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REGIOSELECTIVE SN' ALLYLIC SUBSTITUTION VERSUS 1,4-ADDITION : SYNTHESIS OF α-SUBSTITUTED β,γ-UNSATURATED ESTERS.

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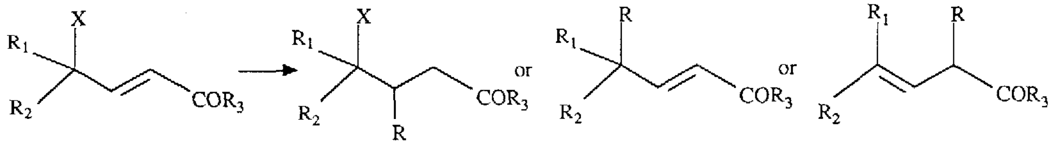
Abstract *: The reaction of the higher order organocuprate reagents $R_2Cu(CN)Li_2$-BF_3 with γ-bromo α,β-unsaturated esters gives with very high selectivity α-substituted β,γ-unsaturated esters arising from a SN' allylic substitution. This reaction allows an easy access to α-silyl β,γ-unsaturated esters.*

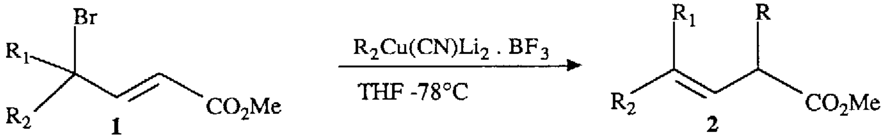
Substitution reactions of allylic substrates with (or without) complete allylic rearrangement have been, these last years, the subject of intense investigations [1]. Important improvements have been made concerning the regioselective substitutions of simple allylic derivatives by organometallic species and a few organocopper reagents leading to highly selective S_N2' reactions have been recently reported in the literature: $RCu.BF_3$ [2], $RCu(CN)MgBr$ [3] and $R_2CuZnCl$ [1b,c]. However, to our knowledge, little is known on the behaviour of organocopper reagents toward a molecule possessing two or more potential attacking positions : within this context , the case of γ-halo (oxy) substituted α,β-unsaturated esters or ketones which can react through either a 1,4-addition or a SN (or SN') allylic substitution is of particular interest :



X = Cl, Br, OAc, OTs ....
R_3 = Me, OMe .

Only few informations relative to such a competition are available in the literature : it is reported that RCu-$(AlCl_3)_n$ gives 1,4-addition with cyclic γ-acetoxy α,β-unsaturated ketones [4] and substitution (SN + SN') with cyclic γ-acetoxy α,β-unsatured esters [5] and that $R_2Cu(CN)Li_2.BF_3$ gives regioselective SN' substitution with γ -tosyloxy (mesyloxy) α,β-unsaturated esters [6].

We report in this note the reaction of γ-bromo α,β-unsatured esters **1** **(a-c)** with the organocopper reagents $R_2Cu(CN)Li_2.BF_3$. The results obtained showed that highly regioselective SN' substitution were realized whatever was the degree of substitution of the carbon bearing the leaving group [8] :



a) $R_1 = R_2 = Me$ b) $R_1 = Me, R_2 = H$ c) $R_1 = R_2 = H$

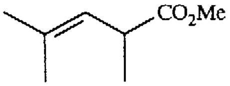
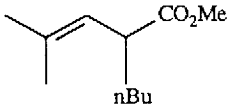
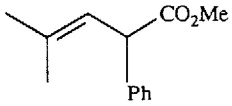
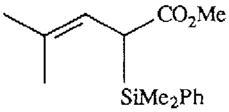
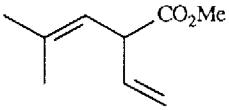
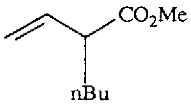
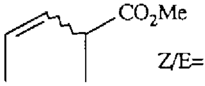
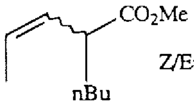
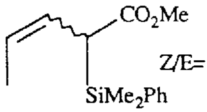
This reaction allowed the synthesis of several α-substituted β,γ-unsaturated esters which are not easily available by others methods.

The bromoesters **1(a-c)** were obtained with excellent yields by allylic bromination of the corresponding α,β-unsaturated esters with N-bromosuccinimide [9]. The products obtained by reaction of these bromides with $R_2Cu(CN)Li_2$ in the presence of BF_3 are gathered in Table 1. In all cases, highly regioselective substitutions α to the ester groups were observed. In some cases very small amounts (less than 5%) of the other regioisomer could be detected by ^1H NMR or capillary gaz chromatography. Interestingly, this formal SN_2' process was quite independent of the degree of substitution of the carbon bearing the bromine atom (compare entries 2,6,8). When R = alkyl (entries 1,2,6,7,8) this reaction constitutes an alternative to the deconjugative alkylation of enolate anions derived from α,β-unsaturated esters already described for the synthesis of α-alkyl β,γ-unsaturated esters [10]. This method was easily applied to the synthesis of α-aryl or α-vinyl β,γ-unsaturated esters (entries 3,5) which cannot be obtained by a reaction similar to the alkylation deconjugation of conjugated esters. Another useful extension of this method is the obtention of α-silyl β,γ-unsaturated esters (entries 4,9) by use of the silylcuprate reagent developed by Fleming [11]. The silyl esters obtained are important synthetic intermediates which undergo clean γ-substitution in the presence of Lewis acids [12] but which were not easily synthesized : since the direct silylation of metal dienolates led exclusively to the silyl dienol ethers [13], they have been prepared by coupling of the anion of ethyl α-trimethylsilyl acetate with vinylic bromides in the presence of $NiBr_2$. This synthesis gives however "generally modest and sometimes erratic yields" [12] so that the method described here seems to be the more efficient for the moment.

The reactions of the secondary bromide **1b** with the organocopper reagents can give rise to two stereoisomers Z or E and effectively the formation of E/Z mixtures was observed in all cases (entries 7,8,9). The Z geometry of the predominant isomer established from the coupling constants (10 - 11 Hz) between the two olefinic protons by ^1H NMR analysis is however quite intriguing. It has been reported in the literature that for simple allylic systems SN_2' reactions products are generally E/Z mixtures where the E compound is the major isomer [2a,14] and that in some cases only the more stable E isomer is formed [15]. With allylic substrates similar to **1** but in which a tosylate or a mesylate groups replaced the bromine atom, only the E isomer has been detected [6]. This latter result has been tentatively explained by the difference of stability of two reactive conformers in which the carbon-leaving group bond is in a plane perpendicular to that of the double bond *i.e.* aligned with the C_β and C_γ p orbitals. This hypothesis seems however not sufficient to explain why one conformer is so greatly destabilized and why a reversal of selectivity was observed in our case just by changing the leaving group.

Experiments are currently underway in our laboratory to obtain more arguments and to try to find a better explanation for these observations.

Table 1 - Synthesis of α-substituted β,γ-unsaturated esters

Entry	Substrate	Reagent[a)]	Product[b)]	Yield[c)]
1	**1a**	$(Me)_2Cu(CN)Li_2$		83%
2	**1a**	$(nBu)_2Cu(CN)Li_2$		71%
3	**1a**	$Ph_2Cu(CN)Li_2$		57%
4	**1a**	$(Me_2PhSi)_2Cu(CN)Li_2$		56%
5	**1a**	$(CH_2{=}CH)_2Cu(CN)Li_2$		51%
6	**1c**	$(nBu)_2Cu(CN)Li_2$		61%
7	**1b**	$(Me)_2Cu(CN)Li_2$	 Z/E=63/37	51%
8	**1b**	$(nBu)_2Cu(CN)Li_2$	 Z/E=79/21	85%
9	**1b**	$(Me_2PhSi)_2Cu(CN)Li_2$	 Z/E=84/16	53%

a)All the reactions were carried in THF at -78°C but for entry 4 (-25°C) using 1.5 equivalent of reagent and 1.5 equivalent of BF_3.

b)Satisfactory ^{1}H NMR,IR and microanalyses were obtained for all new compounds and Z/E ratio were determined by ^{1}H NMR (250 MHz) analysis.

c)Yields are given for pure compounds isolated by distillation and (or) column chromatography on silica gel.

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