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A facile method for the preparation of bishomopropargylic alcohols from acyl chlorides

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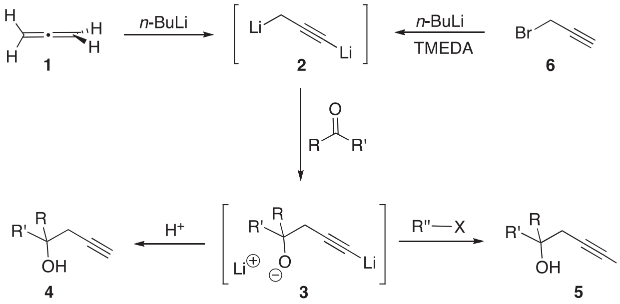
ABSTRACT

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 acid chlorides to produce bishomopropargylic alcohols in a single step route and with high regioselectivity and moderate yields.

The three-carbon homologation, RX → $RCH_2C{\equiv}CH$, is a highly useful transformation, especially in isoprenoid-related synthesis.[1] However, this transformation, is often difficult to achieve cleanly because of the tendency of ambident propargylic nucleophiles, $RC{\equiv}CCH_2M$, to produce mixtures of both the allenic and the acetylenic products[2] which are difficult to separate.[3]

We have previously reported a procedure,[4] based on the controlled lithiation of allene, **1**, that produced the operational equivalent of propargyl dianion, **2**, ($C_3H_2Li_2$, '1,3-dilithiopropyne'), and provided a convenient single-step route to propargylated derivatives,[4] 1,5-diynes[5] and insect pheromones,[5] in excellent yields and without contamination with allenic derivatives. Based on this procedure, we later developed a protocol for the highly efficient transformation of aldehydes and ketones into the corresponding homopropargylic alcohols[6] **4** and **5** (Scheme 1).

Although this procedure produces homopropargyl alcohols in high yields and very good regiochemistry, the high cost of allene, **1**, restricts its use. We envisioned that dianion, **2**, could be prepared from the reaction of propargyl bromide, **6**, with two equivalents *n*-BuLi in the presence of TMEDA. Thus dianion, **2**, obtained from this methodology, reacted with aldehydes or ketones to afford the corresponding homopropargyl alcohols **4** or **5** in very good yields[7] (Scheme 1). Homopropargyl alcohols, **4**, and bishomopropargyl alcohols, **7**, are very useful intermediates in organic synthesis.[8]



Scheme 1.

Numerous methods for the synthesis of bishomopropargyl alcohols have been developed, however most of them produce mixtures of allenic and diacetylenic derivatives and generally they suffer from poor yields. Reaction of propargyl aluminum reagents with acyl chlorides gave inseparable mixtures of allenic and diacetylenic alcohols in 41–50% yield.[9] Reaction of propargyl magnesium bromide with aliphatic and aromatic esters[10a] and with several 3-furanyl propanoates[10b] gave same mixture of alcohols in 32–85% and 31–66% yields, respectively. Reaction of same Grignard reagent with 3-methoxy methylbenzoate produced same mixture of isomers in 45% yield.[10c] Brown[11] reported a method for the allenylboration of acetyl chloride and benzoyl chloride, **8**, using B-allenyl-9-BBN, prepared from B-chloro-9-BBN and allenylmagnesium bromide. This reaction afforded the corresponding bishomopropargyl alcohols in 72% and 76% yields respectively,

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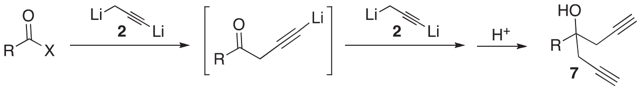


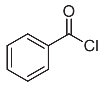
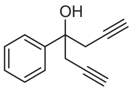
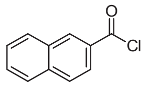
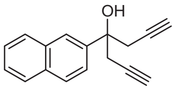
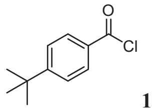
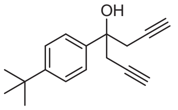
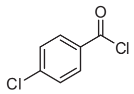
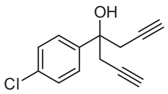
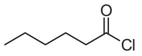
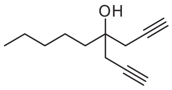
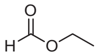
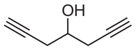
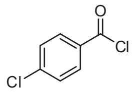
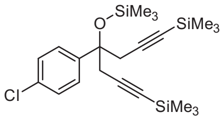
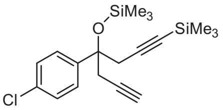
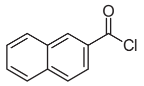
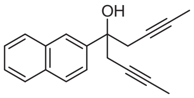
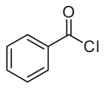
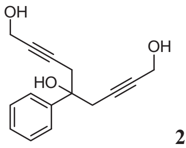
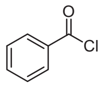
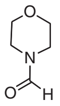
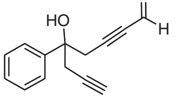
Scheme 2.

without contamination with the allenic isomer. Unfortunately, this method needs a two-step preparation of the reagent and an oxidative work-up to furnish the tertiary alcohols. Oestreich[12] reacted γ-trimethylsilyl propargyl zinc bromide with esters to prepare, after treatment with TBAF, bishomopropargyl alcohols with good regioselectivities and yields (56–94%). This procedure needs the specific preparation of the trimethylsilyl reagent, and subsequent liberation of the terminal alkynes.

We decided to extend our previous studies on the reaction of 1,3-dilithiopropyne, **2**, with aldehydes and ketones. Thus, reaction of **2** with carboxylic acid derivatives would yield the corresponding bishomopropargyl alcohols, **7**, in one-step procedure (Scheme 2).

We wish to report herein a new methodology to obtain bishomopropargyl alcohols, **7**, from acyl chlorides, using 1,3-dilithiopropyne, **2**, in one-pot reaction.

Table 1
Conversion of acid chlorides into different bishomopropargylic alcohols

Entry	Substrate	E2	Product(s)[a]	Isolated yield (%)
1	 **8**	H_3O^+	 **9**	57
2	 **10**	H_3O^+	 **11**	65
3	 **12**	H_3O^+	 **13**	57
4	 **14**	H_3O^+	 **15**	60
5	 **16**	H_3O^+	 **17**	55[b]
6	 **19**	H_3O^+	 **20**	33[b]
7	 **14**	$ClSi(CH_3)_3$	  (83 :17) **21** **22**	53
8	 **10**	CH_3I	 **23**	47
9	 **8**	$(CH_2O)_n$	 **24**	44[c]
10	 **8**	 **25**	 **26**	23

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[a] All products gave satisfactory spectroscopic characteristics ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz).

[b] Yield after isomerization through a 'zipper' reaction.

[c] 2-Butyn-1-ol (by-product obtained by reaction of excess of 1,3-dilithiopropyne with paraformaldehyde) was removed by Kugelrohr distillation and the residue was purified by column chromatography using silica gel.

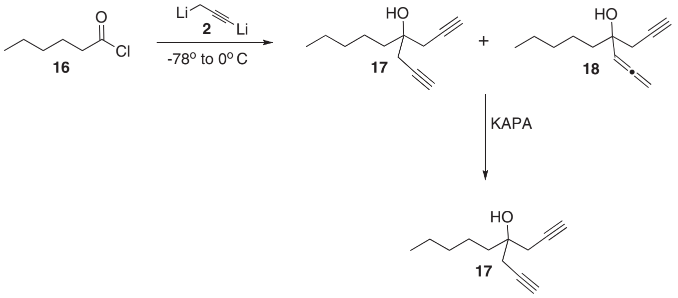
Preliminary reactions at −78 °C, of dianion **2**, (prepared from propargyl bromide, **6**, and *n*-BuLi in the presence of TMEDA, Scheme 1) with carboxylic esters failed to produce the desired bishomopropargylic alcohols, **7**, cleanly and in good yield. However when a cold (−78 °C) ethereal solution of **2**, was reacted with benzoyl chloride, **8**, the corresponding alcohol 4-phenyl-1,6-heptadiyn-4-ol, **9**, was obtained in 57% yield (Table 1, entry 1). Reaction of **2**, with several aromatic acyl chlorides produced the corresponding 1,6-heptadiyne-4-ols in moderate yields without contamination with allenic alcohols (Table 1, entries 1–4).

When 1,3-dilithiopropyne, **2**, was reacted with hexanoyl chloride, **16**, a mixture (1:1) of the diacetylenic (**17**) and allenic (**18**) alcohols was obtained (Scheme 3). Increasing the polarity of the reaction (ether:THF, or higher amounts of TMEDA), increased the amount of allene derivative **18**.

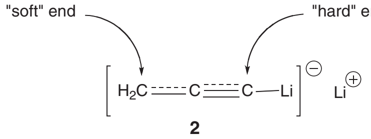
This result is in agreement with our previous findings[6,7] that as the carbonyl group, of the electrophile species, became 'harder' (aromatic vs aliphatic) a significant amount of the allenic derivative was obtained, presumably as a result of the nucleophilic addition of the 'harder' allenyl carbon of the isomeric form of the ambident dianion, **2** (Scheme 4).

It has been reported that internal acetylenes can be isomerized to the corresponding terminal acetylenes through the 'zipper' reaction.[13] It has been proposed that this isomerization proceeds via a series of deprotonation allenil-propargyl rearrangements,[14] using potassium 3-aminopropylamide (KAPA) as a base (Scheme 5).

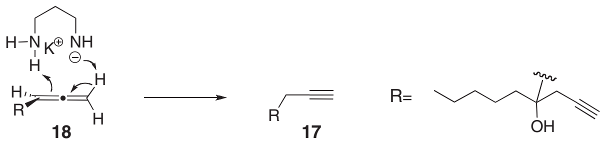
Because an allenic alcohol such as **18** has a similar structure as the proposed intermediates in this isomerization, it may be plausible its isomerization to **17**, under the 'zipper' reaction conditions (Scheme 5). We were pleased to observe that when the crude reaction mixture, obtained from the reaction of **16** and **2**, was treated with potassium 3-aminopropylamide (KAPA), allenic alcohol, **18**, was completely isomerized to **17** (Scheme 3). After this base treatment, 4-pentyl-1,6-heptadiyn-4-ol, **17**, was obtained in 55% overall yield from hexanoyl chloride, **16** (Table 1, entry 5).



Scheme 3.



Scheme 4.



Scheme 5.

Reaction of **2**, with ethyl chloroformate did not result in a clean reaction, instead many unidentified by-products were obtained. However when the reaction was performed with ethylformate, **19**, 1,6-heptadiyn-4-ol, **20**, was obtained in 33% yield[15] (Table 1, entry 6).

One feature of this methodology is the fact that dianion, **2**, can be reacted selectively with two different electrophiles, first at the 'soft' propargyl position and later at the 'hard' acetylide anion. Thus an ethereal solution of dianion **2**, was treated with β-naphthyl chloride, **10**, as the first electrophile and then with methyl iodide as the second electrophile (E2). In this case, 5-(β-naphthyl)-2,7-nonadiyn-5-ol, **23**, was obtained in 47% overall yield (Table 1, entry 8). The triol, 5-phenyl-2,7-nonadiyn-1,5,9-triol, **24**, was obtained in 44% yield, after treating 1,3-dilithiopropyne, **2**, sequentially with benzoyl chloride, **8**, and paraformaldehyde (Table 1, entry 9). Treatment of **2**, with *p*-chlorobenzoyl chloride, **14**, and trimethylsilyl chloride produced a mixture of the silated products **21** and **22** (Table 1, entry 7).

Interestingly, sequential addition of benzoyl chloride, **8**, and *N*-formylmorpholine, **25**, to 1,3-dilthiopropyne, **2**, produced the highly functionalized hydroxy aldehyde, **26**, in 23% isolated yield in one-pot reaction (Table 1, entry 10). In all cases shown in Table 1, viscous reaction mixtures were obtained from which the bishomopropargyl alcohol was the major product and only isomer obtained (except in entries 5 and 6). The target compounds were easily purified by column chromatography.

In summary, we developed a convenient single-step process to obtain bishomopropargylic alcohols, from acyl chlorides, in moderate yields. The reaction selectivity of dianion, **2**, allows synthesis of highly functionalized products in one-pot reaction. In spite of the fact that in some cases overall yields may seem low (e.g. **26**, 23%), this highly functionalized products (**23**, **24**, **26**) are obtained in one-pot procedure. In a multiple-step synthesis (e.g. a three-step synthesis) with good yields, a similar result could be achieved (65% × 60% × 60% = 23% overall yield). We also demonstrated that if formation of the undesired allenic alcohol shall take place, in the case of aliphatic acyl chlorides, the yield of the target bishomopropargylic alcohol can be further enhanced by subjecting the reaction crude to the 'zipper' reaction conditions.

Typical procedure. Preparation of 5-phenyl-2,7-nonadiyne-1,5,9-triol (24)

A solution[16] of dry diethyl ether (7.5 mL), dry hexane (5.0 mL), and *n*-BuLi[17] in hexane (2.5 mL, 6.2 mmol) was cooled to −78 °C and TMEDA added (0.25 mL, 1.55 mmol)[†] followed by dropwise addition of propargyl bromide (0.30 mL, 3.1 mmol) (CAUTION: highly toxic). The resulting mixture was stirred for 40 min at this temperature until the formation of a white precipitate. A solution of benzoyl chloride (0.140 g, 1.0 mmol) in tetrahydrofuran (2.5 mL) was added dropwise over 10 min and the reaction mixture was allowed to warm to room temperature over 2 h and cooled back to −78 °C. THF (3.6 mL) was added to this mixture, followed by addition of paraformaldehyde in one portion (0.444 g, 14.8 mmol). After stirring the suspension, under nitrogen, for 24 h at room temperature, the mixture was poured into ice-cold NH_4Cl solution, then extracted with diethyl 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 with silica gel using ether:hexanes mixtures to obtain 0.110 g (44%) of product.

[†] Increasing amounts of TMEDA resulted in formation of allenic isomer. Lower amounts of TMEDA produced lower yields of product.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.144.

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16. In the current procedure a solvent ratio (v/v) of diethyl ether–hexanes (1:1) must to be used in order to obtain 1,3-dilithiopropyne in good yield, as originally stated.[2a,4]
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