



Organolithium reagents from alkyl phenyl ethers¹

Abderrazak Bachki,² Francisco Foubelo and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Received 3 July 1998; accepted 3 August 1998

Abstract

The reaction of primary alkyl or vinyl phenyl ethers (**1**) as well as 2,3-dihydrobenzofuran (**3**) with an excess of lithium powder and a catalytic amount of DTBB (5 %) in THF at room temperature leads to the corresponding organolithium intermediates, which by treatment with different electrophiles [H_2O , D_2O , Me_3SiCl , Bu^tCHO , PhCHO , Me_2CO , Et_2CO , $(\text{CH}_2)_4\text{CO}$, $(\text{CH}_2)_5\text{CO}$, PhCOMe] and final hydrolysis affords the expected products **2** and **4**. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: lithiation; cyclization; benzofuran; reduction.

From practical purposes the synthesis of organolithium compounds by the cleavage of ethers [1] is limited to the reaction of lithium metal with allylic or benzylic ethers, so generating allyl- or benzyl-lithium derivatives and avoiding Wurtz-type side-reactions [2,3]. However, when the lithiation reaction is applied to normal dialkyl ethers, they are in general inactive, indeed some of them (diethyl ether, THF) are widely used as solvents in lithiation reactions.³ A special case is the lithiation of phenyl alkyl ethers, namely anisole, which is resistant to lithium metal under non-forcing conditions, but can be opened using lithium and an arene (such as biphenyl) as an electron transfer agent, giving phenol as the main product after hydrolysis [5]. On the other hand, lithium and a protic solvent, such as liquid ammonia, have been widely used in Birch-type reduction with aromatic ethers, so converting substituted anisoles to synthetic equivalents of cyclohex-3-enone; this process has been widely used in steroid transformations [6]. However, to the best of our knowledge, the

¹ This paper is dedicated to Prof. Adalbert Maercker for his leading work on this field.

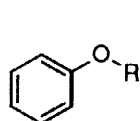
² Postdoctoral student from the Hassan II University of Casablanca (Morocco).

³ Oxiranes, oxetanes as well as tetrahydrofurans in the presence of boron trifluoride can be opened using lithium and an arene in stoichiometric or catalytic amount. For a recent review, see reference [4].

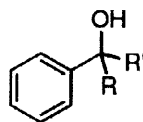
lithiation of alkyl aryl ethers under different reaction conditions has never been used to generate alkyllithium reagents;⁴ in contrast, the same reaction applied to the corresponding aryl thioethers has been shown to be applicable to the preparation of organolithiums [7-9]. In this paper we report for the first time the use of an arene-catalysed lithiation [10,11] for the direct preparation of alkyl lithium reagents from alkyl phenyl ethers, this methodology being specially interesting for the preparation of functionalised organolithium compounds [12,13].

The reaction of anisole (**1a**) or ethoxybenzene (**1b**) with an excess of lithium⁵ (1:14 molar ratio) and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 5 mol %) in THF at room temperature led, after 1.5 h, to a solution of methyl- or ethyl-lithium, which after reaction with benzaldehyde or acetophenone as electrophiles at temperatures ranging between -40 and 0°C yielded, after reaction with water, the expected products **2**.

Almost no reaction was observed with anisole in the absence of the catalyst after 2 h at room temperature; however after 24 h a conversion of 100% was obtained under these reaction conditions. On the other hand, only 75% conversion was observed after 0.5 h using a stoichiometric amount of the arene (in the case of using a catalytic amount of the arene a 92% conversion was obtained under the same reaction conditions). This behaviour can be explained [11] assuming that in the catalytic version an arene-dianion is involved as a reducing agent instead of the corresponding radical-anion, which is the species that takes part in the stoichiometric version.



- 1a:** R=Me
1b: R=Et
1c: R=Prⁱ
1d: R=Bu^t



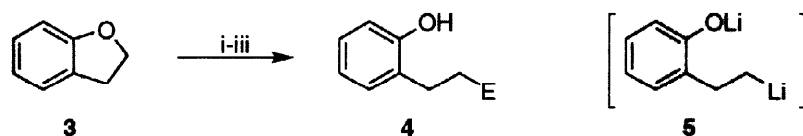
- 2a:** R=Me, R'=H (80%)
2b: R= R'=Me (77%)
2c: R=Et, R'=H (83%)
2d: R=Et, R'=Me (69%)

When the corresponding *iso*-propyl or *tert*-butyl derivatives **1c** or **1d** were used, no reaction with benzaldehyde or acetophenone was observed under the same reaction conditions. In all cases, even with total consumption of starting derivatives, only phenol could be isolated after hydrolysis of the reaction mixture. An explanation for this behavior could be that the initial radical R• (generated by a SET reaction from the aryl ether followed by oxygen-carbon cleavage) can be transformed into the corresponding carbanion only when this last species is primary; for more stable secondary or tertiary radicals the transformation into the corresponding less stable anionic species is inhibited, and either hydrogen-abstraction from the reaction medium or disproportionation to the alkane/alkene mixture occurs.

⁴ For a recent account on DTBB-catalysed lithiation of dibenzofuran, see reference [14].

⁵ Lithium was commercially available (Strem) as a 30% dispersion in mineral oil and was washed four times with dry hexane and dried under vacuum (0.1 Torr) before use.

In the last part of this study we applied the above mentioned lithiation to 2,3-dihydrobenzofuran (**3**), which under the same reaction conditions and reaction with different electrophiles [H_2O , D_2O , Me_3SiCl , Bu^tCHO , PhCHO , Me_2CO , Et_2CO , $(\text{CH}_2)_4\text{CO}$, $(\text{CH}_2)_5\text{CO}$] yielded, after hydrolysis, the compounds **4**, the corresponding functionalised organolithium intermediate **5** was involved in the process (Scheme 1 and Table 1).



Scheme 1. Reagents and conditions: i, Li, DTBB (5%), THF, 20°C , 1.5 h; ii, $\text{E}^+ = \text{H}_2\text{O}$, D_2O , Me_3SiCl , Bu^tCHO , PhCHO , Me_2CO , Et_2CO , $(\text{CH}_2)_4\text{CO}$, $(\text{CH}_2)_5\text{CO}$, -40° to 20°C ; iii, H_2O .

Table 1
Preparation of compounds **4**

Entry	Electrophile E^+	Product ^a			
		No.	E	Yield (%) ^b	R_f ^c
1	H_2O	4a	H	95	0.61
2	D_2O	4b	D	85 ^d	0.61
3	Me_3SiCl	4c	Me_3Si	53	0.65
4	Bu^tCHO	4d	Bu^tCHOH	78	0.35
5	PhCHO	4e	PhCHOH	70	0.30
6	Me_2CO	4f	Me_2COH	72	0.20
7	Et_2CO	4g	Et_2COH	69	0.28
8	$(\text{CH}_2)_4\text{CO}$	4h	$(\text{CH}_2)_4\text{COH}$	77	0.23
9	$(\text{CH}_2)_5\text{CO}$	4i	$(\text{CH}_2)_5\text{COH}$	62	0.32

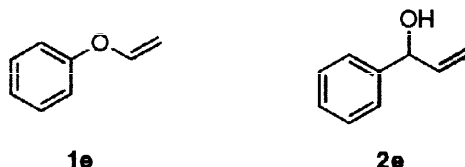
^a All products **4** were characterised by spectroscopic means (IR, ^1H and ^{13}C NMR and MS).

^b Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **3**.

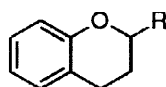
^c Silica gel, hexane/ethyl acetate: 3/1.

^d 85% Deuterium incorporation (from mass spectrum).

We also studied the reductive cleavage of phenyl vinyl ether (**1e**) under the conditions showed in Scheme 1 using benzaldehyde as the electrophilic component. After typical workup 1-phenylprop-2-enol (**2e**) was isolated in 83% yield.



In the last part of this study, we considered the cyclization of some diols **4** under Mitsunobu reaction conditions (PPh_3 , DIAD, PhH reflux). The compounds **6d** and **6e** were isolated in 25 and 95% yield, respectively.



6d: $\text{R}=\text{Bu}^t$

6e: $\text{R}=\text{Ph}$

As a conclusion, we report here a new methodology based on a DTBB-catalysed lithiation which allows the preparation of primary or vinyl organolithiums from the corresponding phenyl ethers, this method being an alternative to the use of phenyl thioethers as starting materials.

Acknowledgements. This project was financially supported by the DGICYT from the Spanish Ministerio de Educación y Cultura (MEC) (project no. 1514).

References

- [1] Maercker A. *Angew. Chem. Int. Ed. Engl.* 1987;26:972-989.
- [2] Wakefield BJ. *Organolithium methods*. London: Academic Press, 1988:47-49.
- [3] Schöllkopf U. In: Müller E, editor. *Houben-Weyl: Methoden der Organischen Chemie*. Stuttgart: G. Thieme Verlag, 1970; 13/I:161.
- [4] Yus M, Foubelo F. *Rev. Heteroatom Chem.* 1997;17:73-107.
- [5] Eisch JJ. *J. Org. Chem.* 1963;28:707-710.
- [6] Mander LN. In: Trost, BM, Fleming I, editors. *Comprehensive organic synthesis*. Oxford: Pergamon Press, 1991; 8:493-495.
- [7] Screttas CG, Micha-Screttas M. *J. Org. Chem.* 1978;43:1064-1071.
- [8] Cohen T, Weisenfeld RB. *J. Org. Chem.* 1979;44:3601-3603.
- [9] Foubelo F, Gutiérrez A, Yus M. *Tetrahedron Lett.* 1997;38:4837-4840.
- [10] Yus M, Ramón DJ. *J. Chem. Soc. Chem. Commun.* 1991:398-400.
- [11] Yus M. *Chem. Soc. Rev.* 1997:155-161.
- [12] Nájera C, Yus M. *Trends Org. Chem.* 1991;2:155-181.
- [13] Nájera C, Yus M. *Recent Res. Devel. Org. Chem.* 1997;1:67-96.
- [14] Kadyrov R, Heinicke J, Kindermann K, Heller D, Fischer C, Selke R, Fischer AK, Jones PG. *Chem. Ber./Recueil* 1997;130:1663-1670.