, CH_2O); 5.01 (s, 2H, CH_2Ph); 6.55–7.52 (m, 8H_{arom})	226 (M^+, 59); 91 (100)
6d	62	39–40 (*n*-hexane)	51–53/0.07[11]	3.11 (t, 2H, J = 9, CH_2); 4.53 (t, 2H, J = 9, CH_2O); 6.67–7.19 (m, 3H_{arom})	154 (M^+, 100)[f]
6e	80	85–86 (*n*-hexane)	$C_{14}H_{12}O$ (196.2)	3.01 (t, 2H, J = 6.5, CH_2); 4.38 (t, 2H, J = 6.5, CH_2O); 6.5–7.5 (m, 8H_{arom})	196 (M^+, 100)

[a] Uncorrected, measured with a Büchi apparatus.
[b] Kugelrohr distillation, bath temperature is given.
[c] Satisfactory microanalyses obtained: C ±0.31, H ±0.1.
[d] Recorded on a Bruker FT 250 MHz spectrometer.
[e] Recorded on a Finnegan MAT TSQ70 spectrometer.
[f] M^+ for ^{35}Cl ion quoted.

reagents.[13-17] Bromination[13] gave the 5-bromo compound **11** in 96% yield, which was converted[18] via the boronic acid **13** into the phenol **15** in 78% yield (Method A). Friedel–Crafts acylation[14-17] of the dihydro compound **6a** gave the ketone **12** in 83% yield. Baeyer–Villiger oxidation of the ketone afforded the ester **14**, which was hydrolysed to give the phenol **15** in 79% yield (Method B).

2-Bromo-4-benzyloxyphenol was prepared by the method of Sammes,[19] and 2-bromo-4-phenylphenol was prepared by the method of Gutsche.[20]

2-(2-Bromophenoxy)ethyl Chlorides 3; General Procedure:
A mixture of the bromophenol **2** (0.4 mol), NaOH (1.2 mol), water (500 mL), benzyltributylammonium chloride (10 mol %), 1,2-dichloroethane (500 mL) and $NaHSO_3$ (5 mol %) is vigorously stirred at reflux for 4–12 h. The mixture is cooled, acidified with 2N HCl, and the phases are separated. The organic layer is washed with water (2 × 100 mL), dried (Na_2SO_4), and evaporated to give the product **3**. The crude product is purified by recrystallization or vacuum distillation (Table 1).

2,3-Dihydrobenzofurans 6; General Procedure:
A portion (90 mL) of a solution of the chloroethyl ether **3** (2 mol) in THF (2 L) containing 1,2-dibromoethane (0.2 mol) is added to a mixture of Mg (3 mol) and THF (500 mL). The mixture is heated to 60 °C to effect initiation, then cooled to 30 °C in an ice-water bath. The remaining chloroethyl ether solution is added dropwise over 1.5 h maintaining the temperature at 30 °C. The mixture is heated at reflux for 2 h, then cooled and acidified with 2N HCl (700 mL). The organic layer is separated, and the aqueous layer is extracted with ether (200 mL). The combined organic layer is washed with 2N NaOH solution (2 × 200 mL), water (200 mL) and dried (Na_2SO_4). The solution is evaporated under reduced pressure to give the product **6**. The crude product is purified by recrystallization or vacuum distillation (Table 2).

5-Bromo-2,3-dihydrobenzofuran (11):
A solution of Br_2 (48 g, 0.3 mol) in CH_2Cl_2 (50 mL) is added, over 45 min, to a stirred solution of 2,3-dihydrobenzofuran (**6a**; 36 g, 0.3 mol) in CH_2Cl_2 (250 mL) at room temperature. After the addition, the mixture is stirred for a further 30 min, then quenched by addition of an aq. $NaHSO_3$ solution (50 mL), and the phases are separated. The organic layer is washed with water (100 mL), dried (Na_2SO_4), and evaporated to a pink solid; yield: 57 g (96%); mp 51–52 °C (Lit. bp 135 °C/27 mbar;[8] mp 45–48 °C[11]).

5-Acetyl-2,3-dihydrobenzofuran (12):
A slurry of $AlCl_3$ (5.0 kg, 37.5 mol) in CH_2Cl_2 (39 L) is cooled to 5 °C and acetyl chloride (3.0 kg, 38 mol) is added maintaining the temperature between 5 and 10 °C. 2,3-Dihydrobenzofuran (**6a**; 3.88 kg, 32.3 mol) is added keeping the temperature < 10 °C. The mixture is stirred for 2 h at < 10 °C, and then quenched by the careful addition of 3N HCl (20 L). The layers are separated, and the aqueous phase re-extracted with CH_2Cl_2 (12 L). The combined organic phase is washed with 2.5 N HCl (20 L), water (20 L), dried (Na_2SO_4); then treated with charcoal, and filtered. The green solution is evaporated, and the residue is crystallized from hexane to give the product **12**; yield: 4.17 kg (83%); mp 56–59 °C (Lit.[15] mp 62 °C).

5-Hydroxy-2,3-dihydrobenzofuran (15):
Method A; *via the Boronic acid* **13**: To a stirred mixture of Mg (21 g, 0.9 mol) and THF (200 mL) is added 50 mL of a solution of 5-bromo-2,3-dihydrobenzofuran (**11**; 114 g, 0.6 mol) in THF (400 mL) containing 1,2-dibromoethane (11 g, 60 mmol). The mixture is heated to 60 °C to effect initiation, then cooled to 30 °C in an ice-water bath. The remaining bromide solution is added over 45 min at 30 °C. The Grignard reagent solution is transferred (via cannula and addition funnel) to a stirred solution of trimethyl borate (68 mL, 0.6 mol) in THF (200 mL) at −10 °C over a 1 h period. The resulting white slurry is stirred at 0 °C for 20 min, then hydrolyzed by addition of 2N HCl (360 mL). The mixture is diluted with *tert*-butyl methyl ether (400 mL), and the phases are separated. The organic layer is washed with water (2 × 100 mL) and transferred to a nitrogen purged, 2 litre flask.

Peracetic acid (97 mL, 40% *w/w* in AcOH) is added dropwise over 30 min to the above solution of the boronic acid **13** maintaining a temperature < 15 °C with ice bath cooling. The mixture is stirred at room temperature for 3 h, quenched by addition of 10% aq. $NaHSO_3$ solution (300 mL), stirred for 20 min, and the phases are separated. The organic layer is dried (Na_2SO_4), evaporated, and the residue is crystallized from toluene/*n*-hexane to give the phenol **15**; yield: 61 g (78%); mp 109–111 °C (Lit.[5] mp 111–112 °C).

Method B; *via the Acetate* **14**: 5-Acetyl-2,3-dihydrobenzofuran (**12**; 162 g, 1 mol) in CH_2Cl_2 (1 L) at 10 °C is treated with peracetic acid (40%, 184 mL, 1 mol) added over 30 min. The reaction temperature increases to 30 °C over 2 h, and the mixture is stirred at 25 °C for 48 h. The reaction is quenched by addition of aq. $NaHSO_3$ solution (10%, 300 mL) and then concentrated to 300 mL. The solution is extracted with aq. $NaHCO_3$ solution (5%, 3 × 200 mL) to remove phenolic impurities and then slowly added to a solution of NaOH (85 g, 2.1 mol) in water (400 mL) at 65 °C over 1 h. The CH_2Cl_2 is distilled from the mixture during the addition. The mixture is stirred for 1 h, cooled, and extracted with cyclohexane (200 mL). The aqueous solution is acidified with 4N HCl, the precipitate formed is filtered, washed with water (100 mL), and dried *in vacuo* to give the product; yield: 85 g (79%); mp 108–110 °C.

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