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Synthesis of substituted 2,3-dihydrobenzofuran in a process involving a facile acyl migration

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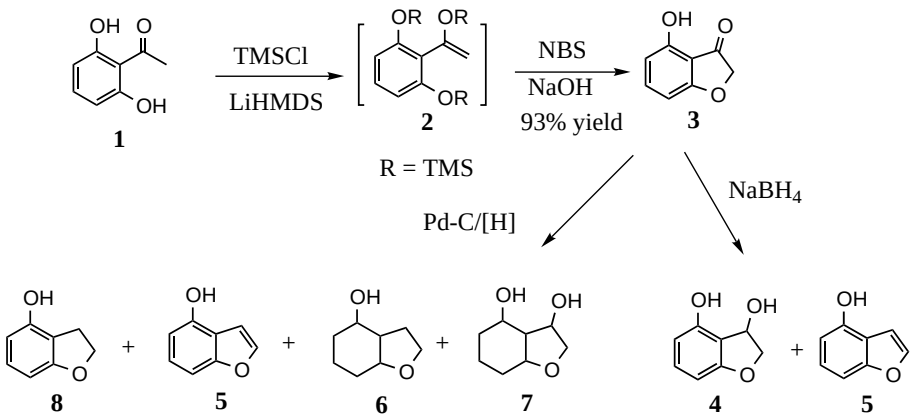
Abstract—Reduction of 2,6-diacetoxy-2′-bromoacetophenone (**10**) with $NaBH_4$ led to 3,4-diacetoxydihydrobenzofuran (**12**) in a process involving acyl migration followed by cyclization. Subsequent hydrogenolysis gave 4-acetoxydihydrobenzofuran which, upon saponification, afforded 4-hydroxydihydrobenzofuran (**8**) in good yield. This approach is shown to be a general method for preparation of substituted dihydrobenzofurans. © 2002 Elsevier Science Ltd. All rights reserved.

We demonstrated previously that 4-hydroxydihydrobenzofuran (**8**) could be attained by Parham cycloalkylation[1] of the appropriate brominated resorcinol derivative. While simple and practical for preparing small amounts of material, this synthesis was not amenable for large scale preparation due to the need for excess *n*-butyl lithium under cryogenic conditions. As a potentially more efficient synthesis of phenol **8**, we chose to investigate deoxygenation of 4-hydroxybenzofuran-3-one (**3**).[2]

Synthesis of 4-hydroxybenzofuran-3-one (**3**) from 2′,6′-dihydroxyacetophenone (**1**) was accomplished in two steps (Scheme 1). Persilylation, followed by treatment with *N*-bromosuccinimide and then NaOH, afforded the desired compound in 93% overall yield. Unfortunately, when this material was subjected to hydrogenolysis in the presence of Pd–C, over-reduction to **6** and **7** was a major problem with little or no formation of the desired **8** being observed. Alternatively, reduction of **3** with $NaBH_4$ gave a mixture of **4** and **5**, with the latter as the major product.

It was felt that diacetate **12** might be an alternative substrate for hydrogenolysis. To explore this possibility, diacetylation of 2′,6′-dihydroxyacetophenone (**1**) (2.2



Scheme 1.

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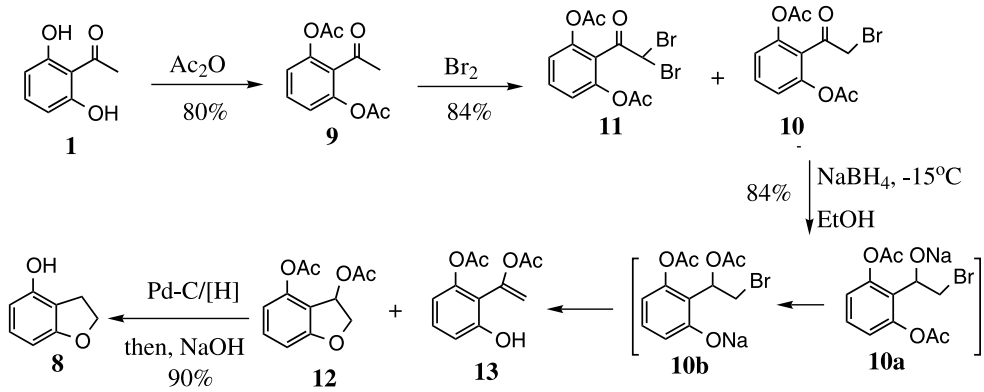
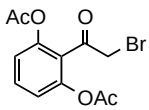
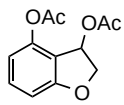
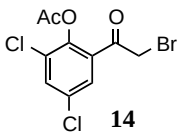
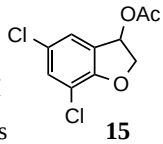
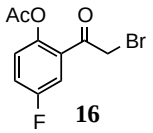
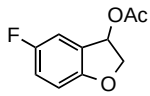
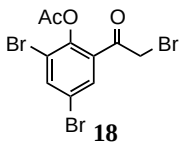
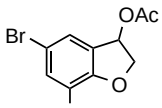
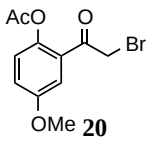
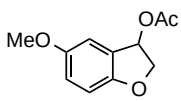
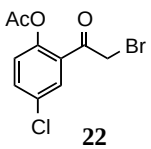
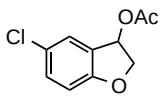
equiv. Ac_2O, 2.3 equiv. Et_3N, ambient temperature) gave an 80% yield of diacetate **9**, which was treated with bromine (1.0 equiv. Br_2, CH_2Cl_2, 0°C) to give an ~85:15 mixture of mono- and dibromide **10** and **11** (Scheme 2). The reaction product was crystallized from isopropanol to afford a 90% recovery of a 93:7 mixture,



Scheme 2.

Table 1. Conversion of bromoacetophenones to acetates by $NaBH_4$

Entry	Bromoacetophenone[a]	Conditions	Product	Yield[b]
1	 **10**	$NaBH_4$ anhydrous EtOH -15°C, 45 minutes	 **12**	84%[c]
2	 **14**	$NaBH_4$ anhydrous EtOH -15°C, 40 minutes	 **15**	98%
3	 **16**	$NaBH_4$ anhydrous EtOH 0°C, 30 minutes	 **17**	81%
4	 **18**	$NaBH_4$ anhydrous EtOH 0°C, 30 minutes	 **19**	90%
5	 **20**	NaBH, anhydrous EtOH 0°C, 30 minutes	 **21**	87%
6	 **22**	$NaBH_4$ anhydrous EtOH 0°C, 30 minutes	 **23**	93%

a) Preparation by bromination of corresponding acetophenones followed by column chromatographic purification (bromination is not selective; better conditions are being developed); b) Purified by column chromatography; c) Isolated by crystallization from EtOAc/heptane.

which was adequate for the subsequent transformation. Treatment of this mixture with $NaBH_4$ in anhydrous EtOH at −15°C afforded a 94:6 mixture of diacetate **12** and the enol acetate **13**. Crystallization from EtOAc/hexane gave an 85% yield of the desired diacetate **12**. We postulate that acyl migration[3] of the phenolacetate to the sodium alkoxide moiety of **10a** provides the phenoxide **10b**. Ring closure by nucleophilic displacement then leads to the observed diacetate **12**. Hydrogenolysis (10 wt% load of 5% Pd–C, MeOH, ~3 psi, ambient temperature) and subsequent saponification of the resulting phenolic acetate furnished the desired 4-hydroxy-2,3-dihydrobenzofuran (**8**) in 90% yield.

To demonstrate the scope and limitations of this method, a number of bromoacetophenones were prepared and subjected to the $NaBH_4$ reduction (Table 1).[4] Efficient acyl migration was found to be general, affording 3-acetoxydihydrobenzofurans in high yields. This methodology is applicable for those acetophenones with both electron-donating and electron-withdrawing substituents.

Acknowledgements

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4. Compound **12**, colorless solid, mp 64–65°C; ^{1}H NMR ($CDCl_3$) δ 7.32 (t, 1H, $J=6.2$ Hz), 6.85 (d, 1H, $J=6.2$ Hz), 6.65 (d, 1H, $J=6.2$ Hz), 6.40 (dd, 1H, $J=6.4$ and 2.4 Hz), 4.66 (dd, 1H, $J=11.2$ and 6.4 Hz), 4.50 (dd, 1H, $J=11.2$ and 2.4 Hz), 2.32 (s, 3H), 2.08 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.2, 168.1, 162.5, 147.9, 132.2, 117.1, 114.3, 108.3, 76.6, 71.5, 20.8 ppm.
Compound **15**: Slightly yellow solid, mp 75.5–77°C; ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 1H, $J=2.2$ Hz), 7.30 (d, 1H, $J=2.2$ Hz), 6.22 (dd, 1H, $J=6.9$, 2.5 Hz), 4.72 (dd, 1H, $J=6.9$ and 12.1 Hz), 4.63 (dd, 1H, $J=2.7$ and 12.1 Hz), 2.23 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.0, 155.4, 130.8, 127.2, 131.7, 125.9, 125.8, 116.4, 77.2, 74.2, 21.6 ppm.
Compound **17**: Oil; ^{1}H NMR ($CDCl_3$) δ 7.15 (dd, 1H, $J=7.9$, 2.5 Hz), 6.98 (ddd, 1H, $J=8.8$, 2.4, and 2.5 Hz), 6.81 (dd, 1H, $J=8.8$, 3.9 Hz), 6.20 (dd, 1H, $J=6.8$, 2.4 Hz), 4.64 (dd, 1H, $J=11.2$, 6.8 Hz), 4.53 (dd, 1H, $J=11.2$, 2.4 Hz), 2.07 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.2, 158.1 (d, $J=149.1$ Hz), 155.8, 125.3 (d, $J=8.5$ Hz), 117.8 (d, $J=24.6$ Hz), 113.5 (d, $J=24.6$ Hz), 110.8 (d, $J=8.5$ Hz), 76.8, 74.4, 21.7 ppm.
Compound **19**: off-white solid, mp 87.5–89°C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1H, $J=2.0$ Hz), 7.50 (d, 1H, $J=2.0$ Hz), 4.72 (dd, 1H, $J=11.2$, 6.8 Hz), 4.61 (dd, 1H, $J=11.7$, 2.4 Hz), 2.08 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.0, 157.3, 136.1, 128.7, 127.3, 113.0, 104.2, 77.0, 74.3, 21.6 ppm.
Compound **21**: Oil; ^{1}H NMR ($CDCl_3$) δ 6.98 (d, 1H, $J=2.4$ Hz), 6.86 (dd, 1H, $J=2.4$ and 8.8 Hz), 6.80 (d, 1H, $J=8.8$ Hz), 6.20 (dd, $J=2.4$ and 6.3 Hz), 4.59 (dd, 1H, $J=6.3$ and 11.7 Hz), 4.48 (dd, 1H, $J=2.4$ and 11.7 Hz), 3.76 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.4, 154.8, 154.0, 124.7, 117.7, 111.2, 110.7, 76.5, 75.0, 56.5, 21.8 ppm.
Compound **23**: Oil; ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 1H, $J=2.4$ Hz), 7.23 (dd, 1H, $J=2.4$ and 8.8 Hz), 6.81 (d, 1H, $J=8.8$ Hz), 6.19 (dd, 1H, $J=2.5$ and 6.4 Hz), 4.63 (dd, 1H, $J=6.4$ and 11.7 Hz), 4.52 (dd, 1H, $J=2.5$ and 11.7 Hz), 2.07 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.2, 159.3, 131.1, 126.6, 126.0, 125.6, 111.5, 76.8, 74.0, 21.7 ppm.