



# 1,3-Bis(phenylmercapto)propane and 1-chloro-3-(phenylmercapto)propane: useful precursors for 1,3-dilithiopropene synthons in the preparation of 1,5-diols

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## Abstract

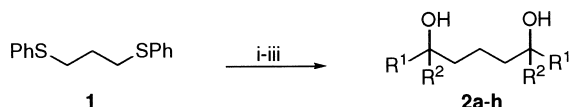
Treatment of 1,3-bis(phenylmercapto)propane (**1**) with an excess of lithium and a catalytic amount of DTBB (3.5 mol%) at  $-78^{\circ}\text{C}$  followed by reaction with a carbonyl compound [*t*BuCHO, PhCHO, (PhCH<sub>2</sub>)<sub>2</sub>CO, Et<sub>2</sub>CO, (CH<sub>2</sub>)<sub>5</sub>CO, (CH<sub>2</sub>)<sub>7</sub>CO, (-)-menthone, Ph<sub>2</sub>CO] leads, after hydrolysis with water, to symmetrically substituted 1,5-diols (**2**). Starting from 1-chloro-3-(phenylmercapto)propane (**3**) and by successive treatment with: (a) lithium–naphthalene at  $-78^{\circ}\text{C}$ ; (b) a carbonyl compound {Me<sub>2</sub>CO, (CH<sub>2</sub>)<sub>5</sub>CO, (CH<sub>2</sub>)<sub>7</sub>CO, (-)-menthone, [CH<sub>3</sub>(CH<sub>2</sub>)<sub>4</sub>]<sub>2</sub>CO} at the same temperature; (c) lithium powder at  $-50^{\circ}\text{C}$ ; and (d) a second carbonyl compound [*t*BuCHO, PhCHO] at the same temperature and final hydrolysis with water yields unsymmetrically substituted 1,5-diols (**4**). © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* 1,3-dilithiopropene synthon; sulfur–lithium exchange; DTBB-catalysed lithiation.

Among the methodologies to generate organolithium reagents,<sup>1</sup> one of the most important uses halogenated starting materials,<sup>2</sup> mainly chlorinated and brominated compounds. An alternative to this general method consists of using a phenylthioether:<sup>3,4</sup> in this case it is necessary to use lithium–arene<sup>5</sup> as the lithiation reagent in order to get the formation of the corresponding alkyl–lithium compound in a regioselective manner. A catalytic version<sup>6,7</sup> of this procedure has been recently used<sup>8</sup> for the preparation of functionalised organolithium compounds.<sup>9</sup> On the other hand, when two phenylmercapto units are present in the same molecule, the stoichiometric lithium–arene reaction works only for dibenzylic derivatives<sup>3b</sup> in order to prepare dilithium reagents.<sup>10</sup> In the case of aliphatic di(phenylthio) ethers only one sulfur/lithium exchange took place.<sup>3</sup> For the above-mentioned reasons, we decided to apply the more potent catalytic version of the arene-promoted lithiation<sup>6,7</sup> to this type of compound, and to study the same reaction with chlorinated phenyl thioethers in order to discriminate both carbon/lithium bonds, so making possible the introduction of two different electrophilic fragments.<sup>11</sup>

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The reaction of 1,3-bis(phenylmercapto)propane (**1**) with an excess of lithium powder and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB, 3.5 mol%) in THF at  $-78^{\circ}\text{C}$  for 2 h, followed by treatment with a carbonyl compound at the same temperature and final hydrolysis with water, led to the formation of the corresponding 1,5-diols **2a–h**, containing the same substituents at both sides of the molecule (Scheme 1 and Table 1). When a prochiral carbonyl compound such as an aldehyde was used, a 1/1 diastereomeric mixture of the corresponding diols was obtained (Table 1, entries 1–3). However, only one diastereoisomer was isolated from (–)-menthone, resulting probably from attack of the organolithium compound to the less hindered face of the ketone (Table 1, entry 7).<sup>11b</sup>

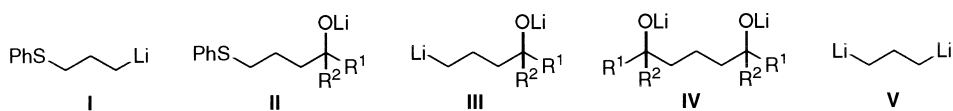


Scheme 1. (i) Li, DTBB cat. (3.5 mol%), THF,  $-78^{\circ}\text{C}$ ; (ii)  $\text{R}^1\text{R}^2\text{CO}$ ,  $-78^{\circ}\text{C}$ ; (iii)  $\text{H}_2\text{O}$ ,  $-78$  to  $20^{\circ}\text{C}$

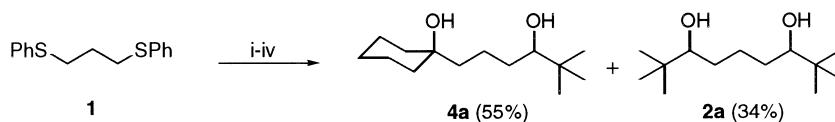
Table 1  
Preparation of compounds **2**

Entry	Carbonyl compound	Product <b>2</b> <sup>a</sup>			
		Structure	No.	Yield (%) <sup>b</sup>	$R_f$ <sup>c</sup>
1 <sup>d</sup>	BuCHO		<b>2a</b>	34 <sup>e,f</sup>	0.31
2 <sup>d</sup>	PhCHO		<b>2b</b>	52 <sup>f</sup>	0.19
3	PhCH <sub>2</sub> CHO		<b>2c</b>	35 <sup>f</sup>	0.14
4	Et <sub>2</sub> CO		<b>2d</b>	59	0.22
5	(CH <sub>2</sub> ) <sub>5</sub> CO		<b>2e</b>	66	0.17
6	(CH <sub>2</sub> ) <sub>7</sub> CO		<b>2f</b>	68	0.15
7	(–)-menthone		<b>2g</b>	58 <sup>g</sup>	0.71
8	Ph <sub>2</sub> CO		<b>2h</b>	45	0.57

<sup>a</sup> All compounds **2** were  $\geq 95\%$  pure (GLC and/or 300 MHz  $^1\text{H}$  NMR) and were fully characterised by spectroscopic means (IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR, and MS). <sup>b</sup> Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting dithioether **1**. <sup>c</sup> Silica gel, hexane/ethyl acetate: 2/1. <sup>d</sup> The lithiation step was carried out during 40 min. <sup>e</sup> A 61% of compound **4** was also isolated. <sup>f</sup> A ca. 1/1 mixture of diastereomers was obtained (75 MHz  $^{13}\text{C}$  NMR). <sup>g</sup> Only one stereoisomer (75 MHz  $^{13}\text{C}$  NMR) was obtained.

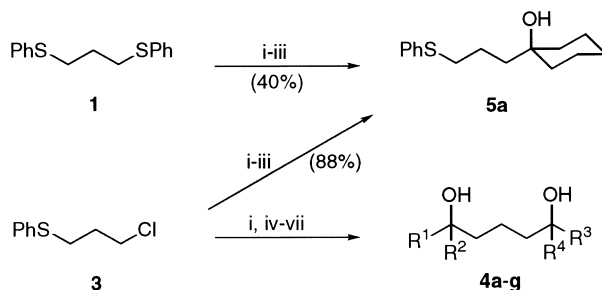


Concerning a possible mechanistic pathway, two alternatives are: (a) a step-by-step lithiation– $S_E$  reaction involving intermediates **I–IV**; or (b) generation of a dilithiated intermediate of type **V**. Since the whole process is carried out in a two-step reaction (first lithiation and then addition of the electrophile in the presence of the excess of lithium), both processes can be possible. In order to clarify this question we tried to introduce two different electrophiles using the protocol shown in Scheme 1. Thus, using pivalaldehyde and cyclohexanone, and allowing the temperature to rise to  $-50^\circ\text{C}$  in the second lithiation– $S_E$  process, we obtained, together with the expected ‘mixed’ product **4a**, an important amount (34%) of the corresponding 1,5-diol **2a** resulting from the double introduction of the first electrophile (Scheme 2). From this result we can conclude that both pathways can occur simultaneously. Pathway (a) can also explain this result if cyclohexanone is more reactive than pivalaldehyde.



Scheme 2. (i) Li, DTBB cat. (3.5 mol%), THF,  $-78^\circ\text{C}$ ; (ii)  $\text{Bu}^t\text{CHO}$ ,  $-78$  to  $-50^\circ\text{C}$ ; (iii)  $(\text{CH}_2)_5\text{CO}$ ,  $-50^\circ\text{C}$ ; (iv)  $\text{H}_2\text{O}$ ,  $-50$  to  $20^\circ\text{C}$

Just to take advantage of the monolithiation of bis(phenylthioethers),<sup>3a</sup> we performed the lithiation of the starting materials **1** with lithium–naphthalene at low temperature: using cyclohexanone as electrophile we obtained the expected compound **5a** (through the corresponding intermediate of type **II**) in 40% yield (Scheme 3). In order to improve this yield we started from the chlorinated thioether **3** and using the same protocol the yield rose to 88% (Scheme 3). The last process is useful for the introduction of two different electrophiles in the molecule of the dianionic synthon of type **V**. Thus, compound **3** was lithiated with lithium–naphthalene and reacted with a first electrophile ( $\text{R}^1\text{R}^2\text{CO}$ ) at temperatures ranging from  $-78$  to  $-50^\circ\text{C}$ . Then the



Scheme 3. (i)  $\text{LiC}_{10}\text{H}_8$ , THF,  $-78^\circ\text{C}$ ; (ii)  $(\text{CH}_2)_5\text{CO}$ ,  $-78^\circ\text{C}$ ; (iii)  $\text{H}_2\text{O}$ ,  $-78$  to  $20^\circ\text{C}$ ; (iv)  $\text{R}^1\text{R}^2\text{CO}$ ,  $-78$  to  $-50^\circ\text{C}$ ; (v) Li,  $-50^\circ\text{C}$ ; (vi)  $\text{R}^3\text{R}^4\text{CO}$ ,  $-50^\circ\text{C}$ ; (vii)  $\text{H}_2\text{O}$ ,  $-50$  to  $20^\circ\text{C}$

reaction mixture was treated with an excess of lithium so that, under these reaction conditions (rather similar to those of the catalytic version of the lithiation), a second lithiation occurred giving an intermediate of type **III**, which, after successive treatment with a second carbonyl compound ( $R^3R^4CO$ ) at  $-50^\circ C$  and hydrolysis with water at the same temperature, gave the expected 'mixed' 1,5-diols **4a–g** (Scheme 3 and Table 2). Also in this case, the use of two prochiral carbonyl compounds, such as (–)-menthone and pivalaldehyde afforded a 4/1 diastereomeric mixture of the corresponding diols **4e** (Table 2, entry 5).

Table 2  
Preparation of compounds **4**

Entry	First carbonyl compound	Second carbonyl compound	Product <b>4</b> <sup>a</sup>			
			Structure	No.	Yield (%) <sup>b</sup>	$R_f$ <sup>c</sup>
1	$(CH_2)_5CO$	Bu <sup>t</sup> CHO		<b>4a</b>	74	0.18
2	$(CH_2)_5CO$	PhCHO		<b>4b</b>	68	0.19
3	$(CH_2)_7CO$	PhCHO		<b>4c</b>	72	0.16
4	Me <sub>2</sub> CO	Bu <sup>t</sup> CHO		<b>4d</b>	60	0.16
5	(–)-menthone	Bu <sup>t</sup> CHO		<b>4e</b>	41 <sup>d</sup>	0.68
6	$[Me(CH_2)_4]_2CO$	Bu <sup>t</sup> CHO		<b>4f</b>	77	0.51
7	$[Me(CH_2)_4]_2CO$	PhCHO		<b>4g</b>	80	0.39

<sup>a</sup> All compounds **4** were  $\geq 95\%$  pure (GLC and/or 300 MHz  $^1H$  NMR) and were fully characterised by spectroscopic means (IR,  $^1H$  and  $^{13}C$  NMR, and MS). <sup>b</sup> Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting chlorothioether **3**. <sup>c</sup> Silica gel, hexane/ethyl acetate: 2/1. <sup>d</sup> A *ca.* 4/1 mixture of diastereomers was obtained (75 MHz  $^{13}C$  NMR).

In conclusion, the use of starting materials **1** and **3** allows the generation of a dianionic synthon of type **III**, which can be successfully used to generate symmetrically or unsymmetrically substituted 1,5-diols, respectively. Compounds of this type are appropriate starting materials for cyclic ethers by intramolecular dehydration.<sup>12,13</sup>

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## References

1. Jenkins, P. R. *Organometallic Reagents in Synthesis*; Oxford University Press: Oxford, 1997.
2. (a) For a recent review on the preparation of organolithium compounds from non-halogenated precursors, see: Guijarro, D.; Yus, M. *Recent Res. Devel. Org. Chem.* **1998**, *2*, 713–744. (b) For a previous paper on this topic from our laboratory, see: Alonso, E.; Guijarro, D.; Martínez, P.; Ramón, D. J.; Yus, M. *Tetrahedron* **1999**, *55*, 11027–11038.
3. For leading references, 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) Kustas, I. D.; Screttas, C. G. *J. Org. Chem.* **1997**, *62*, 5575–5577.
4. For a review on reductive cleavage of phenyl thioethers, see: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152–161.
5. For a review, see: Holy, N. L. *Chem. Rev.* **1974**, *74*, 243–277.
6. For a first account, see: Ramón, D. J.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1991**, 398–400.
7. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, 155–161. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237.
8. (a) Foubelo, F.; Gutiérrez, A.; Yus, M. *Synthesis* **1999**, 503–514 (feature article). (b) Foubelo, F.; Gutiérrez, A.; Yus, M. *Tetrahedron Lett.* **1999**, *40*, 8173–8176. (c) Foubelo, F.; Gutiérrez, A.; Yus, M. *Tetrahedron Lett.* **1999**, *40*, 8177–8180.
9. For reviews, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *1*, 155–181. (b) Nájera, C.; Yus, M. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67–96. (c) Yus, M.; Foubelo, F. *Rev. Heteroatom Chem.* **1997**, *17*, 73–107.
10. For a recent review, see: Foubelo, F.; Yus, M. *Trends Org. Chem.* **1998**, *7*, 1–26.
11. For a related lithiation of chlorinated phenyl ethers, see: (a) Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1999**, *40*, 743–746. (b) Foubelo, F.; Saleh, S. A.; Yus, M. *J. Org. Chem.* submitted.
12. See, for instance: (a) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3351–3364. (b) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3365–3374.
13. (a) *Typical procedure for 2a*: To a cooled ( $-78^{\circ}\text{C}$ ) blue suspension of lithium powder (105 mg, 15.0 mmol) and a catalytic amount of DTBB (40 mg, 0.15 mmol) in THF (3 ml) was added dropwise 1,3-bis(phenylmercapto)propane (**1**, 260 mg, 0.17 ml, 1.0 mmol) under nitrogen and the mixture was stirred at the same temperature for 40 min. Then pivalaldehyde (189 mg, 0.245 ml, 2.2 mmol) was added dropwise. The mixture was stirred at the same temperature for 1.5 h and cyclohexanone (107 mg, 0.113 ml, 1.1 mmol) was added dropwise and after 15 min it was hydrolysed with water (5 ml). The resulting mixture was extracted with ethyl acetate ( $3 \times 15$  ml). The organic layer was dried over anhydrous sodium sulfate and evaporated (15 torr). The residue was then purified by column chromatography (silica gel: hexane:ethyl acetate) to yield 74 mg (34%) of compound **2a** as a 1:1 diastereomeric mixture and 125 mg (55%) of compound **4a**. (b) *Typical procedure for 4a*: To a cooled ( $-78^{\circ}\text{C}$ ) solution of 1-chloro-3-(phenylmercapto)propane (**3**, 190 mg, 0.15 ml, 1.0 mmol) in THF (2 ml) was added dropwise a 0.7 M THF solution (3.2 ml, 2.2 mmol) of lithium–naphthalene and the mixture was stirred at the same temperature for 20 min. Then cyclohexanone (107 mg, 0.113 ml, 1.1 mmol) was added dropwise at  $-78^{\circ}\text{C}$  and after 10 min, lithium powder (28 mg, 4.0 mmol) was also added at once. The reaction mixture was stirred for 1.5 h at around  $-50^{\circ}\text{C}$  and pivalaldehyde was added dropwise (95 mg, 0.123 ml, 1.1 mmol) at the same temperature. The mixture was stirred at the same temperature for 15 min and hydrolysed and work up as for **2a** to yield 168 mg (74%) of compound **4a**.