A Convenient Synthesis of 2,3-Disubstituted 1,4-Benzodioxins via Lithiation and Alkylation

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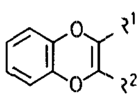
We required a convenient synthesis of 1,4-benzodioxins (**1**) that are substituted at the 2,3-positions, for the preparation of the corresponding 1,2-dioxetanes (**2**).



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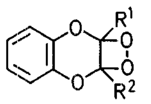

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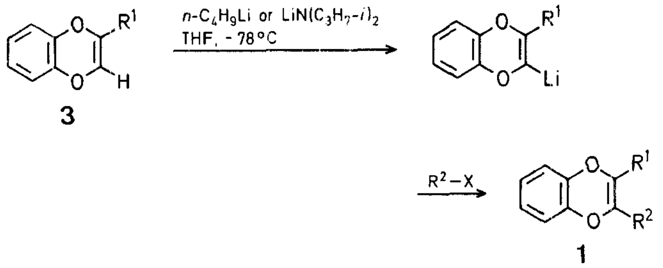
Unfortunately, the 1,4-benzodioxins are a relatively little studied class of compounds and only few synthetic methods are available for their preparation, especially 2,3-substituted derivatives[1,2]. Since α-hydrogens of enol ethers can be directly lithiated via hydrogen-metal interchange with alkyllithium reagents[3], a reaction which was utilized for synthetic purposes in the case of furan some time ago[4] and has recently received much attention[5], we decided to prepare 2,3-substituted 1,4-benzodioxins (**1**) via the synthetic sequence shown below.



The parent 1,4-benzodioxin (**1a**)[2] and its 2-phenyl derivative (**1b**)[1] were obtained according to literature procedures. Our results (Table) show that the above synthetic sequence is a convenient and general method for the preparation of 2-alkyl-, 2,3-dialkyl-, 2-alkyl-3-aryl-, and 2,3-cycloalkyl-1,4-benzodioxins (**1**). While in the mono-alkylation step either butyllithium or lithium diisopropylamide can be used as lithiating reagent, in the dialkylation with 1,ω-dihalides the intramolecular alkylation must be performed with lithium diisopropylamide in view of halogen-metal exchange with butyllithium.

Alkylation of 1,4-Benzodioxins (3); General Procedures:

Method A, using Butyllithium (Monoalkylation): A 50-ml, 3-necked flask, provided with a rubber septum, nitrogen inlet and outlet, and a stirrer, is charged with a solution of 1,4-benzodioxin (**3**, $R^1 = H$; 1.34 g, 10 mmol) in absolute tetrahydrofuran (30 ml). The solution is cooled to −78°C and a 1.6 normal solution (9.5 ml, 15.2 mmol) of butyllithium in hexane is added by means of a syringe. The mixture turns yellow. Stirring is continued for 1 h at −78°C; then, the freshly distilled alkyl halide (50 mmol) is added by a syringe and the mixture allowed to warm to room temperature. After 8 h, the volatile materials are removed by distillation at 20°C/20 torr or 40°C/0.1 torr, depending on the alkyl halide used; to the residue, water (10 ml) is added and the mixture is acified with 2 normal hydrochloric acid (2 ml). Extraction with ether (4×15 ml), washing of the combined ether extracts with saturated sodium hydrogen carbonate solution (15 ml) and with water (15 ml), drying with sodium sulfate, rotoevaporation (20°C/20 torr) of the ether, and silica gel chromatography of the crude product with petroleum ether/dichloromethane (4/1) gives the essentially pure 1,4-benzodioxin product. Final purification is performed by recrystallization in the case of solids and column chromatography on silica gel plus distillation (30°C/10^{-6} torr) in the case of liquids.

Method B, using Lithium Diisopropylamide (Mono- and Dialkylation): A 50-ml, 3-necked flask, provided with a rubber septum, nitrogen inlet and outlet, and a stirrer is charged with a solution of diisopropylamine (133 mg, 1.3 mmol) in absolute tetrahydrofuran (10 ml). The solution is cooled to −78°C, a 1.6 normal solution (0.8 ml, 1.3 mmol) of butyllithium in hexane is added by a syringe, and stirring is continued at room temperature for 30 min. The mixture is then cooled to −60°C, a solution of the 1,4-benzodioxin (1 mmol) in tetrahydrofuran (5 ml) is added by a syringe, and stirring is continued for 8 h. The mixture is worked up as in Method A.

Acknowledgements are made to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, NIH, NSF, and PRF for generous financial support of this work. We thank Dr. G. Lange for her help with the mass spectra.

Received: July 31, 1981
(Revised form: October 7, 1981)

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** *Diplomarbeit*, Universität Würzburg, 1981.

Table. 1,4-Benzodioxins (**1**) prepared

[a]	R^1	R^2	Yield[b] [%]	m.p. (solvent) or b.p./torr [°C]	Molecular formula[c]	M.S. (70 eV) *m/e*	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm]
	CH_3	H	80	b.p. 87°/18[1]	$C_9H_8O_2$ (148.16)	—	3050, 2925, 1720, 1600, 1495, 1335, 1260, 1110, 940	1.62 (t.d, J = 1.5 Hz, 3H, CH_3); 5.60 (t.m, 1H_{olefin}); 6.42-6.80 (m, 4H_{arom})
	$CH_2—CH=CH_2$	H	70	$30°/10^{-6}$[d]	$C_{11}H_{10}O_2$ (174.19)	174 (M^+; 100%); 133 [$M^+ - CH_2—CH=CH_2$, 19%]; 66 [$(HC\equiv C—CH_2—CH=CH_2)^+$, 38%]; 41 [$(CH_2—CH=CH_2)^+$, 17%]	3080, 2980, 2890, 1710, 1600, 1495, 1255, 1100	2.60-2.73 (m, 2H, $—CH_2—$); 5.02-5.29 (m, 2H, $=CH_2$); 5.56-6.00 (m, 2H, $—O—CH=C$ and $C—CH=C$); 6.47-6.83 (m, 4H_{arom})
	$(CH_2)_3—Br$	H	65	$30°/10^{-6}$[d]	$C_{11}H_{11}BrO_2$ (255.11)	254 (M^+, 35%); 147 [$M^+ - (CH_2)_2—Br$, 100%]	3045, 2955, 2905, 2840, 1710, 1600, 1495	1.96-2.22 (m, 4H, $=C—[CH_2]_2—$); 3.37-3.53 (m, 2H, CH_2Br); 5.74 (s, 1H_{olefin}); 6.48-6.83 (m, 4H_{arom})
	$(CH_2)_4—Br$	H	51	$30°/10^{-6}$[d]	$C_{12}H_{13}BrO_2$ (269.15)	268 (M^+, 43%); 147 [$M^+ - (CH_2)_3—Br$, 100%]	2940, 1710, 1600, 1495, 1340, 1255, 1100, 940	1.45-2.09 (m, 6H, $=C—[CH_2]_3—$); 3.29-3.47 (t, 2H, CH_2Br); 5.68 (s, 1H_{olefin}); 6.47-6.83 (m, 4H_{arom})
	$CH_2—C_6H_5$	H	68	48-48.5° (hexane)	$C_{15}H_{12}O_2$ (224.25)	224 (M^+, 100%); 91 ($CH_2—C_6H_5^+$, 93%)	3025, 1715, 1600, 1495, 1255, 1090, 750	3.21 (br. s, 2H, CH_2); 5.61 (t. m, 1H_{olefin}); 6.47-6.77 (m, 4H, C_6H_4); 7.24 (s, 5H, C_6H_5)
	CH_3	CH_3	65	38-39° (hexane)	$C_{10}H_{10}O_2$ (162.2)	162 (M^+, 100%); 147 ($M^+ - CH_3$, 67); 43 ($H_3C—CO^+$, 41%)	2920, 1735, 1605, 1495, 1395, 1275, 1185, 1135	1.71 (s, 6H, CH_3); 6.47-6.77 (m, 4H, C_6H_4)
	$CH_2—C_6H_5$	$CH_2—C_6H_5$	57	64-65° (hexane)	$C_{22}H_{18}O_2$ (314.4)	314 (M^+, 11%); 91 ($CH_2—C_6H_5^+$, 100%)	3060, 3025, 2890, 1715, 1600, 1495, 1265	3.37-3.57 (m, 4H, CH_2); 6.50-6.80 (m, 4H, C_6H_4); 7.07-7.33 (m, 10H, C_6H_5)
	C_6H_5	CH_3	91	38-39°	$C_{15}H_{12}O_2$ (224.25)	—	3035, 2895, 1700, 1605, 1495, 1275	1.88 (s, 3H, CH_3); 6.57-6.82 (m, 4H, C_6H_4); 7.19-7.47 (m, 5H, C_6H_5)
[e]	$—(CH_2)_3—$		62	80.5-81° (hexane)	$C_{11}H_{10}O_2$ (174.2)	174 (M^+, 100%); 66 ($M^+ - C_6H_4O_2$, 35%)	2970, 2905, 2860, 1750, 1595, 1490, 1325, 1260	1.75-2.01 (m, 2H, CH_2); 2.06-2.43 (m, 4H, $CH_2—C=C—CH_2$); 6.52-6.87 (m, 4H_{arom})
[e]	$—(CH_2)_4—$		62	68-69° (pentane/CH_2Cl_2)	$C_{12}H_{12}O_2$ (188.2)	188 (M^+, 100%); 160 ($M^+ - C_2H_4$, 95%)	2925, 2850, 1740, 1600, 1495, 1270, 1190, 1120	1.57-1.83 (m, 4H, $CH_2—CH_2$); 1.91-2.16 (m, 4H, $CH_2—C=C—CH_2$); 6.47-6.78 (m, 4H_{arom})

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[a] In all cases the bromides were used as alkylating agents except for CH_3J.

[b] Yields of isolated product.

[c] The microanalyses of compounds **1g-l** showed the following deviations from calculated values: C, ±0.47; H, ±0.29. Satisfactory analyses of the liquid products **1d, e, f** could not be obtained.

[d] Purified by column chromatography on silica gel using petroleum ether/dichloromethane (4/1) as eluent and bulb-to-bulb distilled since the 1,4-benzodioxins are thermally labile; purity >96% (^{1}H-N.M.R. analysis).

[e] Lithium diisopropylamide was used as lithiating agent in these intramolecular alkylations.

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0039-7881/82/0432-0324 $ 03.00