Pergamon

Tetrahedron Letters 40 (1999) 8173–8176

TETRAHEDRON
LETTERS

Phenyl Vinyl Thioether: A Convenient Source of the Ethylene 1,1-Dianion

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Received 7 July 1999; accepted 10 September 1999

Abstract: The successive reaction of phenyl vinyl thioether (**1**) with *n*-butyllithium and an electrophile [E_1= PhCHO, $(CH_2)_4CO$, $(CH_2)_5CO$] in THF at -78°C gives, after hydrolysis, the expected methylenic hydroxy thioethers (**2**). Deprotonation of **2** with *n*-butyllithium followed by a DTBB-catalysed lithiation and reaction with a second electrophile [E_2= ^{t}BuCHO, PhCHO, Me_2CO, $(CH_2)_5CO$], also at -78 C, gives after hydrolysis the corresponding methylenic 1,3-diols **3**. When carbon dioxide is used as the second electrophile, the expected methylenic hydroxy acid **3cd** is isolated. The whole process can be performed in a one-pot manner without isolation of the intermediates **2**.

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Keywords: Lithiation; Deprotonation; 1,3-Diols.

Non-stabilised polylithium synthons[1] are interesting intermediates in synthetic organic chemistry, because by reaction with an electrophile, they are able to form polyfunctionalised molecules in only one step. More interesting would be a sequential process in order to introduce different electrophilic fragments in the polyanion. Even though they are in general very unstable species, the stability of these type of polyanionic intermediate strongly depends on the relative position of the carbanionic centers. Considering the simplest anionic dilithio compounds, they can be prepared mainly by mercury-lithium exchange,[2] the corresponding *gem*-derivatives being particularly unstable because of the electronic accumulation at the same carbon atom. The only way to generate these latter compounds, by the convenient chlorine-lithium exchange, is to perform the lithiation under Barbier conditions, that is, in the presence of the electrophile.[3] Even using this procedure, it is necessary to perform the lithiation at low temperature activating the metal with a catalytic amount of an arene.[4,5]

In this paper we combine the well-known α-deprotonation of a phenyl thioether[6] with a sulfur-lithium exchange catalysed by an arene[4,7,8] in order to introduce two different electrophiles at one of the carbon atoms of ethylene in a very simple manner.

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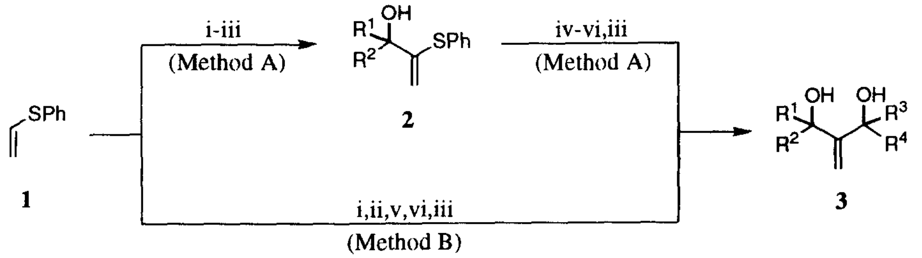
PII: S0040-4039(99)01731-1

The reaction of commercially available phenyl vinyl thioether (**1**) with *n*-butyllithium in the presence of tetramethylethylenediamine (TMEDA) in THF at -78°C followed by treatment with a carbonyl compound [E_1= PhCHO, $(CH_2)_4CO$, $(CH_2)_5CO$] led, after hydrolysis with water, to the expected unsaturated hydroxy thioethers **2**. These compounds, after deprotonation with *n*-butyllithium in THF at 0°C, were reductively lithiated using an excess of lithium and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 5 mol %). Reaction with a second carbonyl compound [E_2= ${}^tBuCHO$, PhCHO, Me_2CO, $(CH_2)_5CO$] gave, after hydrolysis with water, the expected methylenic 1,3-diols **3** (Scheme 1 and Table 1).



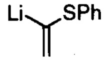
Scheme 1. *Reagents and conditions*: i, ${}^nBuLi$, TMEDA, THF, -78°C; ii, E_1= PhCHO, or $(CH_2)_4CO$, or $(CH_2)_5CO$, -78°C; iii, H_2O, -78 to 20°C; iv, ${}^nBuLi$, THF, 0°C; v, Li, DTBB cat. (5 mol %), -78°C; vi, E_2= ${}^tBuCHO$, or PhCHO, or Me_2CO, or $(CH_2)_5CO$, -78°C.

Table 1. Preparation of Compounds **2** and **3** (Step by Step Process; Method A)

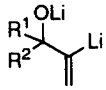
	Compound **2**[a]				Compound **3**[a]			
Entry	No.	R^1	R^2	Yield (%)[b,c]	No.	R^3	R^4	Yield (%)[b,d]
1	**2a**	H	Ph	66	**3aa**	H	Ph	41[e]
2	**2b**	$(CH_2)_4$		56	**3ba**	H	${}^tBu$	43
3	**2b**	$(CH_2)_4$		56	**3bb**	H	Ph	46
4	**2b**	$(CH_2)_4$		56	**3bc**	$(CH_2)_5$		35
5	**2c**	$(CH_2)_5$		74	**3ca**	Me	Me	33

[a] All compounds **2** and **3** were ≥95% pure (GLC and/or 300 MHz ^1H NMR). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate). [c] Based on the starting thioether **1**. [d] Based on the hydroxy thioether **2**. [e] Isolated as a *ca.* 2:1 diastereomeric mixture (75 MHz ^{13}C NMR).

As intermediates in the reaction, compounds **I** and **II**[9] should be involved in the first (**1** → **2**) and second step (**2** → **3**), respectively. On the other hand, when two prochiral carbonyl compounds are used as electrophiles, a mixture of diastereomers was obtained (Table 1, entry 1).

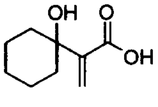


I



II

As a demonstration that other electrophiles different to carbonyl compounds can be used in the reaction, we used carbon dioxide in the second step after having introduced cyclohexanone as the first electrophile, and in this way the methylenic hydroxy acid **3cd** was obtained in 35% isolated yield.



3cd (35%)

Alternatively, the preparation of compounds **3** can be achieved more easily in a one-pot process, without isolation of alcohols **2**. Thus, once the lithium alcoholate derived from **2** was obtained, it was directly lithiated under the above mentioned reaction conditions and reacted with a second electrophile giving compound **3**, after hydrolysis (Method B; Scheme 1 and Table 2).

Table 2. Direct Preparation of Compounds **3** (One-pot Process; Method B)

Entry	No.[a]	R^1	R^2	R^3	R^4	Yield (%)[b]
1	**3ab**	H	Ph	Me	Me	42
2	**3ac**	H	Ph	$(CH_2)_5$		31
3	**3cb**	$(CH_2)_5$		$(CH_2)_5$		62
4	**3da**	H	^{t}Bu	Me	Me	20
5	**3db**	H	^{t}Bu	$(CH_2)_5$		50

[a] All compounds **3** were ≥94% pure (GLC and/or 300 MHz ^{1}H NMR). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate), based on the starting thioether **1**.

In conclusion, we have described here a simple way to generate a 1,1-dilithioethylene synthon starting from phenyl vinyl thioether and taking advantage of two well established reactions: (a) α-deprotonation of a thioether and (b) sulfur-lithium exchange. Following this procedure it is possible to introduce two different electrophilic fragments at the same position of ethylene, thus giving, in the case of carbonyl compounds, substituted 2-methylene 1,3-diols.

In a *typical procedure* for the one-pot reaction; to a 1.6 M solution of *n*-butyllithium in hexane (0.75 ml, 1.2 mmol) and TMEDA (0.15 ml, 1.0 mmol) in THF (3 ml) at -78°C was added phenyl vinyl thioether (**1**; 0.12 ml, 1.0 mmol) allowing the temperature to rise to 20°C during *ca.* 30 min. The first electrophile E_1 (1.2 mmol) was added to the resulting mixture at -78°C and after 5 min stirring at the same temperature, the mixture was added to a dark green suspension of lithium powder (100 mg, 14.0 mmol) and a catalytic amount of DTBB (30 mg, 0.11 mmol) in THF (5 ml) at -78°C. The resulting mixture was stirred for 1 h and then the second electrophile E_2 (1.2 mmol) was added. The mixture was stirred for 10 min, hydrolysed with water (10 ml) and extracted with ethyl acetate (3 x 25 ml). The organic layer was dried with anhydrous Na_2SO_4 and evaporated (15 Torr) to yield a residue which was purified by column chromatography (silica gel, hexane/ethyl acetate) and/or recrystallised to give pure compounds **3**.

Acknowledgements

This work was financially supported by the DGES from the Spanish Ministerio de Educación y Cultura (MEC) (project no. PB97-0133).

References and Notes

1. For a recent review, see: Foubelo, F.; Yus, M. *Trends Org. Chem.* **1998**, *7*, 1-26.
2. For a review, see: Maercker, A. In *Lithium Chemistry, a Theoretical and Experimental Overview*; Sapse, A. M.; Schleyer, P. v. R., Eds.; J. Wiley & Sons: New York, 1995.
3. For reviews, see: (a) Blomberg, C. *The Barbier Reaction and Related One-step Processes*; Springer Verlag: Berlin, 1993. (b) Alonso, F.; Yus, M. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 397-436.
4. (a) First account: Ramón, D. J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1991**, 398-400. (b) For a review, see: Yus, M. *Chem. Soc. Rev.* **1996**, 155-161.
5. Previous paper on this topic from our laboratory: Guijarro, A.; Yus, M. *Tetrahedron* **1996**, *52*, 1797-1810.
6. See, for instance: Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097-4099.
7. (a) For a review on the stoichiometric version of the sulfur-lithium exchange, see: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152-161. (b) For a recent application of this stoichiometric lithiation reaction to a ketene thioacetal, see: Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569-11584.
8. Previous paper on this topic from our laboratory: Foubelo, F.; Gutiérrez, A.; Yus, M. *Synthesis* **1999**, 503-514 (Feature article).
9. For reviews on functionalised organolithium compounds of these type, see: (a) Nájera, C.; Yus, M. *Trends Org.Chem.* **1991**, *2*, 155-181. (b) Nájera, C.; Yus, M. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67-96.