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Propargylation of Carbonyl Compounds: An Efficient Method for the Synthesis of Homopropargyl Alcohols.

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Dedicated to the memory of José Calzada, former mentor.

Abstract: Controlled dilithiation of allene, with two equivalents of n-butyllithium, produces the propargyl dianion 5. The latter couples efficiently with carbonyl compounds to produce homopropargyl alcohols in high yields. © 1998 Elsevier Science Ltd. All rights reserved.

Homopropargyl alcohols are valuable 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 the homopropargylic (3) and allenic (4) alcohols (Scheme 1).



Some of the reagents used (1, 2) employ metals such as Li,² Zn,³ Al,^{3d,4} Mg,⁵ Sn,⁶ Si,⁷ Ti⁸ or B.⁹ The regioselectivity obtained with these reagents is highly dependent upon steric hindrance, solvation, and the metal. Allenyllithium reagents, for example, couple with aliphatic ketones to produce mainly allenic alcohols,^{2a} whereas the reaction with aromatic carbonyl compounds gives homopropargylic alcohols in poor yields.^{2b} Zinc or magnesium reagents, derived from 2-octynyl bromide and zinc or magnesium react with benzaldehyde or hexanal to give mixtures of allenic and propargylic alcohols.^{3b}

The regiochemistry of the reaction using propargylic titanium reagents is highly dependent on the substitution of the organometallic substrate.^{8,9e} Some regio-⁴ and diastereoselective^{3a,6c-d,8} syntheses of homopropargylic alcohols have been developed, however these methods are useful only for the preparation of

2-substituted homopropargylic alcohols. To overcome this difficulty, Brown reported^{9g} an efficient method of allenylboration of carbonyl compounds using 9-allenyl-9-BBN, to produce non substituted homopropargylic alcohols in good yields. A minor inconvenience of this method is that the reagent used has to be prepared, from allenylmagnesium bromide and B-chloro-9-BBN (which also has to be prepared).

Hooz et al reported¹⁰ that the organometallic formed in situ by controlled dilithiation of allene, with two equivalents of *n*-BuLi, behaved as an effective operational equivalent of the propargyl dianion ($C_3H_2Li_2$, 5). Its coupling with geranyl chloride proceeded with high positional selectivity, without obtention of the allenic isomer. We now wish to report that reaction of this "propargyl" dianion with aldehydes and ketones cleanly gives homopropargylic alcohols.

Reactions of ether:hexane solutions of 1.1 and 1.35 equivalents of "propargylide", 5, with benzophenone (1 equivalent) at -20 °C gave, after protonolysis, the desired product without contamination of the allenic isomer. G.C. analysis of the crude reaction mixtures showed the presence of unreacted ketone (1-5%). When a ratio of 1.7:1 was used, no remanent benzophenone was detected and the propargyl alcohol was obtained in 90% isolated yield (Table I, entry 3). A study of the reaction at different temperatures (-15, -40, -78 °C) did not evidence a significant yield change. Reaction with several aliphatic and aromatic ketones and aromatic aldehydes, gave the corresponding hompropargylic alcohol in high yields and to the exclusion of detectable allenic alcohol (Table I, entries 1-6). Surprisingly, reaction with an aliphatic aldehyde, gave a mixture of isomers (Table I, entry 7). In this case, the use of a carbonyl group with different hardness might be responsible for the loss in the regiospecificity. It has been demonstrated that similar polylithium^{11a} reagents and dilithiopropargyl position or at the hard acetylide anion, depending on the electrophile used. These results have been explained in terms of the hard-soft acid-base theory. In our case, the use of "soft" carbonyl compounds could favor attack from the soft "propargyl carbon" of propargylide 5, whereas "harder" carbonyl reagents might favor attack from a harder allenyl carbon of the isomeric form of the ambident intermediate 5.



We are currently extending the scope of the reaction and its applicability to the synthesis of 4-substituted propargylic alcohols.

Typical Procedure:

A solution of the carbonyl compound (7.5 mmol) in diethyl ether (5 mL) was added dropwise over 20 min, to a cold (-20 °C) suspension of the propargylide 5 (13 mmol), prepared as previously described. ^{10b} The mixture was allowed to warm to room temperature (1 h), poured into ice cold NH₄Cl soln., then extracted with ether and dried (MgSO₄). After evaporation of the solvent *in vacuo*, the liquid products were purified by Kugelrohr distillation, and the solid compounds were purified by recrystallization in hexane:ether mixtures.

Entry	Carbonyl Compound	d Product(s) ^a Is	solated Yield (%)
1		OH	90 ⁶
2		OH	93 ^b
3		OH	90 ^c
4	o L	OH	80 ^b
5		OH	90 ^b
6	СНО	OH	93 ^c
7	∽∽дЧн	OH H OH OH (86 : 14)	∕ 84 ^b

 Table 1. Three-Carbon Homologation of Carbonyl Compounds

^a All the products gave satisfactory spectroscopic characteristics ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz). ^bPurified by Kugelrohr distillation. ^c Purified by recrystallization in hexanes:ether 1:1.

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