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Rearrangement of Lithioalkynyltriorganoborates Derived from Propargylic Acetals : a One Pot Synthesis of Homopropargylic Alcohols.

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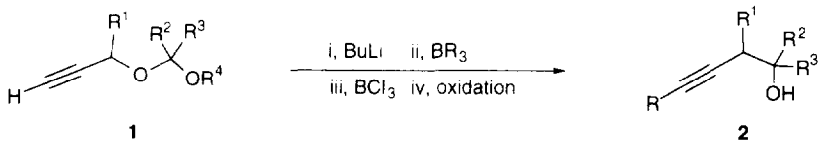
Abstract : Lithioalkynyltriorganoborates generated from the corresponding propargylic acetals rearrange in the presence of boron trichloride thus opening an efficient and convenient route to a variety of homopropargylic alcohols free of the corresponding allenic isomers. Unexpectedly, the parent derivative leads exclusively to the allenic alcohol.

Homopropargylic and α-allenyl alcohols are valuable intermediates in the synthesis of a number of important biologically active substances. They were generally prepared by addition of propargyl- or allenyl organometallic derivatives to carbonyl compounds although the existence of an equilibrium between these two species often induced the formation of a mixture of two isomeric alcohols.[1] A large variety of organometallics (Li, Mg, Zn, Al, Sn, Zr, Ti, In, ...) have been therefore tested to overcome this limitation and considerable progress was realized in terms of yields, regio- and diastereoselectivity.[1]

Organoboranes have also found valuable applications in this area since the results initially obtained by Favre and Gaudemar with the parent allenylboronate dibutylester [2] were later notably improved by using 9-allenyl-9-BBN [3] or, in chiral series, tartrate esters.[4] Other approaches were based on the reaction of allenyldialkylboranes generated *via* the 1,2-alkyl migration of the initially produced alkynylborate. Homopropargylic or allenic alcohols were then obtained from aldehydes or ketones with a high regioselectivy depending on the reaction temperature[5].

In this paper, we report a one pot preparation of homopropargylic alcohols involving the rearrangement of lithioalkynyltrialkylborates derived from the corresponding propargylic acetals in the presence of boron trichloride (Scheme 1)



1 2

Scheme 1

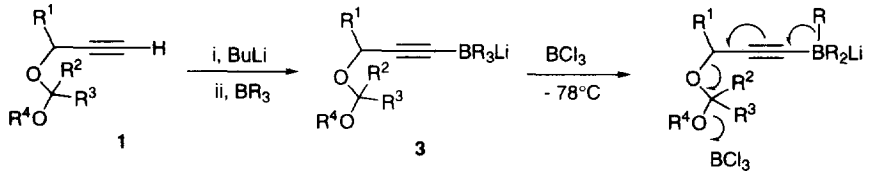
The starting acetals **1** were prepared from the corresponding propargylic alcohols according to literature procedures either by reaction with an α-haloether in the presence of Hunig's base or by addition to an enol ether in presence of acid traces.[6] Treatment of a solution of **1** with one equivalent of n-BuLi at -78°C led to the corresponding lithium acetylide which reacted *in situ* with triorganylboranes to give the borate **3**. After addition of one equivalent of boron trichloride, warming up to room temperature over 2 hrs and oxidative work-up, the homopropargylic alcohols **2** were isolated after distillation and (or) silica gel column chromatography with good yields (Table I).[7] It is worthy to note that this procedure permits the simultaneous alkylation and the homologation of a propargylic alcohol.

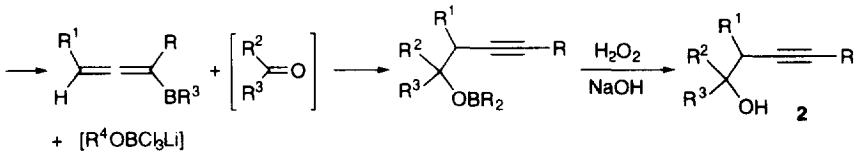
Table I - Synthesis of the homopropargylic alcohols **2**.

Entry	R	R^1	R^2	R^3	Yield (%)[a]
2a	n-Bu	Me	H	H	45
2b	n-Hex	Ph	Me	Me	62
2c	Ph	Ph	H	H	68
2d	n-Hex	Ph	H	H	84
2e	n-Bu	Ph	H	Me	60(56/44)[b]
2f	n-Bu	Ph	H	H	89
2g	n-Hex	Me	H	$(CH_2)_4OH$	65(60/40)[b]
2h	n-Hex	Ph	H	$(CH_2)_4OH$	55(60/40)[b]

[a] Isolated yield based on the starting acetal. [b] Ratio of diastereoisomers determined by ^1H NMR analysis, *syn* stereochemistry for the major isomer.[8]

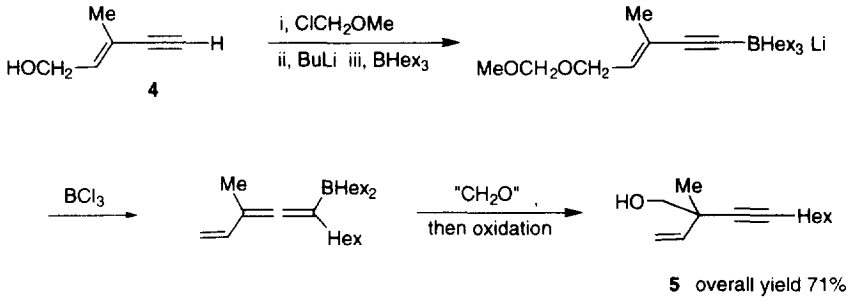
From a mechanistic point of view, these results indicated the intermediate formation of an allenyl boron compound as shown in scheme 2. First, the ate complex **3** rearranged in the presence of boron trichloride with one R group migrating from boron to the adjacent carbon and concomittant elimination of the complexed acetal moeity. Such a 1,2 migration was currently observed when unsaturated organoborates possess a leaving group (Cl, OAc) on the α-carbon or in a vinylogous position.[9] Here, the leaving group was generated by a preliminary coordination of the Lewis acid to one of the two oxygen atoms. The exact nature of the species acting as a potential aldehyde or ketone has not been yet determined. Addition of this carbonyl derivative to allenylboranes afforded, after oxydation, *via* an usual allylboration type reaction [10] , and after oxydation, the alcohol **2**.





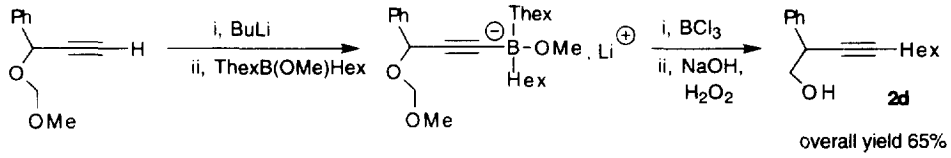
Scheme 2

The same methodology can be extended to the enynol **4** and provided the corresponding homopropargylic alcohol **5** with a good yield (Scheme 3).[11]



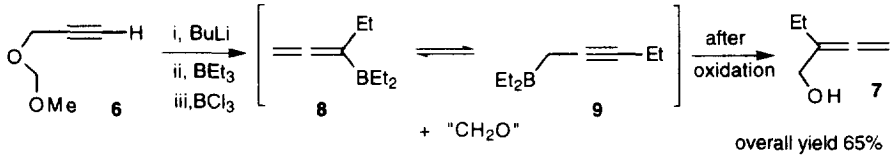
Scheme 3

The previous procedure suffers from a significant disadvantage since only one of the three alkyl or aryl substituents of R_3B was transfered. This drawback was circumvented by using a methyl thexylalkylborinic ester that led to the preferential migration of the primary alkyl moiety and then prevented the loss of two R groups (Scheme 4).With a 9-BBN derivative, competitive migrations took place.



Scheme 4

Finally, the reaction of the acetal **6** derived from propargylic alcohol was investigated. Unexpectedly, homoallenic alcohol **7** was only obtained. This result suggested that formaldehyde (or its precursor) was generated at relatively elevated temperature where the equilibration between the two isomeric species **8** and **9** occured. The allenic borane **8** initially produced rearranged to the thermodynamically more stable propargylic borane and therefore afforded the homoallenic alcohol **7** (Scheme 5).



Scheme 5

In summary, we have reported a simple and efficient one-pot procedure for the synthesis of homopropargylic alcohols from the corresponding propargylic acetals. The obtention of homoallenic alcohol from alkyne **6** suggested a more complete study of the equilibrium allenyl-propargylborane to confirm this quite surprising result. Further work concerning the *in situ* generation of unstable carbonyl derivative and the intramolecular version of this approach are now in progress.

References and notes

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7. In a typical procedure, 2 mmol of the acetal **1** dissolved in 5 ml of anhydrous THF were treated at -78°C with 1.25 ml of n-BuLi (1.6 M in hexane, 2 mmol). After 15 mn, 2.2 mmol of borane were added dropwise and the solution was allowed to warm to room temperature. 15 mn later, it was cooled again at -78°C and 1.6 ml (1.4 M in hexane, 2.25 mmol) of boron trichloride was added. The reaction mixture was allowed to warm slowly to room temperature overnight and was then quenched with 2 ml of MeOH. The oxidation was carried out by addition of 30% H_2O_2 (2.5 ml) in the presence of sodium hydroxide (1M, 5ml). After stirring an additional hour at 40°C, Et_2O (20 ml) was added and the organic layer was washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave an oil which was purified by bulb to bulb distillation and flash column chromatography. Homopropargylic alcohols prepared in this study are known compounds, except **2b**, **2e**, **2f**, **2g**, **2h**. All new products (or their *para*nitrobenzoates for some elemental analysis) gave satisfactory spectroscopic and analytical data. For exemple : **2b** ^{1}H NMR (300 MHz, $CDCl_3$) : 0.89 (t, 3H, J = 6.8) ; 1.24 (s, 6H) ; 1.28-1.57 (m, 8H) ; 1.95 (br s, 1H) ; 2.25 (dt, 2H, J = 2.3 and 6.8) ; 3.67 (t, 1H, J = 2.3) ; 7.20-7.45 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) : 14.0 ; 18.8 ; 22.5 ; 26.8 ; 26.9 ; 28.7 ; 30.0 ; 31.4 ; 50.9 ; 72.8 ; 79.7 ; 85.1 ; 127.1 ; 127.5 ; 129.5 ; 138.7.
8. The stereochemistry of the major isomer was established according to ^{1}H NMR characteristic chemical shifts (-C<u>H</u>OH- δ = 3.35 ppm for the *syn* isomer, δ =3.49 ppm for the *anti* isomer). We thank Pr J.A. Marshall for sending the ^{1}H NMR spectra of two mixtures of diastereomeric homopropargylic alcohols (see Marshall, J.A. ; Wang, W-J. *J. Org. Chem.*, **1990**, *55*, 6246-6248).
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11. **5 :** bp = 80-85°C (0.01 mm Hg). ^{1}H NMR (300 MHz, $CDCl_3$) : 0.89 (t, 3H, J = 6.8) ; 1.25 (s, 3H) ; 1.25-1.58 (m, 4H) ; 1.87 (br s, 1H) ; 2.22 (t, 2H, J = 6.8) ; 3.41 (d, J = 10.4) ; 3.43 (d, J = 10.4) ; 5.16 (dd, 1H, J = 1.5 and 10.2) ; 5.42 (dd, 1H, J = 1.5 and 17.0) ; 5.73 (dd, 1H, J = 10.2 and 17.0) . ^{13}C NMR (75.5 MHz, $CDCl_3$) : 14.0 ; 18.9 ; 22.6 ; 24.1 ; 28.6 ; 29.2 ; 31.4 ; 42.0 ; 70.7 ; 81.9 ; 85.4 ; 115.1 ; 141.2.

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