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Arene-Catalysed Reductive Lithiation of Tetrahydrofuran: Improved Synthesis of 1,5-Diols

Diego J. Ramón and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, 03080 Alicante, Spain

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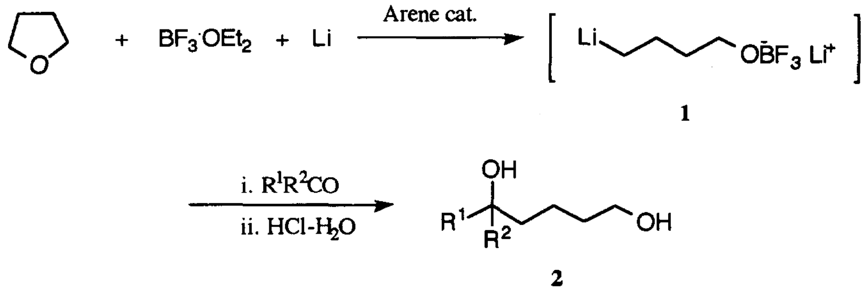
Abstract: *The reductive cleavage of tetrahydrofuran at -78°C can be easily achieved by using an excess of lithium powder in the presence of $BF_3{\cdot}OEt_2$ and a catalytic amount (<8%) of an arene (naphthalene, biphenyl, 4,4'-di-tert-butylbiphenyl or anthracene), the best results being obtained with naphthalene. The dianion prepared by this method reacts with carbonyl compounds yielding 1,5-diols.*

Introduction

Very recently it has been reported that tetrahydrofurans can be reductively cleaved to yield δ-lithioalkoxides at -78°C by means of a mixture of lithium 4,4'-di-*tert*--butylbiphenyl and $BF_3{\cdot}OEt_2$.[1] On the other hand, we have recently found that lithium powder and a catalytic amount of an arene can be even more effective than the lithium-arene in lithiation reactions at low temperature.[2] Both of these considerations prompted us to study the possibility of opening tetrahydrofuran reductively using lithium powder and a catalytic amount of an arene at low temperature.

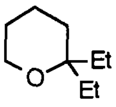
Results and Discussion

The treatment of tetrahydrofuran with $BF_3{\cdot}OEt_2$ and an excess of lithium powder (1:14 molar ratio) and a catalytic amount of an arene (0.08 mol of naphthalene, biphenyl, 4,4'-di-*tert*-butylbiphenyl, or anthracene) at -78°C led to a solution of the dianion **1**, which by reaction with isobutyraldehyde yielded the corresponding diol **2a** (Scheme and Table, entries 1 and 4-6). The best results were obtained using naphthalene under the above described conditions: when the amounts of naphthalene or lithium decreased the yields were lower (Table, entries 2 and 3). When the intermediate **1** was allowed to react with other carbonyl compounds, the expected 1,5-diols **2b-g** were isolated (Table, entries 7-12).



Scheme.

Finally, this methodology can be used to prepare directly substituted tetrahydropyrans by performing the final hydrolysis with concentrated hydrochloric acid; for instance, starting from 3-pentanone, 2,2-diethyltetrahydropyran **3** was isolated in 41% yield. We think that this last process opens a new route for transforming tetrahydrofuran into substituted tetrahydropyrans in an one-pot procedure.



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From the results described in this paper we conclude that this methodology represents an important improvement with respect to the use of stoichiometric amounts of lithium arenes in the reductive lithiation of tetrahydrofurans.[1]

Experimental Section

For general information see ref 8.

General Procedure for the Preparation of 1,5-Diols **2**. To a suspension of lithium powder (56 mmol) in dry THF (10 mL) and naphthalene (0.32 mmol) was added $BF_3{\cdot}OEt_2$ (4 mmol) at -78°C and the mixture was stirred 2 h at the same temperature. The corresponding carbonyl compound (5 mmol) was then added and the resulting mixture was stirred overnight allowing the temperature to rise to 20°C. The excess of lithium was filtered off and the obtained solution was neutralized with 2 M HCl, extracted with ether and the organic layer dried over Na_2SO_4. Solvents were evaporated *in vacuo* (15 torr) and the resulting residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 1/1) to afford the corresponding products **2**. In the case of the tetrahydropyran **3** the crude product of the reaction was finally acidified with 6 M HCl and then worked up as for products **2**. Yields and lithiation times are reported in Table. Physical, analytical and spectral data follow. In the case of known compounds, their data are in agreement with those reported in the literature.

Table. Catalytic cleavage of tetrahydrofuran with lithium powder. Obtention of 1,5-diols 2

Entry	Arene[a]	Lithiation time (h)	Carbonyl compound	1,5-Diols[b]	
				R^1,R^2/No.	Yield(%)[c]
1	N	2	Pr^{i}CHO	Pr^i,H/**2a**	76
2	N[d]	4	Pr^{i}CHO	Pr^i,H/**2a**	49
3	N[e]	5.5	Pr^{i}CHO	Pr^i,H/**2a**	60
4	B	2.5	Pr^{i}CHO	Pr^i,H/**2a**	52
5	DBB	2.5	Pr^{i}CHO	Pr^i,H/**2a**	61
6	A	1.5	Pr^{i}CHO	Pr^i,H/**2a**	35
7	N	2	Bu^{n}CHO	Bu^n,H/**2b**	78
8	N	2	Bu^{t}CHO	Bu^t,H/**2c**	80
9	N	2	PhCHO	Ph,H/**2d**	64
10	N	2	MeCOBu^t	Me,Bu^t/**2e**	72
11	N	2	MeCOPh	Me,Ph/**2f**	50
12	N	2	EtCOEt	Et,Et/**2g**	60

[a] N=naphthalene; B=biphenyl; DBB=4,4'-di-*tert*-butylbiphenyl; A=anthracene; 8% of arene was used unless otherwise stated. [b] All isolated compounds were ≥95% pure by g.l.c. [c] Isolated yield after flash chromatography based on the amount of $BF_3{\cdot}OEt_2$ used. [d] 1% of naphthalene was used as catalyst. [e] 3.5 mmol of lithium were used.

6-Methyl-1,5-heptanediol (**2a**):[1] R_f=0.29 (hexane/ethyl acetate: 1/4); IR (film) 3340 (OH), 1050, 980 cm^{-1} (C-O); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.91 (d, J=6.7 Hz, 6 H, 2xCH$_3$), 1.20-1.70 [m, 7 H, C*H*CH(C*H*$_2$)$_3$], 2.50 (s, 2 H, 2xOH), 3.20-3.45 (m, 1 H, C*H*OH), 3.64 (t, J=6.1 Hz, 2 H, C*H*$_2$OH); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 17.25, 18.75, 22.15, 32.4, 33.45, 33.55, 62.35, 76.5; MS 146 (M$^+$, <1), 103 (28), 85 (100), 73 (30), 67 (41), 57 (48), 56 (10), 55 (31), 44 (16), 43 (48), 41 (51).

1,5-Nonanediol (**2b**):[3] R_f=0.28 (hexane/ethyl acetate: 1/4); IR (film) 3420 (OH), 1050, 1010 cm^{-1} (C-O); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.90 (t, J=6.9 Hz, 3 H, CH$_3$), 1.15-1.70 [m, 12 H, (C*H*$_3$)$_3$CH(C*H*$_2$)$_3$], 3.32 (s, 2 H, 2xOH), 3.5-3.7 (m, 3 H, CHO, CH$_2$O); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 13.95, 21.7, 22.65, 27.8, 32.3, 36.7, 37.1, 62.05, 71.4; MS 159 (M$^+$-1, <1), 117 (16), 103 (17), 87 (35), 85 (100), 69 (49), 67 (23), 57 (31), 56 (18), 55 (12), 44 (11), 43 (22), 41 (36).

6,6-Dimethyl-1,5-heptanediol (**2c**):[4] R_f=0.32 (hexane/ethyl acetate: 1/4); IR (film) 3420 (OH), 1050, 1030 cm^{-1} (C-O); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.90 [s, 9 H, (CH$_3$)$_3$C], 1.15-1.85 [m, 6 H, (CH$_2$)$_3$], 2.25 (s, 2 H, 2xOH), 3.50-3.75 [m, 3 H, C*H*(CH$_3$)$_3$C*H*$_2$]; ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.15, 25.65, 30.85, 32.45, 34.9, 62.5, 79.8; MS 143 (M$^+$-17, <1), 103 (21), 87 (15), 85 (100), 69 (10), 67 (26), 57 (46), 43 (30), 41 (31).

1-Phenyl-1,5-pentanediol (**2d**):[5] R_f=0.33 (hexane/ethyl acetate 1/4); IR (film) 3340 (OH), 3040, 3020, 1600 (Ph), 1060, 1030 cm^{-1} (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15-1.90 [m, 6 H, $CH(CH_2)_3$], 3.05 (s, 2 H, 2xOH), 3.50 (t, *J*=5.9 Hz, 2 H, CH_2OH), 4.58 (dd, *J*=7.4, 5.5 Hz, 1 H, CH), 7.27 (s, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.85, 32.05, 38.55, 62.05, 74.05, 125.75, 127.2, 128.2, 144.8; MS 181 (M$^+$+1, 5), 180 (M$^+$, 30), 137 (12), 133 (15), 120 (12), 108 (32), 107 (100), 105 (53), 91 (25), 80 (14), 79 (91), 78 (32), 77 (81), 55 (10), 51 (30), 43 (12), 41 (11).

5,6,6-Trimethyl-1,5-heptanediol (**2e**): R_f=0.43 (hexane/ ethyl acetate: 1/4), mp 79°C (hexane/ether); IR (melted) 3340 (OH), 1050, 1030 cm^{-1} (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 [s, 9 H, $(CH_3)_3C$], 1.12 (s, 3 H, CH_3CO), 1.35-1.65 [m, 8 H, $C(OH)(CH_2)_3CH_2OH$], 3.68 (t, *J*=6.0 Hz, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.1, 20.8, 25.3, 33.4, 35.45, 38.05, 62.85, 76.4; MS 160 (M$^+$-18, <1), 141 (12), 117 (10), 101 (99), 99 (100), 83 (35), 58 (10), 57 (24), 55 (18), 43 (93), 41 (20). Anal. Calcd for $C_{10}H_{22}O_2$: C, 68.92; H, 12.72. Found: C, 69.2; H, 12.6.

5-Phenyl-1,5-hexanediol (**2f**): R_f=0.34 (hexane/ethyl acetate: 1/4); IR (film) 3380 (OH), 3060, 3040, 1600 (Ph), 1070, 1030 cm^{-1} (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10-1.90 [m, 9 H, $CH_3C(CH_2)_3$], 3.20-3.65 (m, 4 H, CH_2OH, OH), 7.05-7.60 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 29.85, 32.4, 43.4, 61.9, 74.45, 124.65, 126.2, 127.9, 147.95; MS 194 (M$^+$, 1), 121 (100), 105 (23), 77 (14), 43 (46).

5-Ethyl-1,5-heptanediol (**2g**):[6] R_f=0.39 (hexane/ethyl acetate : 1/4); IR (film) 3360 (OH), 1080, 1060 cm^{-1} (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, *J*=7.5 Hz, 6 H, $2xCH_3$), 1.20-1.80 [m, 10 H, $(CH_2)_3C(CH_2)_2$], 2.55 (s, 2 H, 2xOH), 3.65 (t, *J*=6.5 Hz, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.7, 19.3, 30.75, 32.95, 37.6, 62.2, 74.7; MS 132 (M$^+$-44, 1), 131 (10), 113 (58), 87 (82), 69 (11), 57 (100), 45 (21), 43 (14), 41 (11).

2,2-Diethyltetrahydropyran (**3**):[7] R_f=0.41 (hexane/ethyl acetate: 19/1); IR (film) 1090, 1045 cm^{-1} (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, *J*=7.5 Hz, 6 H, $2xCH_3$), 1.00-1.80 [m, 10 H, $(CH_2)_3C(CH_2)_2$], 3.61 (t, *J*=5.3 Hz, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.3, 19.05, 26.0, 26.95, 32.55, 61.0, 76.6; MS 157 (M$^+$-1, <1), 99 (23), 98 (24), 57 (100), 55 (15), 41 (19).

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