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NUCLEOPHILIC SUBSTITUTION OF α-ALLENIC ALCOHOLS VIA THE MURAHASHI METHOD : 1,3-DIENES SYNTHESIS .

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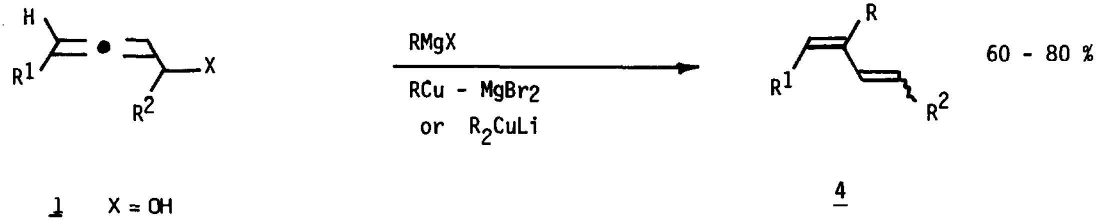
Summary : The alkylation of α-allenic alcohols 1 by the Murahashi procedure leads to 1,3-dienes 4 . This process allows the direct nucleophilic substitution of labile or hindered α-allenic alcohols by organolithium reagents.

Conjugated dienes are one of the most studied polyunsaturated compounds because of their large occurrence in nature (terpenoïds, insect pheromones, leukotrienes,...) and their useful potentiality as synthetic intermediates (1). In spite of the already wide spectrum of their preparations, organic synthesis still required new stereoselective access to such substrates in a high state of chemical and stereochemical purity (2).

We recently described a new regiospecific and stereoselective synthesis of "branched" 1,3-dienes 4 , starting from derivatives of α-allenic alcohols 1 (3,4). This procedure involves the 1,3-substitution of their esters, acetates 2 or phosphates 3 , by Grignard reagents or organocopper species as shown below (5) .

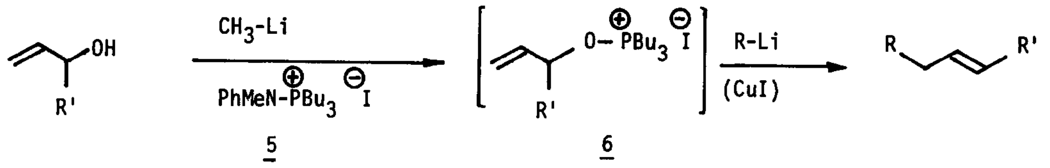


1 $X = OH$
2 $X = O\text{-}CO\text{-}CH_3$
3 $X = O\text{-}PO(OEt)_2$

However the synthetic application of this reaction seemed limited to the use of Grignard reagents reacting with phosphates 3 , or organocopper reagents with acetates 2 , because the reaction of an alkyllithium proceeds mainly through the nucleophilic attack on the phosphorous atom (6) and none dienic compound is obtained.

The reaction was also limited to primary and secondary phosphates as substrates, because hindered tertiary ones can't be easily prepared . Furthermore some of these phosphates may be too labile (as 3b for example) because of a proximate unsatured substituent.

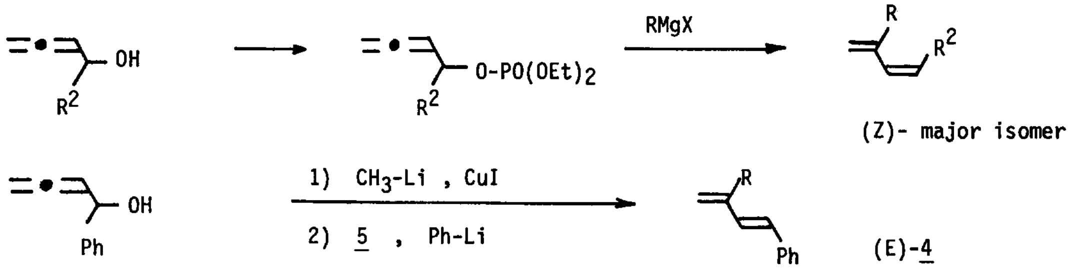
We now report on an extension of our previous work which takes advantage of the so called MURAHASHI method ; this procedure involves the "in situ" transformation of the hydroxy group of an unsaturated alcohol in an alkoxyphosphonium salt 6 and the reaction of this latter species 6 with a nucleophile (7,8).



Thus several α-allenic alcohols 1 a-d (9) were treated through standard Murahashi's conditions : alcohol 1 (5 mmol) was successively treated in THF with methyllithium (1 equiv.) and copper iodide (1 equiv.) for 3 h at 20°C ; N,N-methylphenylaminotributylphosphonium iodide 5 (1 equiv.) and phenyl-lithium (1 equiv.) were added at -78°C . The reaction mixture was then allowed to warm to room temperature and stirred for 3 h before work-up.

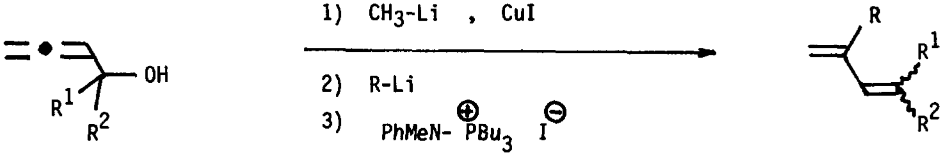
Preliminary results are reported on the Table . Yields of this one step reaction range 35-55 % ; these are however comparable to the overall yields of our previous two steps procedure [1 ⟶ 3 (67-90 %) ⟶ 4 (50-80 %)].

The stereoselectivity seems to be dependent on both the nucleophile (compare entries 1 and 2) and the nature of the substituent on the α-allenic carbon atom (compare entries 1 and 3). Alcohol 1b is a good example of an alcohol the phosphate (3b) of which can't be used ; in fact every purification technic of this phosphate 3b failed in our hands. This demonstrates the utility of the new procedure . Thus, alcohol 1b leads stereoselectively in every case to the (E)-4 stereoisomer . This stereoselectivity is in good agreement with the one observed with allylic alcohols (7,8) . However it is the reverse one of the stereoselectivity which was encountered with the phosphates 3 of α-allenic alcohols 1 [(Z)-4 isomer is then the major one] (3,4,5b). This may reflect either a different mechanistic pathway, either a favored isomerisation of the 1,3-dienes 4 c,d,e in the reaction conditions.

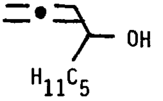
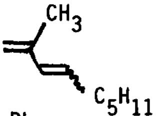
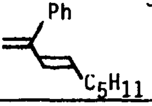
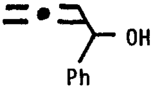
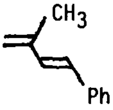
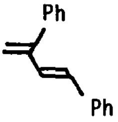
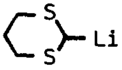
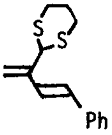
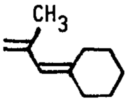
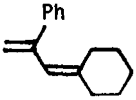
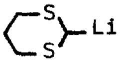
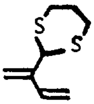


The main interest of the described reaction lies on the possible use of various orgalithium carbonucleophiles. As an example, 2-lithio-1,3-dithiane (10) was tested and gave the expected functionalized 1,3-dienes 4e and 4h (11) [entries 5 and 8]. This last dithiane derivative 4h

Table



1 4

Entry	α-allenic alcohol 1		R-Li	1,3-Dienes 4			(E/Z)
1		1a	CH$_3$-Li	4a		55%	(50/50)
2			Ph-Li	4b		45%	(E)
3		1b	CH$_3$ -Li	4c		53%	(E)
4			Ph-Li	4d		31%	(E)
5				4e		21%	(E)
6		1c	CH$_3$-Li	4f		40%	
7			Ph-Li	4g		41%	
8		1d		4h		20%	

Yields (non optimized) correspond to pure compounds isolated by silica gel chromatography These dienes are fully caraterized by spectroscopic data (IR, NMR).

represents a masked equivalent of the unknown 2-methylene-3-butenal (12) ; it should provide a valuable equivalent of this C_5 dienic aldehyde, which is currently studied as well as the scope and limitation of the reported reaction.

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5. a) The presence of a R^1 substituent on the terminal allenic carbon atom gives as high as E/Z = 98/2 stereoselectivity for the $R^1HC=CR-$ double bond because of an anti attack of the nucleophile referred to this R^1 substituent (3).
   b) The stereoselectivity of the $-CH=CHR^2$ double bond depends on the nature of the leaving group X of the substrate : (Z)-configuration is favored with phosphates 3 , whereas (E)-configuration is the major one with acetates 2 (3).
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    ^1H NMR of 4e (60MHz, CCl_4) : δ ppm , 1.8-2.2 (m,2H) ; 2.5-3.0 (m,4H) ; 4.9 (s, 1H, S-CH-S) ; 5.4 and 5.5 (2 s, 2H, $H_2C=C$) ; 6.8 (AB system, J_{AB} = 17 Hz, 2H, $-CH_A=CH_B-Ph$).
    ^1H NMR of 4h (60MHz, CCl_4) : δ ppm , 1.7-2.2 (m, 2H) ; 2.5-3.0 (m, 4H) ; 4.8 (s, 1H, S-CH-S) ; 4,9-5.6 (m, 4H, $H_2C=C-C=CH_AH_B$) ; 6.2 (X part of an ABX system, J_{cis} = 11 Hz and J_{trans} = 17 Hz, 1H, $-CH_X=C$).
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