Tetrahedron Letters,Vol.25,No.29,pp 3079-3082,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

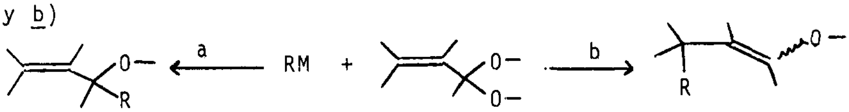
REACTIVITY OF RCu,BF_3 AND R_2CuLi,BF_3 TOWARDS ALLYLIC ACETALS AND ETHERS

A. Ghribi, A. Alexakis*, J.F. Normant
Laboratoire de Chimie des Organo-Eléments
Tour 44, 4 place Jussieu 75230 PARIS Cédex 05 France

Summary : Organocopper and cuprate reagents associated with Lewis acids, are highly reactive towards allylic acetals and ethers. Displacements of the alkoxy group occurs by SN_2' attack according to the various parameters of the reaction.

The reactivity of α-ethylenic acetals with organometallic reagents was explored some years ago[1-5] and recently reinvestigated again[6]. These last developments prompt us to report our recent results in this field.

Aside deprotonation, such acetals may afford two products, by a direct displacement of an alkoxy group (pathway a) or by an SN_2' displacement (pathway b)



Pathway a is selectively followed by titanium tetrachloride catalyzed aliphatic Grignard reagents[3], whereas pathway b is exclusively prefered by organolithium reagents[2,6] and copper catalyzed Grignard reagents[4,5]. Our finding that acetals are rapidly cleaved by organocopper and cuprate reagents associated with strong Lewis acids(see preceding letter), prompted us to examine the case of α-ethylenic acetals. A systematic study of the various parameters :

- organocopper or organocuprate reagent
- nature of the main metal (Mg or Li)
- choice of solvent (Et_2O or THF)

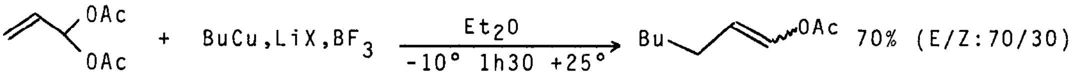
shows that all of these reagents are highly reactive towards acetals (10-30min at -35°C). In most cases both SN_2 and SN_2' attacks (pathway a and b) are observed. Moreover the SN_2/SN_2' ratio is the same from the begining up to the end of the reaction, indicating that this ratio depends exclusively on the intrinsic nature of the organometallic reagent, of the acetal and of the solvent. The reaction temperature as well as the nature of the counterion (reagents prepared either from RMgX or RLi) do not modify significantly this ratio. Pathway b (SN_2') is exclusively followed, only in the case of the unhindered acrolein diethyl acetal, and only with RCu,BF_3 in Et_2O (entry 1 and 4). In THF solvent or with cuprate reagents R_2CuM,BF_3 (M=Li or MgX) a mixture of both SN_2 and SN_2' is obtained. Pure SN_2 attack cannot be attained. Interestingly the E/Z ratio of the obtained enol ether is completely reversed as compared with BuLi alone (entry 3).

Crotonaldehyde diethyl acetal shows the dramatic influence of a substituent in γ position. This time, pure SN_2' attack cannot be attained with any reagent (except BuLi alone, entry 9). On the other hand RCu,BF_3 in THF (entry 6) reacts exclusively by pathway a (SN_2 attack). Copper catalyzed Grignard reagents react sluggishly but cleanly by pathway b with this acetal[4]. Thus, the highly increased reactivity of these organo copper, BF_3 complexes is obtained at the expense of their selectivity.

Cinnamaldehyde diethyl acetal reacts in a strikingly different manner with RCu,BF_3 than with organolithium[2,6] or Grignard reagents[1,4] (with or without copper catalysis). With the organolithium reagents only addition to the double bond is observed (entry 13), whereas with the former reagent,pure SN_2 attack occurs (entry 12).

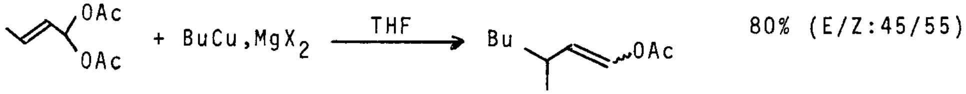
Finally a last example is offered by cyclohexenone ethylene glycol ketal. Organolithium reagents react by proton abstraction in the dioxolan ring[6], and copper catalyzed Grignard reagents react only by pathway b (SN_2')[5]. The same pathway is exclusively followed by R_2CuLi,BF_3 in Et_2O.Moreover, the increased reactivity of such cuprates allows the reaction of Me_2CuLi introducing the methyl group which could not be transferred previously[4,5].

An alternative to acetals can be found in certain cases with acylates. These compounds are easily prepared from the corresponding aldehyde[7,8] (and an acid anhydride). Although it has been reported that they react with R_2CuLi to afford a mixture of various products, we found that BuCu,LiX,BF_3 is an efficient reagent for a clean SN_2' attack.

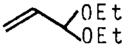
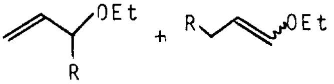
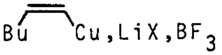
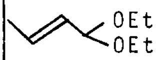
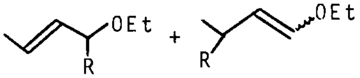
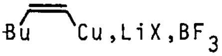
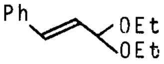
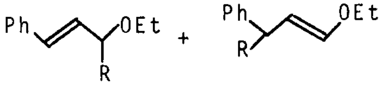
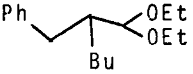
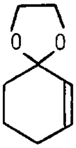
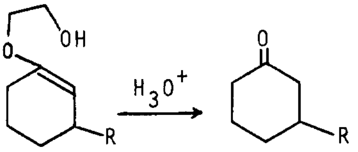


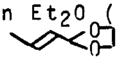
The same reaction may also be performed in a simpler manner with BuCu,MgX_2 in THF without BF_3 (-15°, 10min) (83%, E/Z:45/55).

Crotonaldehyde acylate reacts also by pathway b[10] :

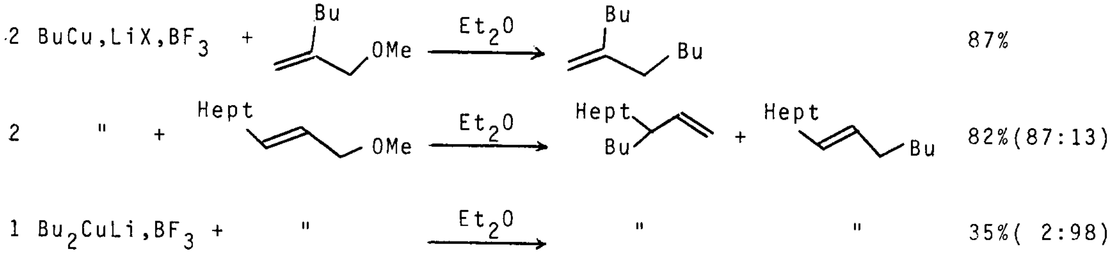


Reactions of R"Cu",BF_3 with various α-ethylenic acetals and ketals(-35°,1h)

Entry	Acetal	Copper reagent 2 eq.	Solvent	Product[a] (E/Z ratio)		Yield[b]
						
1		BuCu,LiX,BF_3[c]	Et_2O	0	100(15/85)	77%
2		" [c]	THF	26	74(12/88)	65%
3		BuLi [d]	Et_2O	0	100(86/14)	80%
4		 Bu Cu,LiX,BF_3	"	0	100(15/85)	66%
						
5		BuCu,LiX,BF_3[c,e]	Et_2O	50	50(73/37)	90%
6		" [c]	THF	100	0	87%
7		Bu_2CuLi,BF_3	Et_2O	69	31(66/33)	67%
8		" [c]	THF	50	50(54/46)	69%
9		BuLi [d]	Et_2O	0	100(80/20)	78%
10		 Bu Cu,LiX,BF_3	Et_2O	31	69 -	60%
						
11		BuCu,LiX,BF_3	Et_2O	52	48(90/10)	91%
12		"	THF	100	0	90%
13		BuLi [d]	Et_2O			60%
						
14		Et_2CuLi,BF_3	Et_2O			85%
15		Me_2CuLi,BF_3	"			92%

a. Ratio determined by G.C. and by ^1H NMR
b. Yield of isolated products, by distillation.
c. BuCu,MgX_2,BF_3 and $Bu_2CuMgCl$,BF_3 behave similarly
d. Analogous results were obtained in Et_2O (réf.2) and in hexane (réf.6)
e. The same reaction performed with  afforded exactly the same result

Lastly, preliminary studies shows that allylic ethers are able to react, contrary to a previous report dealing only with cinnamyl substrates[9].



As was the case for acetals, RCu,BF_3 shows a preference for S_N2' attack, whereas R_2CuLi,BF_3 prefers pathway a (S_N2).

It appears that organocopper and cuprate reagents associated with Lewis acids are of increased reactivity towards allylic ethers, acetals and acylates. A better control of their regioselectivity may be attained by variing the Lewis acid and these studies are presently under way.

Aknowledgements : *We thank the C.N.R.S. for financial support (ERA 825)*

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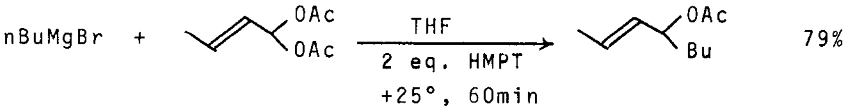
10. We also found that RMgX, 2 HMPT gives a clean S_N2 type product :



(Received in France 5 April 1984)