A Facile Synthesis of the Unsymmetrically Methyl-Substituted 2-Hydroxybiphenyls by the Regioselective Cleavage of Dibenzofuran Derivatives with Lithium Metal

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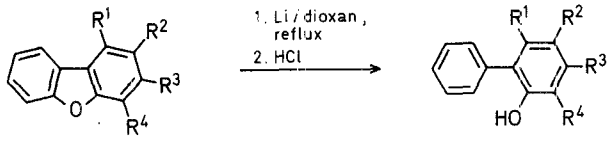
2-Hydroxybiphenyl derivatives are of interest in connection with intramolecular interactions of the π-OH type in the field of structural organic chemistry, so they have been studied actively[1,2,3]. However, they are comparatively difficult to synthesize, especially unsymmetrically substituted derivatives. We report a facile synthesis of the unsymmetrically methyl-substituted 2-hydroxybiphenyls **2** by a regioselective cleavage of the ether linkage of dibenzofuran derivatives **1** with lithium in dioxan.

The cleavage reaction of dibenzofuran itself with lithium had been previously attempted by Gilman and Esmay[4] but further developments of the reaction for the aim of synthetic applications have not been made. We have reinvestigated the reactions of dibenzofuran with the alkali metals lithium, sodium, and potassium in a variety of ethereal solvents in order to obtain the optimum conditions to give the cleavage product. We found that 2-hydroxybiphenyl was obtained in quantitative yield in the reaction of three equivalents of lithium in dioxan (5 ml per g ether) with the aryl ether under reflux for 3 h. On the basis of these reaction conditions, the cleavage reactions of compounds **1a–g** were carried out. The results are summarized in Table 1.



1a-g **2a-g**

The structures of the products were confirmed by microanalysis, M.S., N.M.R., and I.R. data as shown in Table 1 and 2. Compounds **2a–g** were obtained in excellent yields by the regioselective cleavage of the ether linkage of compounds **1a–g** with lithium and no traces of other isomers were detected. Only a few routes for the synthesis of **2** are known[1,5]. For example, compound **2a** was synthesized by Ōki and Iwamura by a circuitous processes starting from 2-amino-3-nitrotoluene[1]. In contrast, we can obtain **2a** directly from **1a**. Furthermore, we can prepare a wide variety of **2** by this reaction using other alkyldibenzofurans which can be easily derived from the combinations of 2-bromocyclohexanone with alkylphenols according to the procedures described by Trippett[6].

0039-7881/80/0832-0634 $ 03.00 © 1980 Georg Thieme Verlag · Stuttgart · New York

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Table 1. Preparation of 2-Hydroxybiphenyls **2**

Compound No.	R^1	R^2	R^3	R^4	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr (Lit. m.p. [°C])	Molecular formula[b]	M.S. *m/e* (M^+)
2a	CH_3	H	H	H	99	54–55° (55–56°)[1]	$C_{13}H_{12}O$ (184.2)	184
2b	H	H	H	CH_3	96	129°/5	$C_{13}H_{12}O$ (184.2)	184
2c	CH_3	H	CH_3	H	97	55–57°	$C_{14}H_{14}O$ (198.3)	198
2d	CH_3	H	H	CH_3	98	49–51°	$C_{14}H_{14}O$ (198.3)	198
2e	H	CH_3	H	CH_3	94	121°/3	$C_{14}H_{14}O$ (198.3)	198
2f	CH_3	H	CH_3	CH_3	86	104°/1.5	$C_{15}H_{16}O$ (212.3)	212
2g	CH_3	CH_3	CH_3	CH_3	70	42–43°	$C_{16}H_{18}O$ (226.3)	226

[a] Yield of isolated phenolic product, purity ≥98% as determined by G.L.C. analysis (3% Dexil 300 GC on chromosorb W).
[b] The microanalyses were in satisfactory agreement with the calculated values (C ±0.22%, H ±0.21%).

Table 2. Spectroscopic Data for 2-Hydroxybiphenyls **2**

Compound No.	I.R.[a] [cm^{-1}]			^{1}H-N.M.R.[b] δ [ppm], *J* [Hz]		
	δ_{C-H} of C_6H_5	out-of-plane n_{C-H}	ν_{O-H}	CH_3	OH	H_{arom}
2a	705 765	780 (n=3)	3550	2.04 (s, 3H)	4.43 (s, 1H)	6.99–7.50 (m, 5H); 6.50–6.78 (m, 3H)
2b	708 755	782 (n=3)	3560	2.21 (s, 3H)	4.98 (s, 1H)	7.30–6.60 (m, 8H)
2c	705 775	864 (n=1)	3550	1.98 (s, 3H); 2.27 (s, 3H)	4.32 (s, 1H)	7.10–7.30 (m, 5H); 6.40 (s, 2H)
2d	705 768	803 (n=2)	3550	1.98 (s, 3H); 2.18 (s, 3H)	4.46 (s, 1H)	7.16–7.52 (m, 5H); 6.58 (d, 1H, *J*=8); 6.88 (d, 1H, *J*=8)
2e	708 765	862 (n=1)	3560	2.18 (s, 6H)	4.88 (s, 1H)	7.10–7.28 (m, 5H); 6.72 (d, 1H, *J*=2); 6.80 (d, 1H, *J*=2)
2f	708 765	870 (n=1)	3550	1.94 (s, 3H); 2.09 (s, 3H); 2.22 (s, 3H)	4.44 (s, 1H)	7.10–7.50 (m, 5H); 6.48 (s, 1H)
2g	705 765	—	3540	1.90 (s, 3H); 2.13 (s, 3H); 2.15 (s, 3H); 2.19 (s, 3H)	4.30 (s, 1H)	7.13–7.50 (m, 5H)

[a] The I.R. spectra were recorded on a Shimadzu IR-430 spectrophotometer (KBr pellet or neat).
[b] The ^{1}H-N.M.R. spectra were measured as CCl_4 solutions at 100 MHz with a JEOL Model PS-100 spectrometer using TMS as internal standard.

Consequently, we believe that the selective cleavage reactions of **1** with lithium is a valuable method for the synthesis of **2**.

Methylbenzofurans 1:
Compounds **1a–e**[6] and **1g**[7] are prepared by literature methods.
Compound **1f:** A mixture of 1,3,4-trimethyl-6,7,8,9-tetrahydrobenzofuran[7] (5.0 g, 0.023 mol) and 5% palladium on charcoal (2.5 g) is heated at 220–230 °C for 4 h under a slow stream of nitrogen. The resultant product is extracted with ether, the solvent removed, and the residue recrystallized from ethanol to give *1,3,4-trimethyldibenzofuran* (**1f**); yield: 4.0 g (81%); m.p. 65–66 °C.

$C_{15}H_{14}O$	calc.	C 85.68	H 6.71
(210.3)	found	85.95	6.58

I. R. (KBr): ν = 3050–2850 (CH); 1250 (COC); 750 cm^{-1} (δ_{C-H}).
^{1}H-N.M.R. (CCl_4): δ = 2.32 (s, 3H, 3-CH_3); 2.40 (s, 3H, 4-CH_3); 2.63 (s, 3H, 1-CH_3); 6.77 (s, 1H, 2-H); 7.0–7.6 (m, 3H, H-6, 7, 8); 7.8–8.0 ppm (m, 1H, H-9).

6-Methyl-2-hydroxybiphenyl (2a); Typical Procedure:
To a solution of **1a** (4.00 g, 0.022 mol) in dried dioxan (20 ml), lithium (0.46 g, 0.066 mol) is added, and the mixture is heated under reflux for 3 h. The mixture is cooled and filtered to remove excess lithium on a pad of glass fiber. The filtrate is evaporated under reduced pressure, and then, to the residue is added water (50 ml). The solution is filtered again to separate off any unreacted **1** and is acidified with aqueous hydrochloric acid. The formed precipitate is filtered and washed with water (3 × 10 ml) to give crude **2a**; yield: 4.00 g (99%); m.p. 52–54 °C. Crystallization from ethanol gives pure **2a**; yield: 3.56 g (88%); m.p. 54–55 °C (Ref.[1], m.p. 55–56 °C).

Received: January 28, 1980

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