Tetrahedron Letters 49 (2008) 5182–5185

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

1,3-Dilithio-2-(diphenylmethylene)propane

Victor J. Lillo, Cecilia Gómez *, Miguel Yus *

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

ARTICLE INFO

Article history:
Received 14 April 2008
Revised 10 June 2008
Accepted 13 June 2008
Available online 18 June 2008

Dedicated to Professor Gregorio Asensio on occasion of his 60th birthday

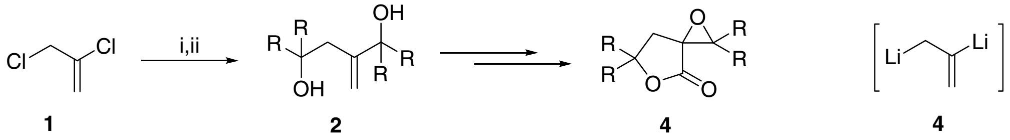
Keywords:
1,3-Dilithiopropane derivative
Cyclopropane ring opening
DTBB-catalysed lithiation
Aliphatic S_E reaction
Lithium

ABSTRACT

The reaction of 2,2-diphenylmethylenecyclopropane (**5**) with an excess of lithium and a catalytic amount of DTBB (4 mol %) in THF at −78 °C leads to the formation of dilithiated species **6**–**8** by reductive opening of the cyclopropane ring. Further reaction of these intermediates with different electrophiles [E = H_2O, D_2O, $CH_2{=}CMeCH_2Cl$, Me_3SiCl, Me_3SiCH_2Cl, *t*-BuCHO, Me_2CO, Et_2CO, *n*-Pr_2CO, *i*-Pr_2CO, *t*-Bu_2CO, $(CH_2)_5CO$, Ph_2CO and adamantanone] is highly regioselective, yielding exclusively the corresponding products **9**, after hydrolysis with water. However, when 3-chloro-2-(chloromethyl)propene (**14**) is used as a dielectrophile, the cyclisation to give a six-membered ring takes place through intermediate **6**, giving compound **16** as the only reaction product.

The world of dilithium intermediates,[1] which can be considered as functionalised organolithium compounds,[2] has some similarities with that of simple organolithium reagents.[3] Most of the general methods for their preparation, including deprotonation, halogen–lithium exchange or metal–lithium transmetallation, can be applied to generate these dianionic synthons, the main problem being their low stability even under very mild reaction conditions. Amongst the different possible methodologies available, the double chlorine–lithium exchange of an adequate dichlorinated material using an arene-catalysed lithiation[4] has shown to be a practical procedure for the in situ generation of dilithium synthons. These species are able to react with an electrophile present in the reaction medium (Barbier-type reaction conditions)[5] to give the expected difunctionalised products.[6] As an example, Scheme 1 shows the 4,4′-di-*tert*-butylbiphenyl (DTBB)-catalysed lithiation of 2,3-dichloropropene (**1**) in the presence of different carbonyl compounds to yield, after hydrolysis, the corresponding unsaturated diols **2**. These compounds are appropriate precursors for dioxaspiroheptanones **3**, which are present in many naturally occurring compounds.[7] The formation of compounds **2** would involve a dilithiated species of type **4**.

Concerning the generation of dilithio derivatives by reductive ring opening of substituted cyclopropanes, and related to the well-known topic of Y-aromaticity in the trimethylenemethane dianion,[8–10] Maercker[11] and more recently our group[12] have studied the formation of dilithiated species by reaction of substituted cyclopropanes with lithium metal or lithium in the presence of a catalytic amount of an arene,[4] respectively. In general, these reactions show a series of problems associated with (a) lithium migrations, (b) lithium-hydride eliminations, (c) lithium–hydrogen exchange (hydrogen abstraction), (d) *ortho*-lithiation in phenyl derivatives, and (e) carbon–carbon coupling reactions through

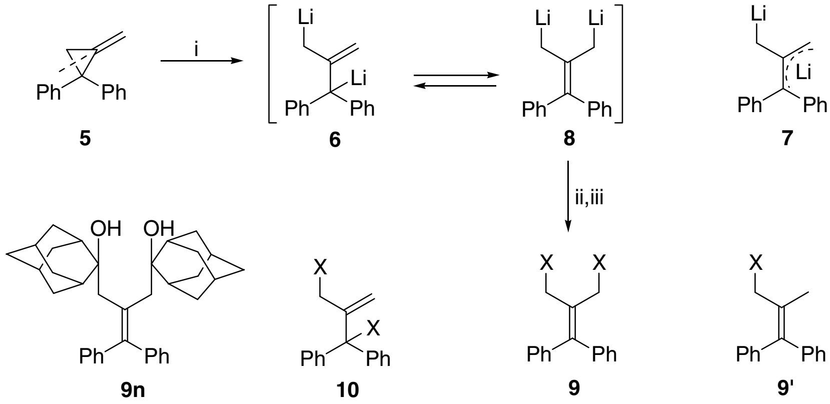


Scheme 1. Reagents and conditions: (i) Li, DTBB (4%), R_2CO, THF, 0 °C to rt; (ii) H_2O.

---

* Corresponding authors. Fax: + 34 965 903549.
E-mail addresses: cgomez@ua.es (C. Gómez), yus@ua.es (M. Yus).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.065



Scheme 2. Reagents and conditions: (i) Li (1:7 molar ratio), DTBB (4% molar), THF, −78 °C, 1.5 h; (ii) E = H_2O, D_2O, $CH_2{=}CMeCH_2Cl$, Me_3SiCl, Me_3SiCH_2Cl, *t*-BuCHO, Me_2CO, Et_2CO, *n*-Pr_2CO, *i*-Pr_2CO, *t*-Bu_2CO, $(CH_2)_5CO$, Ph_2CO and adamantanone (2.2 equiv), −78 to −65 °C, 30 min; (iii) H_2O, −65 °C to rt, 1 h.

the initially formed radical-anions. Therefore, mixtures of different products are frequently obtained, limiting the applicability of this methodology from a synthetic point of view.

In this Letter, we report the generation of a 2-substituted 1,3-dilithio compound through an arene-catalysed regioselective lithiation of a substituted methylenecyclopropane.

The reaction of 2,2-diphenylmethylenecyclopropane (**5**)[11d] with an excess of lithium (1:7 molar ratio) and a catalytic amount of DTBB (1:0.08, 4% molar) in THF at −78 °C for 1.5 h led to the initial formation of a dilithio derivative **6**, which is in equilibrium with the intermediate **8** through the allyl-delocalised species **7**. After treatment of the reaction mixture with different electrophiles [E = H_2O, D_2O, $CH_2{=}CMeCH_2Cl$, Me_3SiCl, Me_3SiCH_2Cl, *t*-BuCHO, Me_2CO, Et_2CO, *n*-Pr_2CO, *i*-Pr_2CO, *t*-Bu_2CO, $(CH_2)_5CO$, Ph_2CO and adamantanone; 1:2.2 molar ratio] at temperatures ranging between −78 and −65 °C for 30 min, followed by hydrolysis with water at −65 °C to rt, compounds **9** were obtained (Scheme 2 and Table 1).

Table 1
Preparation of compounds **9**

Entry	Electrophile E	Product[a]		
		No.	X	Yield[b] (%)
1	H_2O	**9a + 10a**	H	85 (3:2)
2	D_2O	**9b + 10b**	D	79 (3:2)[c]
3	$CH_2{=}CMeCH_2Cl$	**9c**	$CH_2{=}CMeCH_2$	49[d]
4	Me_3SiCl	**9d**	Me_3Si	45[d]
5	Me_3SiCH_2Cl	**9e**	Me_3SiCH_2	53[d]
6	*t*-BuCHO	**9f**	*t*-BuCHOH	55[d,e]
7	Me_2CO	**9g**	Me_2COH	44[f]
8	Et_2CO	**9h**	Et_2COH	48
9	*n*-Pr_2CO	**9i**	*n*-Pr_2COH	56[f]
10	*i*-Pr_2CO	**9j**	*i*-Pr_2COH	42[g]
11	*t*-Bu_2CO	**9k′**	*t*-Bu_2COH	58[f]
12	$(CH_2)_5CO$	**9l**	$(CH_2)_5COH$	46
13	Ph_2CO	**9m**	Ph_2COH	40
14	Adamantanone	**9n**	—[h]	76[f]

[a] All products **9** (and **10**) were fully characterised by analytical (microanalysis and/or HRMS) and spectroscopic means (IR, ^1H and ^{13}C NMR, and MS).

[b] Isolated yield of pure compounds (>95% from NMR and/or GLC) after column chromatography (silica gel, hexane–EtOAc) unless otherwise stated.

[c] The content of D was found to be >95% by MS.

[d] The excess of lithium was removed by filtration at the same temperature after the lithiation step.

[e] A ca. 1:1 mixture of diastereomers (NMR) was obtained.

[f] Yield after recrystallisation from hexane/Et_2O.

[g] A 16% of the corresponding monosubstituted product **9j′** was also obtained.

[h] See Scheme 2.

Only for very reactive electrophiles, such as H_2O and D_2O, we obtained a mixture of compounds **9** and **10**, resulting from the reaction of the electrophile with the intermediates **8** and **6**, respectively (Table 1, entries 1 and 2). In all the other cases, the formation of compounds **10** was not detected in the reaction crudes. For chlorinated electrophiles (Table 1, entries 3–5) and pivalaldehyde (Table 1, entry 6), the best results were obtained by filtering off the excess of lithium at the end of the first step (Table 1, footnote d). In almost all cases [except for the diisopropylketone derivative (Table 1, entry 10 and footnote g)] we detected small amounts (<10%, GLC) of the monosubstituted product of type **9′**. This product is formed by hydrogen abstraction,[13] either from intermediate **8** or after the incorporation of the first electrophilic fragment, by lithium–hydrogen exchange from the reaction medium.[13] Chromatographic separation of compounds **9′** during purification of products **9** was easily performed, although in the case of the hindered di(*tert*-butyl)ketone, compound **9k′** was the only reaction product isolated, due probably to steric problems (Table 1, entry 11). Concerning the reaction conditions, the reaction gave lower yields and not so clean reaction crudes when the process was performed in the presence of the electrophile (Barbier conditions)[5] or at higher temperatures.

The X-ray structure of compound **9h** (Fig. 1) confirmed all the analytical and spectroscopic data obtained for this selected example and for all the members of the series.

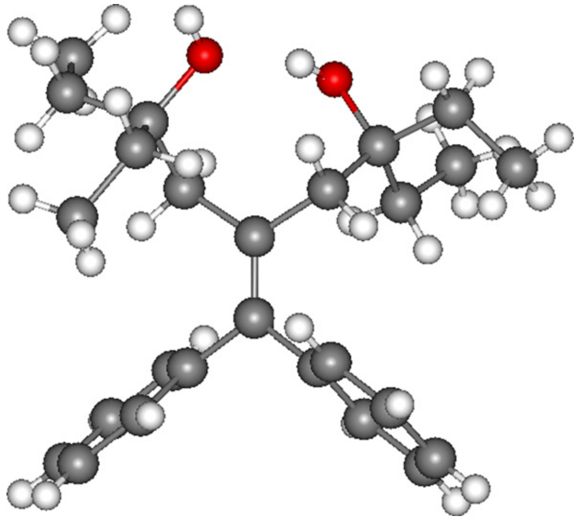
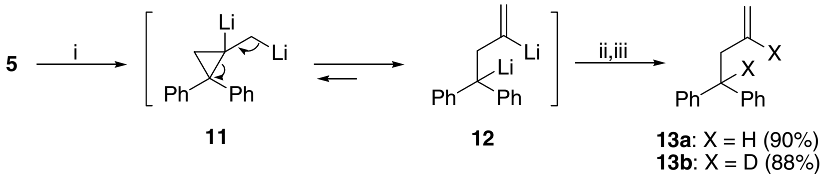


Figure 1. X-ray structure of compound **9h**.

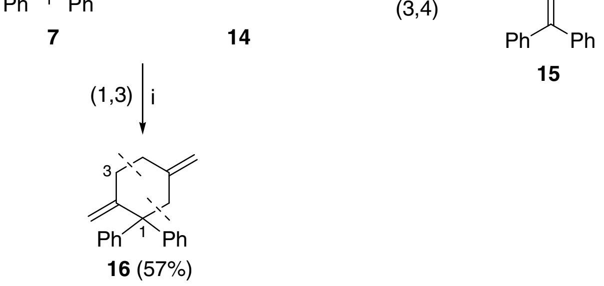


Scheme 3. Reagents and conditions: (i) Li (1:7 molar ratio), naphthalene (4% molar), Et$_2$O, rt, 3 h; (ii) E = H$_2$O, D$_2$O, −78 °C, 1 h; (iii) H$_2$O, −78 °C to rt, 1 h.

As regards the role of the catalyst, we observed that the process could also be carried out in the absence of DTBB under the same reaction conditions, but reaction times were slightly longer, the reaction crudes were not clean and yields were lower. An interesting effect was observed when naphthalene[14] was used instead of DTBB and ether as the solvent at room temperature: in this case, compounds **13** were the reaction products when using water and deuterium oxide as electrophiles, resulting from an initial addition of two lithium atoms to the double bond (generally proposed by Maercker in similar cases[11]) to form intermediate **11**.[15] This species undergoes subsequent ring opening to give the most stable benzylic derivative **12** (Scheme 3). Compounds **13a** and **13b** (>95% D from MS) were obtained in good yields after quenching with H$_2$O or D$_2$O. As it can be seen, the reaction results can be controlled depending on the reaction conditions: in our case (THF, low temperature, DTBB-catalysis), only compounds **9** were isolated, whereas isomers **13** were obtained by using Maercker conditions (and naphthalene as the electron carrier catalyst). Finally, since the same results (compound **13**) were obtained in the absence of any arene, we conclude that the effects of temperature[16] and/or solvent are responsible of the different behaviour observed in Schemes 2 and 3. However, even this case being, we do not have any simple explanation for these facts.

In the last part of this study, we tried to take advantage of the dianionic character of intermediates **6–8** in order to obtain cyclic compounds by reaction with a dielectrophile. Thus, once the dianionic species was generated as described above (Scheme 2), it was treated with 3-chloro-2-(chloromethyl)propene (**14**) and hydrolysed with water. Surprisingly, we obtained exclusively the corresponding di-*exo* olefin **16**, resulting from the reaction of the intermediate **6** with the electrophile, instead of the expected cyclic product **15** (by cyclisation with intermediate **8**), (Scheme 4). So far, we do not have any explanation to rationalise the regiochemistry shown in Scheme 4.

In summary, we have described herein the easy generation of a 2-substituted 1,3-dilithiopropane using a very simple methodology, the DTBB-catalysed lithiation of a substituted methylenecyclopropane. This dianion has been trapped with different electrophiles, especially carbonyl compounds affording interesting 1,5-diols.



Scheme 4. Reagents and conditions: (i) −78 to −50 °C, 1 h and then H$_2$O, −50 °C to rt, 1 h.

Acknowledgements

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; Grants CTQ2007-65218/BQU and Consolider Ingenio 2010, CSD2007-00006). V.L. thanks the University of Alicante for a predoctoral fellowship. We also thank Medalchemy S.L. for a gift of chemicals, especially lithium powder.

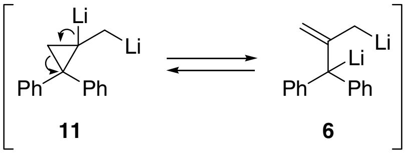
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.065.

References and notes

1. For reviews, see: (a) Foubelo, F.; Yus, M. *Trends Org. Chem.* **1998**, *7*, 1–26; (b) Foubelo, F.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 459–490. For a monograph, see: (c) Strohmann, C.; Schildbach, D. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, UK, 2004; pp 941–996.
2. For reviews, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155–181; (b) Nájera, C.; Yus, M. *Org. Prep. Proced. Int.* **1995**, *27*, 383–457; (c) Nájera, C.; Yus, M. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67–96; (d) Yus, M.; Foubelo, F. *Rev. Heteroatom Chem.* **1997**, *17*, 73–107; (e) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867–926; (f) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255–9303; (g) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667–2722; (h) See also the special issue of Tetrahedron Symposium-in-Print: Nájera, C., Yus, M., (Eds.), devoted to 'Functionalised Organolithium Compounds', *Tetrahedron* **2005**, *61*, 3139–3450.; (i) Yus, M.; Foubelo, F. In *Functionalised Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005. Chapter 2.
3. For monographs, see: (a) Wakefield, B. J. *Organolithium Methods*; Academic: London, 1988; (b) *Lithium Chemistry: A Theoretical and Experimental Overview*; Sapse, A. M., von Ragué Schleyer, P., Eds.; John Wiley & Sons: New York, NY, 1995; (c) Gray, M.; Tinkel, M.; Sniekus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., McKillop, A., Eds.; Pergamon: Oxford, 1995; Vol. 11, pp 1–92; (d) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002; (e) *The Chemistry of Organolithium Compounds*; Rappopoprt, Z., Marek, I., Eds.; Wiley: Chichester, UK, 2004.
4. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155–161; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237; (c) Yus, M. *Synlett* **2001**, 1197–1205; (d) Yus, M.; Ramón, D. J. *Lat. J. Chem.* **2002**, 79–92; (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 75–115; (f) Yus, M. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: Chichester, 2004; Vol. 1, Part 2, Chapter 11. For mechanistic studies, see: (g) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455–3458; (h) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574–2584; (i) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 1309–1312; (j) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 1313–1316; (k) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 5025–5027; (l) Melero, C.; Guijarro, A.; Baumann, V.; Pérer-Jiménez, A. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, 5514–5526; (m) Melero, C.; Herrera, R. P.; Guijarro, A.; Yus, M. *Chem. Eur. J.* **2007**, *13*, 10096–10107. For a polymer supported arene-catalysed version of this reaction, see: (n) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1397–1400; (o) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017–7026; (p) Yus, M.; Candela, P.; Gómez, C. *Tetrahedron* **2002**, *58*, 6207–6210; (q) Alonso, F.; Gómez, C.; Candela, P.; Yus, M. *Adv. Synth. Catal.* **2003**, *345*, 275–279; (r) Candela, P.; Gómez, C.; Yus, M. *Russ. J. Org. Chem.* **2004**, *40*, 795–801.
5. For a review on Barbier-type reactions, see: Alonso, F.; Yus, M. *Recent Devel. Org. Chem.* **1997**, *1*, 397–436.
6. For some examples from our group, see: (a) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1992**, *33*, 2217–2220; (b) Gómez, C.; Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 4117–4126; (c) Alonso, F.; Lorenzo, E.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 2187–2190; (d) Lorenzo, E.; Alonso, F.; Yus, M. *Tetrahedron* **2000**, *56*, 1745–1757; (e) Alonso, F.; Falvello, L. R.; Fanwick, P. E.; Lorenzo, E.; Yus, M. *Synthesis* **2000**, 949–952; For a review, see: (f) Alonso, F.; Meléndez, J.; Yus, M. *Russ. Chem. Bull.* **2003**, *52*, 2628–2635.
7. Alonso, F.; Meléndez, J.; Yus, M. *Helv. Chim. Acta* **2002**, *85*, 3262–3271.

8. See, for instance: (a) Klein, J. *Tetrahedron* **1983**, *39*, 2733–2759; (b) Klein, J. *Tetrahedron* **1988**, *44*, 503–518; (c) See also Refs. 6a,b.
9. For X-ray structural determination[9a] and reactivity of a triphenyl derivative, see: (a) Wilhelm, D.; Dietrich, H.; Clark, T.; Mahdi, W.; Kos, A. J.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1984**, *106*, 7279–7280; (b) Witt, O.; Mauser, H.; Friedl, T.; Wilhelm, D.; Clark, T. *J. Org. Chem.* **1998**, *63*, 959–967.
10. For studies (mainly DFT calculations) of a radical anion[10a] or a radical cation[10b] derivative from a diphenyl derivative, see: (a) Ikeda, H.; Namai, H.; Kato, N.; Ikeda, T. *Tetrahedron Lett.* **2006**, *47*, 1501–1504; (b) Ikeda, H.; Namai, H.; Kato, N.; Ikeda, T. *Tetrahedron Lett.* **2006**, *47*, 1857–1860.
11. (a) Maercker, A.; Klein, K.-D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 83–84; (b) Maercker, A.; Girreser, U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 667–669; (c) Maercker, A.; Daub, V. E. E. *Tetrahedron* **1994**, *50*, 2439–2458; (d) Maercker, A.; Oeffner, K. S.; Girreser, U. *Tetrahedron* **2004**, *60*, 8245–8256.
12. Gómez, C.; Lillo, V. J.; Yus, M. *Tetrahedron* **2007**, *63*, 4655–4662.
13. The proton abstraction can occur at the α-position of THF. See, for instance: Clayden, J.; Yasin, S. A. *New J. Chem.* **2002**, *26*, 191–192.
14. The reaction in the absence of naphthalene[11] gave the same reaction products but much slower. For instance, by using water as the electrophile, total conversion was achieved after 3 h in the presence of naphthalene, whereas only ca. 30% conversion was observed in its absence.
15. One referee suggested that intermediate **6** (Scheme 2) could also be generated from intermediate **11** through a different β-elimination process as follows:



We thank the referee for this interesting suggestion.

16. The same process at room temperature gave the same results but with poorer yield, and the reaction crude was not clean. Under these conditions a proton abstraction from the solvent decomposed partially the lithiated intermediates (see Ref. 13).