Pergamon

Tetrahedron Letters 42 (2001) 6819–6822

TETRAHEDRON
LETTERS

A new method for the preparation of 1,3-dilithiopropyne: an efficient synthesis of homopropargyl alcohols[†]

Jorge A. Cabezas,* Albán R. Pereira and Adam Amey

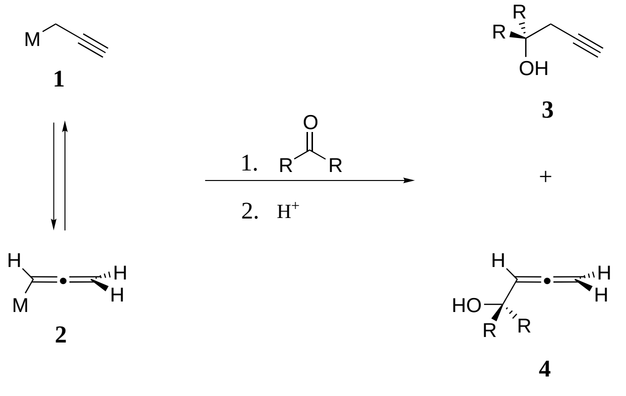
Escuela de Química, Universidad de Costa Rica, San José 2060, Costa Rica

Received 9 July 2001; accepted 3 August 2001

Abstract—Controlled dilithiation of propargyl bromide with two equivalents of *n*-butyllithium, in the presence of TMEDA, produces the operational equivalent of the dianion 1,3-dilithiopropyne. The latter reacts efficiently with aldehydes and ketones to produce homopropargyl alcohols in a single step route and in high yields. © 2001 Elsevier Science Ltd. All rights reserved.

Homopropargyl alcohols are very useful intermediates in organic synthesis.[1] Their syntheses usually involve reaction of monoanionic propargyl (**1**) or allenyl (**2**) organometallic reagents, with a carbonyl compound. The major drawback of this methodology comes from the tendency of such ambident nucleophiles (**1**, **2**) to produce mixtures of both homopropargylic (**3**) and allenic (**4**) alcohols (Scheme 1).

Numerous methods for the synthesis of homopropargyl alcohols have been developed,[2] using different organometallic reagents; however, in most of these methodologies the regiochemistry of the product is highly dependent upon steric hindrance, substitution of the organometallic substrate, solvation and nature of the metal.



Scheme 1.

Allenyllithium reagents, for example, react with aliphatic ketones producing mainly allenic alcohols,[3] whereas reaction with aromatic carbonyl compounds gives homopropargylic alcohols in poor yields.[4] Zinc or magnesium reagents, derived from 2-octynyl bromide couple with aromatic or aliphatic aldehydes to produce mixtures of allenic and propargylic alcohols.[5]

We previously reported[6] that the propargyl dianion **5**, obtained from the treatment of allene with two equivalents of *n*-BuLi, reacted with aldehydes and ketones to produce homopropargyl alcohols regioselectively.

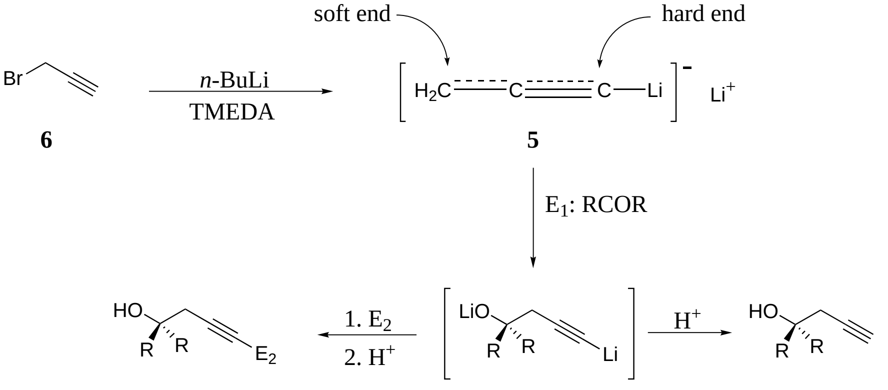
Although this method produces homopropargyl alcohols in high yields and very good regiochemistries, the high cost of allene restricts use of this procedure. To overcome this difficulty, we have developed a new procedure for the preparation of 1,3-dilithiopropyne, **5**. We envisioned that 1,3-dilithiopropyne **5** could be prepared from the reaction of propargyl bromide **6** with an alkyl lithium, thus acid–base reaction of acetylenic proton of **6**, followed by halogen–metal exchange would produce **5** (Scheme 2). We wish to report that treatment of propargyl bromide **6** with two equivalents of *n*-BuLi, in the presence of TMEDA, produces the operational equivalent of propargyl dianion **5**, that reacts with aldehydes or ketones to produce the corresponding homopropargyl alcohols regioselectively in good yields.

Keywords: 1,3-dilithiopropyne; homopropargyl alcohols; homopropargylation.

* Corresponding author. Tel.: (506) 207-4656; fax: (506) 253-5020; e-mail: jcabezas@calzada.equi.ucr.ac.cr

[†] Dedicated to Professor Cam Oehlschlager: Senior Supervisor and Friend, on the occasion of his 60th birthday.

PII: S0040-4039(01)01429-0



Scheme 2.

Initial reactions where cold (−78°C), ethereal solutions of **6** were treated with *tert*-BuLi (3 equivalents) followed by treatment with benzophenone **7** and warmed to room temperature, failed to produce the expected alcohol **8**. Inverse addition of propargyl bromide **6** to cold (−78°C) solutions of *tert*-BuLi, followed by reaction with benzophenone **7** gave after protonolysis at 25°C, the alcohol **8** in 25% yield. It is well known that the basicity of lithium reagents is increased by strongly coordinating agents such as hexamethylphosphoramide (HMPA) or tetramethylethylenediamine (TMEDA). The *n*-BuLi–TMEDA complex has been used to remove protons from benzylic, allylic[7] and propargylic[8] positions to form the corresponding carbanions. 1,3-Dilithiopropyne has been prepared from propyne by this method.[8] We decided to use this complexed base to attempt the metal–halogen exchange in **6**, thus when 1 equivalent of propargyl bromide **6** was added to a cold (−78°C) ethereal solution of *n*-BuLi (2 equivalents) and TMEDA (0.5 equivalents), followed by treatment with benzophenone **7** the alcohol **8** was obtained, after protonolysis, in 96% yield (Table 1, entry 1). To demonstrate the utility of this procedure, we prepared several propargyl alcohols by the reaction of anion **5** with some aldehydes and ketones as shown in Table 1. As in our previous communication,[6] we noted that as the carbonyl group became 'harder' (aliphatic ketones or aldehydes) a significant amount of the allenic derivative was obtained (Table 1, entry 5), presumably as a result of the nucleophilic addition of the 'harder' allenyl carbon of the isomeric form of the ambident dianion **5** (Scheme 2).

To demonstrate the selectivity of dianion **5**, we reacted it with two different electrophiles, first at the 'soft' propargyl position and later at the 'hard' acetylide anion. Thus, an ethereal solution of dianion **5** was treated with benzophenone as the first electrophile (E1) and then with paraformaldehyde (E2) (Scheme 2); in this case 1,1-diphenyl-3-pentyn-1,5-diol was obtained in 82% yield (Table 1, entry 6). This reaction, between anion **5** and benzophenone, was repeated using trimethylsilyl chloride and ethyl chloroformiate as the second electrophile, and products **19** and **20** were obtained respectively (Table 1, entries 7 and 8)

The present procedure provides a convenient single-step process to obtain homopropargyl alcohols in good yield. The products reported here were obtained in similar yields and purities as in our previous procedure.[6] An additional advantage is that the initially-formed lithium acetylide intermediate (Scheme 2) may be further reacted, in situ, with a second electrophile (E2) to obtain disubstituted homopropargyl alcohols (Table 1, entries 6, 7, 8).

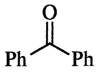
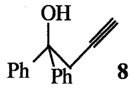
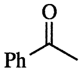
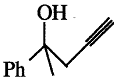
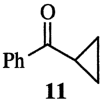
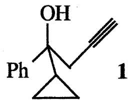
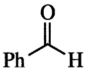
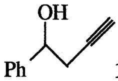
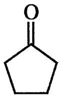
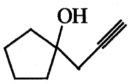
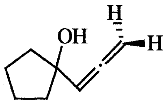
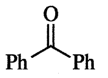
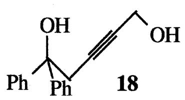
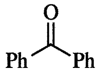
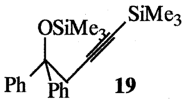
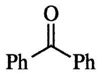
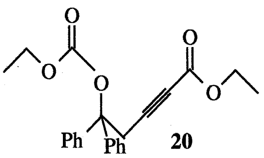
Typical procedure. Preparation of 1,1-diphenyl-3-pentyn-1, 5-diol (18)

A solution[9] of dry diethyl ether (12.4 mL), dry hexane (7.0 mL) and *n*-BuLi[10] (5.4 mL, 16.4 mmol) was cooled to −78°C and TMEDA added (0.62 mL, 4.1 mmol), followed by dropwise addition of propargyl bromide (0.78 mL, 8.2 mmol) (CAUTION: highly toxic) and the resulting mixture stirred for 20 minutes at this temperature. After this time a white precipitate formed. A solution of benzophenone (0.709 g, 3.90 mmol) in diethyl ether (5 mL) was added dropwise over 5 min and the reaction mixture was allowed to warm to room temperature over 2 h. THF (7 mL) was added to this mixture, followed by addition of paraformaldehyde in one portion (0.861 g, 28.7 mmol). After stirring the mixture, under nitrogen, for 24 h at room temperature, the resulting suspension was poured into ice cold NH_4Cl solution, then extracted with ether and the organic extracts dried (Na_2SO_4). After evaporation of solvent in vacuo, impurities (2-butyn-1-ol) were distilled by Kugelrohr and the residue was purified by column chromatography (silica gel) using ether:hexanes mixtures to obtain 0.795 g (82%) of product.

Acknowledgements

We wish to thank 'Consejo Nacional para Investigaciones Científicas y Tecnológicas' (CONICIT, Costa Rica) and Vicerrectoría de Investigación (UCR) for financing this project through a research grant, and Chem Tica International of Costa Rica for a generous donation of chemicals.

Table 1. Conversion of 1,3-dilithiopropyne into different homopropargyl alcohols

Entry	Carbonyl compound (E1)	E2	Product(s)[a]	Isolated Yield (%)
1	 **7**	H^+	 **8**	96[b]
2	 **9**	H^+	 **10**	86[c]
3	 **11**	H^+	 **12**	96[c]
4	 **13**	H^+	 **14**	83[c]
5	 **15**	H^+	 +  **16** (8:2) **17**	91[c]
6	 **7**	$(CH_2O)n$	 **18**	82[d,e]
7	 **7**	Me_3SiCl	 **19**	91[d]
8	 **7**	ClCO(OEt)	 **20**	70[d,f]

[a] All products gave satisfactory spectroscopic characteristics ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz). [b] Purified by recristallization in hexanes: ether (1:1) (m.p: 61-62 °C). [c] Purified by Kugelrohr distillation. [d] Impurities (obtained by reaction of excess of 1,3-dilithiopropyne with E2) were distilled by Kugelrohr, and the residue was purified by column chromatography using silica gel. [e] m.p.: 83-84 °C. [f] m.p.: 99-101 °C.

References

1. (a) Nicolau, K. C.; Skokotas, G.; Furuya, S.; Nicolau, D. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1064; (b) Fryhle, C. B.; Williard, P. G.; Rybak, C. M. *Tetrahedron Lett.* **1992**, *33*, 2327.
2. (a) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 878; (b) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104; (c) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 8976; (d) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812; (e) Dollinger, L. M.; Howell, A. R. *J. Org. Chem.* **1998**, *63*, 6782; (f) Kundu, A.; Prabhakar, S.; Vairamani, M.; Roy, S. *Organometallics* **1999**, *18*, 2782; (g) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201; (h) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696 also see Ref. 3 and references cited therein.
3. Clinet, J. C.; Linstrumelle, G. *Synthesis* **1981**, 875.
4. Michelot, D. *Synth. Commun.* **1989**, *19*, 1705.

5. Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 5198.
6. Cabezas, J. A.; Alvarez, L. X. *Tetrahedron Lett.* **1998**, *39*, 3935.
7. (a) Akiyama, S.; Hooz, J. *Tetrahedron Lett.* **1973**, 4115; (b) Cardillo, G.; Contento, M.; Sandri, S. *Tetrahedron Lett.* **1974**, 2215; (c) Wilson, S. R.; Phillips, L. R. *Tetrahedron Lett.* **1975**, 3047.
8. Bhanu, S.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1975**, 817.
9. In the current procedure, a solvent ratio (v/v) of ether:hexanes of 1:1 was used, as previously reported: Hooz, J.; Cabezas, J.; Musmanni, S.; Calzada, J. *Org. Synth.* **1990**, *69*, 120.
10. *n*-BuLi was titrated according to: Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, 165.