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Conversion of substituted benzyl ethers to diarylmethanes. A direct synthesis of diarylbenzofurans

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ABSTRACT

The Lewis acid catalyzed rearrangement of substituted benzyl ethers affords diarylmethanes in good yields. One of the products was converted into a diarylbenzofuran using a benzoylation/P4-*t*Bu cyclization protocol.

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The diarylmethane subunit is contained in a variety of natural products. Representative members are shown in Figure 1 and include procyanidin B2 (**1**),[1] diarylbenzofuran (**2**),[2] and justicidin H (**3**).[3] Because many of these compounds exhibit useful biological activity, a number of synthetic approaches to the diarylmethane subunit have been reported. Organometallic-based approaches[4] and Friedel–Crafts-based approaches[5] are the most commonly reported strategies. In some cases the former approach is limited by the requirement for regioselective metallation. The latter approach has the disadvantage that after the acylation, a one- to two-step conversion of the benzophenone to the diarylmethane still needs to be accomplished. We describe herein the Lewis acid mediated rearrangement of a substituted benzyl aryl ether that is strategically different from the commonly reported strategies and is flexible with regard to substituent patterns.

The rearrangement shown below in Scheme 1 was originally discovered when purification of **4** by silica gel chromatography produced phenol **5** in 72% yield. This selective reaction was mediated by the acidic surface of the silica gel and occurred at ambient temperature. To the best of our knowledge, reports of rearrangements of functionalized aryl benzyl ethers are limited.[6] A recent report by Luzzio and Chen described a clever camphorsulfonic acid mediated rearrangement of 2-nitroresorcinol ethers.[7]

Compounds such as **5** were of interest because we had previously demonstrated that even weakly acidic subunits such as benzyl ethers could be deprotonated by the strong base P4-*t*Bu.[8] If the methylene group of the diarylmethane unit could be efficiently deprotonated, a flexible route to these phenols could lead to a direct synthesis of substituted diarylbenzofurans by an acylation/rearrangement/cyclization protocol.

We evaluated the ethers shown in Scheme 2 and found that ethers bearing only one electron-donating substituent required a Lewis acid such as boron trifluoride etherate for rearrangement. Interestingly, a benzyl ether (X = H) did not react under our conditions. This selectivity may be useful in complex systems.

Benzyl ethers of sesamol were synthesized and subjected to the rearrangement conditions as shown in Scheme 3. Although two isomeric phenols could have been produced, the rearrangement was regioselective in generating phenols **8** and **9**. These regioselectivities parallel the results observed in Friedel–Crafts acylation of sesamol.[9]

Substituted benzyl ethers of 2,6-dimethoxyphenol were prepared and were reacted with boron trifluoride etherate as shown in Scheme 4. In these cases the rearrangement produced the 4-benzyl phenols in good yields.

In an approach to the synthesis of benzofuran, the ether was regioselectively rearranged in 70% yield as shown in Scheme 5. Benzoylation of the resulting phenol **13** followed by reaction with P4-*t*Bu in benzene at 80 °C afforded benzofuran **14** in 47% yield after chromatography.

The Lewis acid mediated rearrangement[10] of benzyl ethers into diarylmethanes provides a facile entry into this subunit. One of the rearrangement products was converted into a 2,3-diaryl-benzofuran by benzoylation followed by cyclization with P4-*t*Bu.

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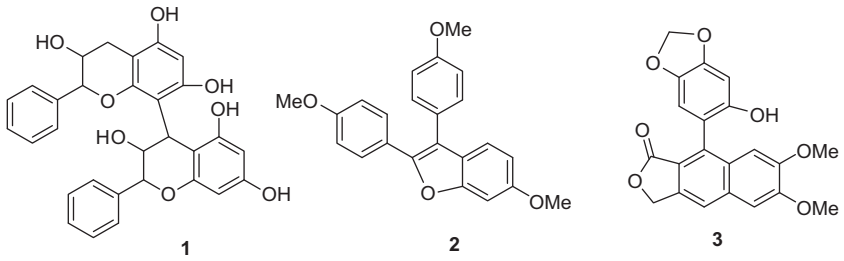
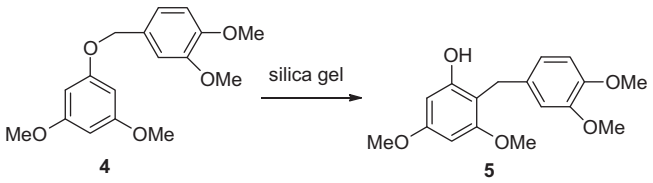
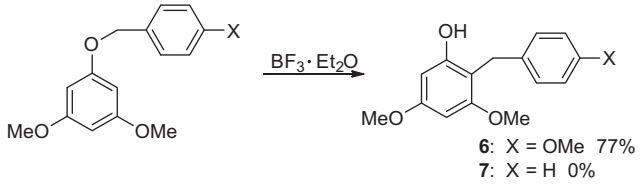


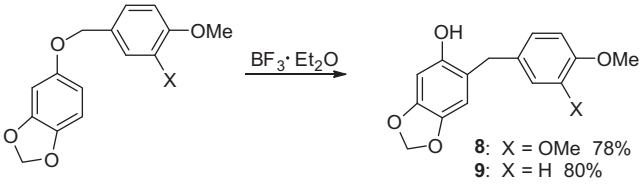
Figure 1. Compounds containing the diarylmethane subunit.



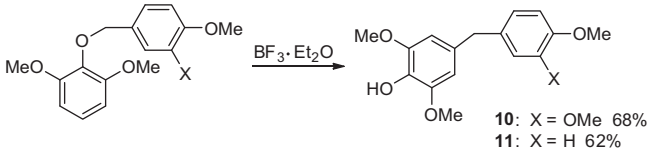
Scheme 1. Rearrangement during column chromatography.



Scheme 2. Rearrangement of phloroglucinol ethers



Scheme 3. Rearrangement of sesamol ethers.



Scheme 4. Rearrangement of 2,6-disubstituted phenol ethers.

Acknowledgment

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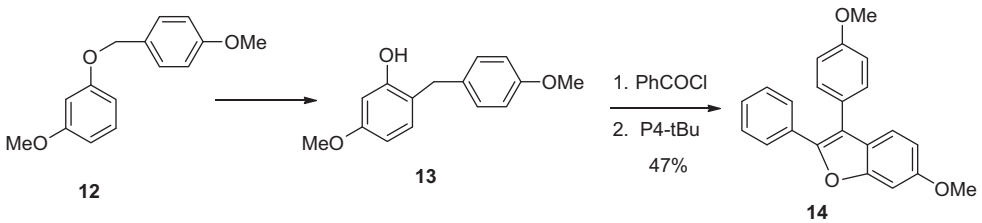
10. *General Procedure for the rearrangement*
To a solution of aryl ether (1.43 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added $BF_3.Et_2O$ (0.13 mL, 1.0 equiv) dropwise at 0 °C under argon. Reaction mixture was allowed to stir at rt overnight. After the completion of the reaction, water was added. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified on silica gel by column chromatography using EtOAc–hexanes as the eluent.
The reactions were typically run on a 1.0–1.5 mmol scale.
(***5***) *2-(3,4-dimethoxybenzyl)-3,5-dimethoxyphenol*
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 1H), 6.75–6.76 (m, 2H), 6.12 (d, J = 2.0 Hz, 1H), 6.03 (d, J = 2.0 Hz, 1H), 5.50 (s, 1H of OH), 3.91 (s, 2H), 3.81 (s, 6H), 3.79 (s, 3H), 3.71 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 159.3, 155.6, 149.0, 147.3, 133.9, 120.2, 112.1, 111.4, 108.4, 94.0, 91.6, 56.1, 56.0, 55.5, 28.2.
HRMS (ESI) m/z exact mass calculated for $C_{17}H_{21}O_5$ $[M+H]^+$ 305.1384. Found 305.1388.
(***6***) *3,5-dimethoxy-2-(4-methoxybenzyl)phenol*
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 9 Hz, 2H), 6.78 (d, J = 9 Hz, 2H), 6.13 (d, J = 2.4 Hz, 1H), 6.01 (dd, J = 7.8, 2.4 Hz, 1H), 4.81 (s, 1H of OH), 3.90 (s, 2H), 3.79 (s, 3H), 3.76 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 159.3, 157.9, 155.6, 133.2, 129.4, 114.0,



Scheme 5. Synthesis of a diarylbenzofuran.

108.5, 94.4, 91.5, 60.8, 55.9, 55.5, 27.6.
HRMS (ESI) *m*/*z* exact mass calculated for $C_{16}H_{19}O_4$ $[M+H]^+$ 275.1278. Found 275.1268.

(***8***) *6-(3,4-dimethoxybenzyl)benzo[d][1,3]dioxol-5-ol*
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73–6.80 (m, 3H), 6.58 (s, 1H), 6.41 (s, 1H), 5.87 (s, 2H), 4.79 (s, 1H of OH), 3.84 (s, 3H), 3.83 (s, 2H), 3.82 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 148.5, 147.8, 146.8, 141.6, 132.6, 120.6, 119.2, 112.0, 111.6, 110.1, 101.2, 98.9, 56.1, 56.0, 36.1.
HRMS (ESI) *m*/*z* exact mass calculated for $C_{16}H_{15}O_5$ $[M-H]^-$ 287.0925. Found 287.0923.

(***9***) *6-(4-methoxybenzyl)benzo[d][1,3]dioxol-5-ol*
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.59 (s, 1H), 6.40 (s, 1H), 5.88 (s, 2H), 4.61 (s, 1H of OH), 3.83 (s, 2H), 3.78 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 148.4, 146.8, 141.7, 132.1, 129.7, 119.4, 114.3, 110.2, 101.2, 98.9, 55.5, 35.6.
HRMS (ESI) *m*/*z* exact mass calculated for $C_{15}H_{13}O_4$ $[M-H]^-$ 257.0808. Found 257.0797.

(***10***) *4-(3,4-dimethoxybenzyl)-2,6-dimethoxyphenol*
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74–6.79 (m, 3H), 6.58 (s, 2H), 5.56 (s, 1H of OH), 3.89 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 147.4, 146.5, 145.5, 138.8, 134.1, 127.8, 120.9, 120.2, 112.4, 111.3, 106.5, 60.7, 56.4, 56.1, 56.0, 35.4.
HRMS (ESI) m/z exact mass calculated for $C_{17}H_{19}O_5$ $[M-H]^-$ 303.1227. Found 303.1232.

(***11***) *2,6-dimethoxy-4-(4-methoxybenzyl)phenol*
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, J = 8.4 Hz, 2H), 6.8 (d, J = 8.8 Hz, 2H), 6.58 (s, 2H), 5.53 (s, 1H of OH), 3.88 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 146.5, 145.5, 138.8, 133.7, 129.9, 128.0, 120.3, 113.9, 106.5, 60.7, 56.4, 55.5, 35.0.
HRMS (ESI) *m*/*z* exact mass calculated for $C_{16}H_{17}O_4$ $[M-H]^-$ 273.1132. Found 273.1135.

(***13***) *5-methoxy-2-(4-methoxybenzyl)phenol*
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 2H), 6.46 (dd, J = 8.4,2.4 Hz, 1H), 6.39 (d, J = 2.4 Hz,1H), 4.95 (s, 1H of OH), 3.88 (s, 2H), 3.79 (s, 3H), 3.76 (s,3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 158.3, 154.9, 132.3, 131.5, 129.7, 119.7, 114.3, 106.3, 102.3, 55.6, 55.5, 35.2.
HRMS (ESI) *m*/*z* exact mass calculated for $C_{15}H_{17}O_3$ $[M+H]^+$ 245.1172. Found 245.1174.

Procedure for the preparation of 6-methoxy-3-(4-methoxyphenyl)-2-phenylbenzofuran (**14**)
To a solution of the benzoyl derivative of phenol **13** (0.76 mmol, 1 equiv.) in dry benzene (10 mL) was added 1 M solution of P4-*t*Bu in hexane (0.84 mL, 1.1 equiv). The reaction mixture was refluxed for 3 h. After the completion of the reaction the benzene was evaporated in vacuo. The resulting liquid was purified on silica gel by column chromatography using 5% EtOAc–hexanes as eluent to get a pure compound in 47% yield.

(***14***) *6-methoxy-3-(4-methoxyphenyl)-2-phenylbenzofuran*
^{1}H NMR (300 MHz, CDCl3): δ 7.63 (d, J = 6.6 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.29 -7.37 (m, 4H), 7.09 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.87 (dd, J = 8.7, 2.1 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 158.6, 155.1, 149.6, 131.1, 131.0, 128.6, 128.0, 126.7, 125.3, 124.2, 120.4, 117.3, 114.6, 112.1, 95.9, 56.0, 55.5
HRMS (ESI) *m*/*z* exact mass calculated for $C_{22}H_{19}O_3$ $[M+H]^+$ 331.1334. Found 331.1187.