JOC Note

A General Synthetic Route to 6,6-Substituted-6*H*-dibenzo[*b*,*d*]pyrans from Dibenzofuran

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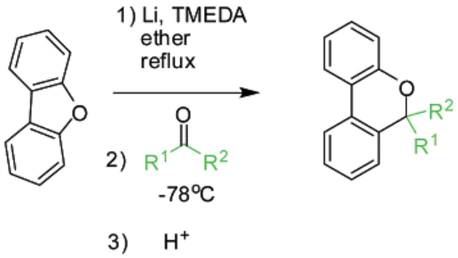


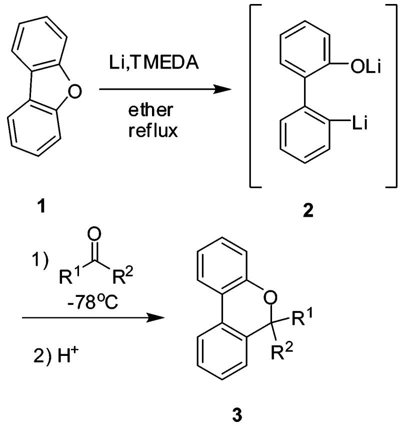
The reaction of dibenzofuran **1**, lithium pieces (2.2 equiv), and TMEDA (2.2 equiv) in dry ether under reflux led to a solution of the corresponding C,O-dilithiated intermediate **2** which, upon treatment with different ketones or aldehydes (0.8 equiv) at −78 °C, afforded, after hydrolysis and dehydration, 6,6-substituted-6*H*-dibenzo[*b*,*d*]pyrans **3** in good yields. The reaction undergoes reductive ring opening and cyclization, and the intermediate diol **4e** was isolated.

Pyran derivatives are a kind of well-known heterocyclic compounds[1] and the important intermediates in the synthesis of many natural products.[2] Benzopyrans occur in a wide range of natural products and pharmaceutical compounds,[3] and what is more, benzopyrans and naphthopyrans are of special interest as photochromic compounds, which have a wide variety of applications such as opthalmic glasses, electronic display systems, optical switches, and temporary or permanent memories.[4]

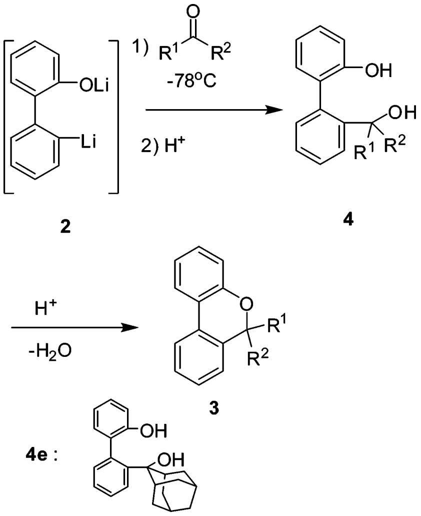
The 6*H*-dibenzo[*b*,*d*]pyran ring system has been of interest pharmacologically.[5−7] The natural product cannabinol, a constituent of cannabis, has been characterized to have this structural unit.[8−10] On the other hand, this system can afford an interesting photochemical reaction via the proposed o,o′-biphenyl quinone intermediate and will be useful as photoswitches.[11−13] Previous reports for the synthesis of 6,6-substituted-6*H*-dibenzo[*b*,*d*]pyrans are few, and their total yields are low.[5,11,14,15] Therefore, development of a synthetically useful methodology for 6,6-substituted-6*H*-dibenzo[*b*,*d*]pyrans has attracted our attention and interest.

Different from classical methods for the generation of functionalized organolithium compounds, including halogen−

SCHEME 1. Synthesis of 6,6-Substituted-6*H*-dibenzo[*b*,*d*]pyrans



SCHEME 2. Proposed Reaction Pathway



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[2] See, for example: (a) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59. (b) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250.

[3] See, for example: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 734. (b) Nicolaou, K. C.; Cao, G.-Q.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 739. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (d) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968.

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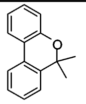
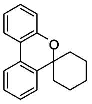
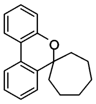
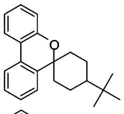
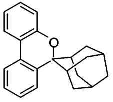
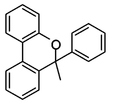
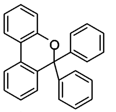
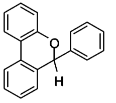
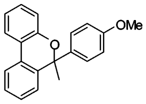
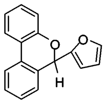
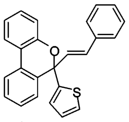
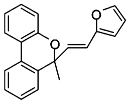
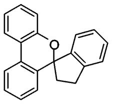
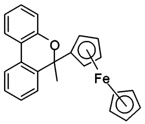
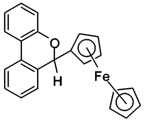
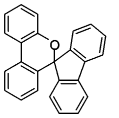
10.1021/jo061415r CCC: $33.50

TABLE 1. Synthesis of 6,6-Substituted-6*H*-dibenzo[*b*,*d*]pyrans

entry	product		yield, %
1		**3a**	73
2		**3b**	83
3		**3c**	82
4		**3d**	80
5		**3e**	90
6		**3f**	81
7		**3g**	86
8		**3h**	75
9		**3i**	76
10		**3j**	65
11		**3k**	63
12		**3l**	72
13		**3m**	55
14		**3n**	57
15		**3o**	68
16		**3p**	68

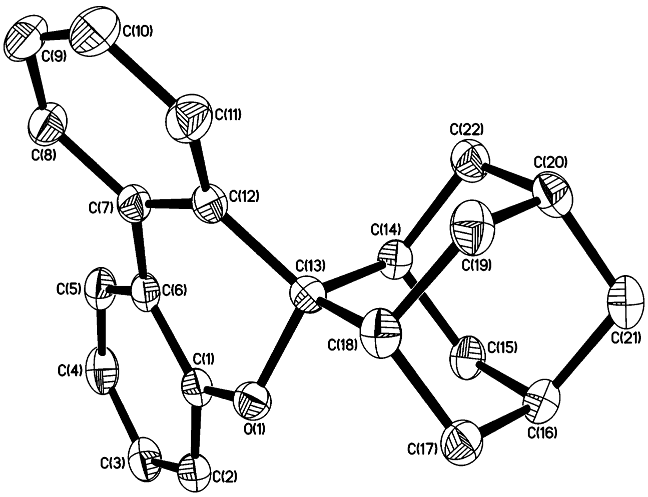


FIGURE 1. ORTEP diagram of **3e**. Thermal ellipsoids are shown at the 30% level.

lithium exchange or metal−lithium transmetalation,[16] here the C,O-dilithium reagent was prepared from dibenzofuran with lithium (Scheme 1).[17,18]

The C,O-dilithiated intermediate **2** was obtained by C−O bond cleavage of dibenzofuran with lithium (2.2 equiv) under reflux in ethyl ether. This methodology has been used successfully in the reductive ring opening of many oxygen-, nitrogen-, or sulfur-containing heterocycles.[19−23] The presence of TMEDA was found to make the reaction of dibenzofuran with lithium more complete.

The C,O-dilithiated intermediate **2** reacted with different ketones or aldehydes (0.8 equiv) at −78 °C and afforded, after hydrolysis and dehydration with concentrated hydrochloric acid, the expected products 6,6-substituted-6*H*-dibenzo[*b*,*d*]pyrans **3** (Scheme 1). Listed in Table 1 are representative examples of 6,6-substituted-6*H*-dibenzo[*b*,*d*]pyrans **3**.

The reaction mechanism that we assumed is shown in Scheme 2. The C,O-dilithiated intermediate **2** reacted with aldehydes or ketones at −78 °C and afforded the diols **4** after hydrolysis. Then, the diols **4** were dehydrated and cyclized upon concentrated hydrochloric acid to generate the products **3**.

To obtain evidence to understand the reaction mechanism, the following experiment was carried out. The dilithiated intermediate **2** reacted with 2-adamantanone (0.8 equiv) at −78 °C. The reaction was quenched with 3 N hydrochloric acid. As expected, the corresponding diol **4e** was obtained in 93% yield. Then **4e** was converted to **3e** upon concentrated hydrochloric acid in 95% yield.

The absorption maxima of **3a**−**3p** are similar ($\lambda_{\max} = 308-312$ nm), but they are much higher than the absorption maxima of **4e** ($\lambda_{\max} = 281$ nm) (Supporting Information). This might

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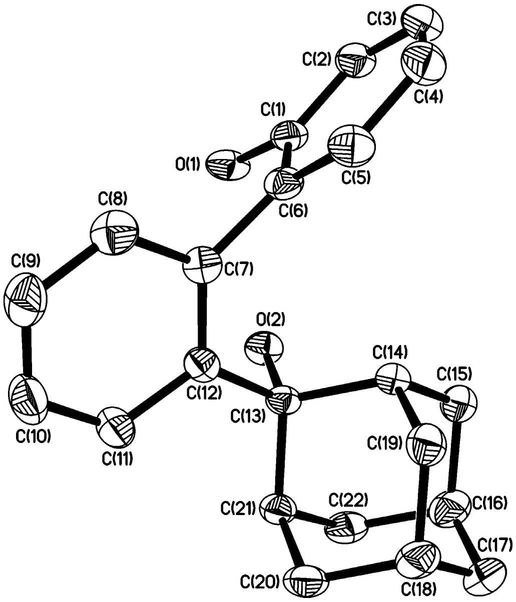

FIGURE 2. ORTEP diagram of **4e**. Thermal ellipsoids are shown at the 30% level.

be caused by the overlap of the π-systems of the two benzene rings. The dihedral angles between the two benzene rings for **3a**−**3p** might be much smaller than that of **4e**. Therefore, the structures of **3e**, **3f**, **3k**, **3m**, **3o**, **3p**, and **4e** were determined by single-crystal X-ray analysis (Figures 1 and 2 and Supporting Information), and they are in accord with their UV absorptions.

Experimental Section

General. All reactions were conducted under nitrogen using standard Schlenk line techniques. Unless otherwise noted, all starting materials were commercially available and were used without further purification.

Representative Procedure for the Synthesis of 6,6-Substituted-6*H*-dibenzo[*b*,*d*]pyrans from Dibenzofuran. A mixture of dibenzofuran (1.680 g, 10 mmol), fresh and clean lithium pieces (0.153 g, 22 mmol), TMEDA (3.3 mL, 22 mmol), and dry diethyl ether (50 mL) was stirred for 24 h under reflux. Then, the reaction mixture was cooled to −78 °C, and the corresponding ketone or aldehyde (8 mmol) was added to the resulting mixture. The mixture was stirred for 2 h, slowly warmed to room temperature, and stirred overnight. The reaction was quenched with 3 N hydrochloric acid and extracted with ether. The organic layer was added to concentrated hydrochloric acid, and the mixture was stirred for 2 h. Then, the organic layer was separated, and the acid layer was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NH_4Cl and dried over Na_2SO_4. The solvent was evaporated in vacuo to give a residue, which was purified by column chromatography or recrystallization.

For detailed experimental procedures and full characterization and copies of ^1H and ^{13}C NMR spectra of all new compounds, see the Supporting Information.

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Supporting Information Available: Experiment details and full characterization and copies of ^1H and ^{13}C NMR spectra of all new compounds, including the crystal data for **3e**, **3f**, **3k**, **3m**, **3o**, **3p**, and **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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