Tetrahedron Letters, Vol. 34, No. 21, pp. 3487-3490, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

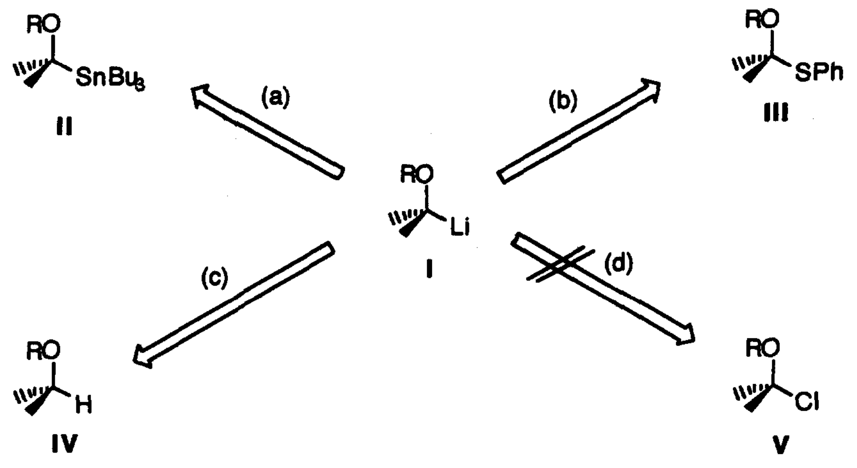
4,4'-Di-*tert*-butylbiphenyl-Catalysed Lithiation of Chloromethyl Ethyl Ether: A Barbier-Type New and Easy Alternative to Ethyl Lithiomethyl Ether

Albert Guijarro and Miguel Yus*

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

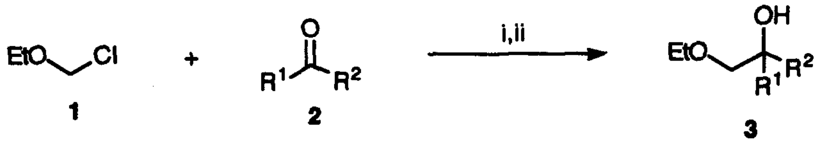
Abstract: The reaction of an equimolar amount of chloromethyl ethyl ether (**1**) and different carbonyl compounds (**2**) with an excess of lithium powder (1:7 molar ratio) in the presence of a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (5 mol %) in THF at 0°C leads, after hydrolysis, to the corresponding hydroxyethers **3**.

Organolithium compounds bearing α-heteroatoms[1], also called "carbenoids", are interesting functionalized carbanionic intermediates[2] in organic synthesis and should be consider as typical d^1-reagents with umpolung reactivity[3]. The preparation of sp^3-hybridized non-stabilized carbanions bearing an ether functionality of the type **I** has been already achived at low temperature by three different ways: (a) tin/lithium transmetallation from the adequate α-stannylethers **II** with *n*-butyllithium[4]; (b) sulphur/lithium exchange from phenylthioketals of the type **III** by reductive cleavage with a lithium-arene[5]; (c) deprotonation ot *t*-butyl[6a] or benzyl[6b] ethers, or esters [6c,d] and related compounds[6e,g] of the type **IV** with strong bases (usually *s*-BuLi and a co-reagent such as TMEDA or *t*-BuOK). However, to our best knowledge, the *direct*[7] route (d) by chlorine/lithium exchange from chloroethers **V** has not been used for the preparation of intermediates of the type **I** (Scheme 1). In general, non-stabilized α-lithioethers of the type **I** are unstable species, even at low temperatures, due to their tendency to undergo α-elimination[8a] or Wittig rearrangement [8b] processes. On the other hand, in the last time we have used the arene-catalysed lithiation[9] of different chlorinated substrates at low temperatures[10] for the preparation of very reactive functionalized organolithium intermediates[11,12]. Among the arenes, naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB) are the most commonly employed[13]. In this paper we report a solution to the preparation of α-lithioethers of the type **I** by chlorine/lithium exchange [way (d), Scheme 1] using a combination of a DTBB-catalysed lithiation of chloromethyl ethyl ether and a Barbier-type reaction in the presence of carbonyl compounds.



Scheme 1.

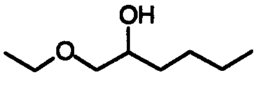
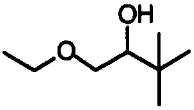
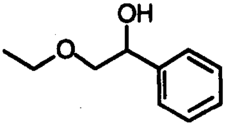
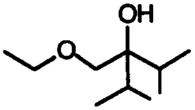
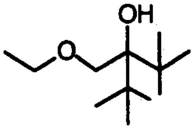
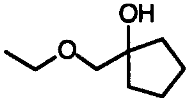
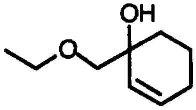
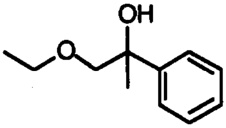
The slow addition (*ca.* 45 min) of a mixture of equimolar amounts of chloromethyl ethyl ether (**1**) and a carbonyl compound in THF to a blue suspension of an excess of lithium powder (1:7 molar ratio) and a catalytic amount of DTBB (5 mol %) in THF at 0°C gave, after hydrolysis, the corresponding ethoxyalcohols **3** (Scheme 2 and Table 1). The reaction worked very nicely with aldehydes and ketones even with very hindered systems, such as diisopropyl or di-*tert*-butyl ketone (Table 1, entries 4 and 5, respectively). When naphthalene was used as the arene catalyst instead of DTBB the yields are, in general, lower (Table 1, entry 8 and footnote e). In some cases the yields are better by adding the reagents **1** and **2** at once onto the activated lithium suspension (Table 1, entries 3-5 and footnote d).



Scheme 2. *Reagents and conditions*: i, Li powder-DTBB cat (5 mol %), THF, 0°C; ii, H_2O.

Concerning the possible mechanistic pathway, we think that the first process is an electron transfer from the lithium-arene to the starting material **1** giving the corresponding intermediate of the type **I**, ethyl lithiomethyl ether, which in the presence of the carbonyl compound at 0°C reacts very rapidly before decomposition[8] yielding after hydrolysis the obtained products **3**.

Table 1. Preparation of Compounds **3**

	Carbonyl compound **2**		Product **3**			
Entry	R^1	R^2	Structure[a]	No.	Yield (%)[b]	R_f[c]
1	Bu^n	H		**3a**	87	0.25
2	Bu^t	H		**3b**	81	0.31
3	Ph	H		**3c**	70 (84)[d]	0.18
4	Pr^i	Pr^i		**3d**	65 (75)[d]	0.63
5	Bu^t	Bu^t		**3e**	70[d]	0.75
6	-[CH$_2$]$_4$-			**3f**	94	0.29
7	-[e]			**3g**	98	0.20
8	Ph	Me		**3h**	94 (57)[f]	0.33

[a] All compounds were >95% pure by GLC and were fully characterized spectroscopically (IR, ^{1}H and ^{13}C NMR, and mass spectra). [b] Isolated yield of pure compounds after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting chloroether **1**. [c] Hexane/ethyl acetate: 9/1. [d] Isolated yield corresponding to the reaction carried out by adding the reactants **1**+**2** at once (not slowly, see text) to the activated lithium suspension. [e] 2-Cyclohexenone was used as electrophile. [f] Naphthalene was used instead of DTBB as the arene catalyst.

From the results described in this paper we conclude that this methodology represents the first direct lithiation of chloromethyl ethyl ether to give the corresponding α-lithioether at 0°C and the *in situ* reaction of this very reactive intermediate with carbonyl compounds in a Barbier-type process.

Acknowledgement

This work was financially supported by the Dirección General de Investigación Científica y Técnica (DGICYT nos. PB88-0287 and PB91-0751) from the Ministerio de Educación y Ciencia (MEC) of Spain. A. G. thanks the MEC for a fellowship.

References and Notes

1. For a review see: Saaveedra, J. E. In *Umpoled Synthons*, Hase, T. A. Ed.; John Wiley & Sons: New York, 1987; pp. 101-143.
2. For a review, see: Nájera, C.; Yus, M. *Trends in Organic Chemistry* **1991**, *2*, 155-181.
3. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239-258.
4. See, for instance: (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481-1487. (b) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927-1928. (c) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201-1202. (d) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *242*, 3163-3164. (e) Hutchison, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930-4939. (f) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336-1338. (g) Johnson, C. R.; Medich, J. R. *J. Org. Chem.* **1988**, *53*, 4131-4133. (h) Linderman, R. J.; Mckenzie, J. R. *J. Organomet. Chem.* **1989**, *361*, 31-42. (i) Chan, P. C.-M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1985-1988. (j) Lohse, P.; Lower, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615-618. (k) Soderquist, J. A.; Lopez, C. *Tetrahedron Lett.* **1991**, *32*, 6305-6306. (l) Tomooka, K.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795-5798.
5. For a review, see: (a) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152-161. For recent reports, see also: (b) Kruse, B.; Brückner, R. *Tetrahedron Lett.* **1990**, *31*, 4425-4428. (c) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1992**, *57*, 4336-4339.
6. (a) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3165-3168. (b) Yeh, M. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1652-1653. (c) Beak, P.; McKinnie, B. G. *J. Am. Chem. Soc.* **1977**, *99*, 5213. (d) Beak, P.; Carter, L. G. *J. Org. Chem.* **1981**, *46*, 2363-2373. (e) Paetow, M.; Ahrens, H.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5323-5326. (f) Ahrens, H.; Paetow, M.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5327-5330. (g) Schwerdtfeger, J.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1505-1507.
7. An alternative route consists in the transformation of a chloromethylether into the corresponding trichlorostannyl derivative followed by low temperature tin/lithium exchange with *n*-butyllithium (ref 4d).
8. (a) Schöllkopf, U.; Küppers, H. *Tetrahedron Lett.* **1964**, 1503-1506. (b) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763-773.
9. Choi, H.; Pinkerton, A. A.; Fry, J. L. *J. Chem. Soc., Chem. Commun.* **1987**, 225-226.
10. Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398-400.
11. (a) Yus, M.; Ramón, D. J. *J. Org. Chem.* **1992**, *57*, 750-751. (b) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1992**, *33*, 2217-2220. (c) Guijarro, A.; Ramón, D. J.; Yus, M. *Tetrahedron*, **1993**, *49*, 469-482. (d) Guijarro, A.; Yus, M. *Tetrahedron Lett.*, in press.
12. For other related processes from our laboratory involving the use of an arene-catalysed lithiation, see: (a) Ramón, D. J.; Yus, M. *Tetrahedron* **1992**, *48*, 3585-3588. (b) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron* **1992**, *48*, 4593-4600. (c) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron Lett.* **1992**, *33*, 5597-5600. (d) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.*, in press. (e) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron*, in press. (f) Gómez, C.; Ramón, D. J.; Yus, M. *Tetrahedron*, in press. (g) Gil, J.; Ramón, D. J.; Yus, M. *Tetrahedron*, submitted.
13. For a comparative study on the use of both arenes, see: Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924-1930.

(Received in UK 9 March 1993)