Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4837-4840, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01008-3

β-Functionalised Organolithium Compounds through a Sulfur-lithium Exchange†

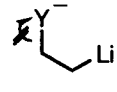
Francisco Foubelo, Ana Gutiérrez and Miguel Yus*

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

Abstract: The successive reaction of different β-hydroxy or β-amino thioethers **1a-d** with *n*-butyllithium and an excess of lithium powder and a catalytic amount of DTBB in THF at -78°C leads to the formation of the corresponding β-functionalised organolithium compounds **2a-d**, which by reaction with several electrophiles [D_2O, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_5CO$] at temperatures ranging between -78 and 20°C yields, after hydrolysis with water, the expected functionalised alcohols or amines **3aa-de** in a regioselective manner. © 1997 Elsevier Science Ltd.

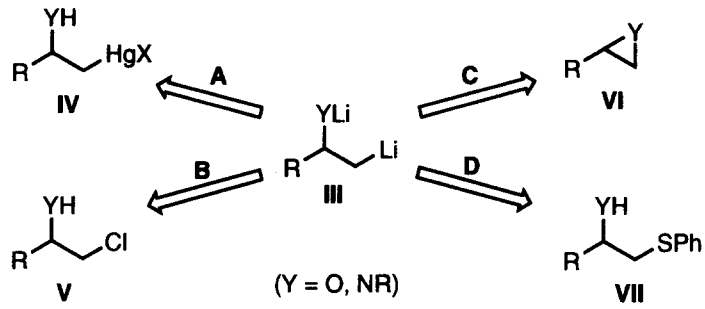
β-Functionalised organolithium compounds[1] of type **I** are unknown species because they are very unstable even at very low temperatures (<-100°C) suffering spontaneous β-elimination to give an olefin and the corresponding lithium salt.[2] This problem has been overcome by locating a negative charge on the heteroatom at the β-position with respect to the lithium atom (see **II**), so the ability of the substituent to act as a leaving group is inhibited at low temperature. Thus, oxygen- or nitrogen-containing β-substituted organolithium compounds of general type **III** have already been prepared by three different routes: (a) mercury-lithium transmetallation from the corresponding hydroxy or amino mercurials **IV**[3] (route **A**); (b) chlorine-lithium exchange from the adequate chlorinated alcohols[4] or amines[5] **V** with lithium naphthalenide[6] (route **B**); (c) reductive ring opening of oxiranes[7] or aziridines[8] **VI** using either the last lithiation mixture[6] or an excess of lithium powder and a catalytic amount of an arene, naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB) being the most commonly used[9] (route **C**). In the present paper we describe the application of this last methodology, arene-catalysed lithiation, to the preparation of β-functionalised organolithium intermediates of type **III** by a sulfur-lithium exchange[10,11] from β-functionalised phenylthioethers of type **VII** (route **D**). Intermediates **III** are of general interest because by reaction with electrophilic reagents they are able to transfer their own functionality to the electrophile, producing in one only step polyfunctionalised molecules.

I (X = Hal, OR, NR_2)

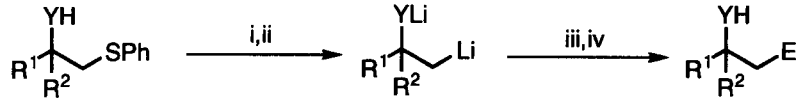


II (Y = O, NR)

† This paper is dedicated to Professor A. I. Meyers on occasion of his 65th birthday.



The reaction of different β-hydroxy or β-phenylamino phenylthioethers **1** with *n*-butyllithium (1:1 molar ratio) in THF at -78°C for 2 min followed by treatment with a dark green suspension of an excess of lithium powder (*ca.* 1:14 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio; 5 mol %) in THF at the same temperature for *ca.* 2 h (after this time the dark green colour appeared again) gave a solution of the corresponding dilithiated intermediate **2**, which by reaction with different electrophiles [D_2O, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_5CO$] at temperatures ranging between -78 and 20°C afforded, after hydrolysis with water, the expected functionalised alcohols or amines **3** (Scheme 1 and Table 1). In all case a variable amount (<25%) of the corresponding "reduced" products (**3** with E = H), resulting from a partial decomposition of dianions **2** abstracting a proton from the reaction medium,[12] was detected in the reaction mixture, which could be easily separated by column chromatography, except when deuterium oxide was used as electrophile.



a : Y = O, R^1= Ph, R^2= H
b : Y = O, R^1= *n*-C_6H_{13}, R^2= H
c : Y = PhN, R^1= R^2= H
d : Y = PhN, R^1= Ph, R^2= H

Scheme 1. *Reagents and conditions*: i, Bu^nLi, THF, -78°C, 2 min; ii, Li, DTBB cat. (5 mol %), THF, -78°C; iii, E^+ = D_2O, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_5CO$, -78 to 20°C, *ca.* 12 h; iv, H_2O.

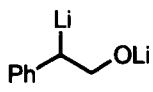
Starting materials **1** were prepared following classical methodologies. Hydroxythioethers **1a,b** were obtained by reaction of the corresponding epoxides with lithium thiophenolate. Successive reaction of 1-bromo-2-chloroethane with aniline and lithium thiophenolate yielded aminated thioether **1c**. Finally, compound **1d** was prepared by treatment of benzylideneaniline with lithiomethyl phenyl thioether. In all case the final hydrolysis with water afforded the corresponding compounds **1**.

Table 1. Preparation of Compounds **3**

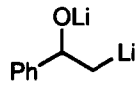
Entry	Starting material	Inter-mediate	Electrophile E+	Product[a] No.	R1	R2	Y	E	Yield (%)[b]	R_f[c]
1	**1a**	**2a**	D_2O	**3aa**	Ph	H	O	D	(90)	0.31
2	**1a**	**2a**	Bu^tCHO	**3ab**	Ph	H	O	Bu^tCHOH	27 (47)[d,e]	0.16[d]
3	**1a**	**2a**	PhCHO	**3ac**	Ph	H	O	PhCHOH	48 (69)[d,f]	0.18[d,g]
4	**1a**	**2a**	Me_2CO	**3ad**	Ph	H	O	Me_2COH	62 (93)	0.47[g]
5	**1a**	**2a**	$(CH_2)_5CO$	**3ae**	Ph	H	O	$(CH_2)_5COH$	32 (42)	0.25[g]
6	**1b**	**2b**	D_2O	**3ba**	n-C_6H_{13}	H	O	D	65 (88)	0.26[h]
7	**1b**	**2b**	Bu^tCHO	**3bb**	n-C_6H_{13}	H	O	Bu^tCHOH	49 (59)[d,i]	0.30[d]
8	**1b**	**2b**	Me_2CO	**3bd**	n-C_6H_{13}	H	O	Me_2COH	50	0.25
9	**1b**	**2b**	$(CH_2)_5CO$	**3be**	n-C_6H_{13}	H	O	$(CH_2)_5COH$	24 (32)	0.32
10	**1c**	**2c**	D_2O	**3ca**	H	H	PhN	D	43 (99)	0.52
11	**1c**	**2c**	PhCHO	**3cc**	H	H	PhN	PhCHOH	61[d]	0.36[d,j]
12	**1d**	**2d**	D_2O	**3da**	Ph	H	PhN	D	99	0.46[h]
13	**1d**	**2d**	Bu^tCHO	**3db**	Ph	H	PhN	Bu^tCHOH	43 (78)[d,k]	0.43
14	**1d**	**2d**	PhCHO	**3dc**	Ph	H	PhN	PhCHOH	52 (61)[d,l]	0.39
15	**1d**	**2d**	$(CH_2)_5CO$	**3de**	Ph	H	PhN	$(CH_2)_5COH$	28	0.21[g]

[a] All products were >94% pure (GLC and 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR, and mass spectra); for deuteriated compounds >90% deuterium incorporation was measured by mass spectrometry (entries 1, 6, 10 and 12). [b] Isolated non-optimised yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**; in parenthesis isolated crude yield. [c] Silica gel, hexane/ethyl acetate: 5/1 unless otherwise noted. [d] Diastereoisomers mixture (NMR), which could not be separated by TLC. [e] 1.7/1 Ratio (^{13}C NMR). [f] 1.2/1 Ratio (^{13}C NMR). [g] Silica gel, hexane/ethyl acetate: 3/1. [h] Silica gel, hexane/ethyl acetate: 10/1. [i] 1.3/1 Ratio (^{13}C NMR). [j] Silica gel, hexane/ethyl acetate: 2/1. [k] 4/1 Ratio (^{13}C NMR). [l] 1/1 Ratio (^{13}C NMR).

From the results described in this paper we conclude that the present methodology is a new way to prepare highly reactive oxygen- or nitrogen-containing β-functionalised organolithium compounds. The here described procedure is complementary to the already reported ways **B** or **C** (see above): for instance, whereas the opening of styrene oxide or its chlorohydrin (2-chloro-2-phenylethanol) afford the corresponding benzylic derivative **2'a**, the successive treatment of the same epoxide with lithium thiophenolate followed by lithiation yielded the corresponding regioisomer **2a**.[13]



2'a



2a

REFERENCES AND NOTES

1. For reviews, see: (a) Nájera, C.; Yus, M. *Trends Organic Chemistry* **1991**, *2*, 155-181. (b) Nájera, C.; Yus, M. *Transworld Research Network*, in press.
2. This process has been used for the regioselective preparation of olefins. For leading references, see: (a) Barluenga, J.; Yus, M.; Bernad, P. *J. Chem. Soc., Chem. Commun.* **1978**, 847. (b) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Chem. Research (S)* **1980**, 41; *(M)* **1980**, 677-692. (c) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Chem. Research (S)* **1980**, 324-325. (d) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Org. Chem.* **1981**, *46*, 2721-2726. (e) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Org. Chem.* **1983**, *48*, 609-611. (f) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Org. Chem.* **1983**, *48*, 3116-3118. (g) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P.; Alvarez, F. *J. Chem. Research (S)* **1984**, 122-123. (h) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P.; Alvarez, F. *J. Chem. Research (S)* **1985**, 128-129. (i) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1665.
3. (a) Barluenga, J.; Fañanás, F. J.; Yus, M.; Asensio, G. *Tetrahedron Lett.* **1978**, 2015-2016. (b) Barluenga, J.; Fañanás, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798-4801. (c) Barluenga, J.; Villamaña, J.; Fañanás, F. J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1982**, 355-356. (d) Barluenga, J.; Fañanás, F. J.; Villamaña, J.; Yus, M. *J. Org. Chem.* **1982**, *47*, 1560-1564. (e) Barluenga, J.; Fañanás, F. J.; Villamaña, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2685-2692.
4. (a) Barluenga, J.; Flórez, J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1153-1154. (b) Barluenga, J.; Flórez, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1983**, 3019-3026. (c) Nájera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289-300. (d) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1987**, 915-916. (e) Wittmann, V.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1091-1093. (f) Frey, O.; Hoffmann, M.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2026-2028.
5. (a) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *Tetrahedron Lett.* **1988**, *29*, 2859-2860. (b) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *Tetrahedron* **1989**, *45*, 2183-2192. (c) Barluenga, J.; Monserrat, J. M.; Flórez, J. *Tetrahedron Lett.* **1992**, *33*, 6183-6186. (d) Barluenga, J.; Monserrat, J. M.; Flórez, J. *J. Org. Chem.* **1993**, *58*, 5976-5980. (e) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2911-2922.
6. For a review, see: Holy, N. L. *Chem. Rev.* **1974**, *74*, 243-277.
7. (a) Bartmann, E. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 2653-654. (b) Cohen, T.; Jeong, I.-H.; Mudryk, B.; Bhupathy, M.; Awad, M. A. *J. Org. Chem.* **1990**, *55*, 1528-1536. (c) Conrow, R. E. *Tetrahedron Lett.* **1993**, *34*, 5553-5554. (d) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1907-1910. (e) Bachki, A.; Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2997-3008.
8. (a) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 1649-1652. (b) Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210-3215.
9. For a review, see: Yus, M. *Chem. Soc. Rev.* **1996**, 155-161.
10. Yus, M.; Ramón, D. J. *J. Chem. Soc., Chem. Commun.* **1991**, 398-400.
11. For leading references on the reaction of alkyl phenyl thioethers with lithium naphthalenide, see: (a) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064-1071. (b) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713-719. (c) Cohen, T.; Weisenfeld, R. B. *J. Org. Chem.* **1979**, *44*, 3601-3603.
12. An alternative possibility to the formation of 'reduced' products **3** (with E = H) from radical anion and/or radical intermediates can not be ruled out. We thank a referee for this suggestion.

13. This study was generously supported by DGICYT from the Spanish MEC (PB94-1514).

(*Received in UK* 24 *April* 1997; *revised* 20 *May* 1997; *accepted* 23 *May* 1997)