

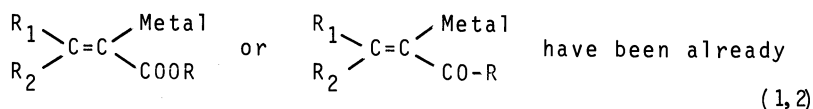
CARBOCUPRATION OF ACETYLENIC ACETALS AND KETALS * SYNTHESIS OF
 α - β ETHYLENIC ACETALS, AND OF DIENALS AND DIENONES

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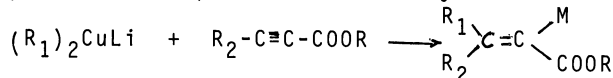
Abstract - The regio selectivity of the carbocupration reaction of substituted and non substituted α -acetylenic ketals and acetals is discussed. Lithium diorganocuprates add regio and stereo-selectively. The functionalized vinyl cuprates thus obtained, can be trapped by a large variety of electrophiles : alkyl, alkenyl, alkynyl and aryl halides, α - β unsaturated esters or ketones. The reaction is illustrated by the synthesis of manicone, of pure E geranial, and of 2,4-(E,Z) dienals.

INTRODUCTION

Synthons of type :

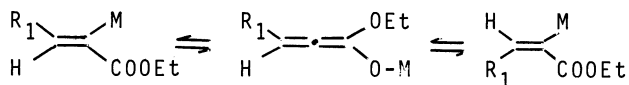


prepared successfully via carbocupration of α -acetylenic esters and ketones



They represent potent synthons but two important limitations have been observed :

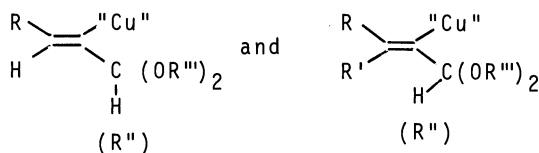
- Stereoselectivity : The reaction temperature must be kept very low, or else they isomerise readily through the corresponding allenolate (3)



and dealing with ketones, it is practically impossible to avoid this process (4). In this regard, use of alkyl copper, trialkyl boron reagents proves useful (5).

- Reactivity : These organometallics react very sluggishly with electrophiles which have to be used in large excess, and raising the temperature is often necessary, at the expense of isomerization (1,6) except in some case (7).

We have developed synthons of type :



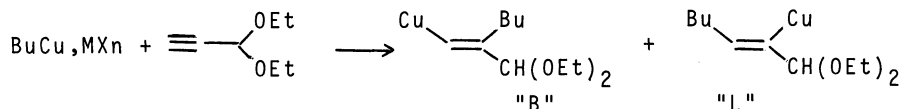
which are easily attainable via carbocupration of α , β -acetylenic acetals (ketals) ; they are stable towards isomerisation, and much more reactive than the corresponding allenolates. The first members of this series (R=R'=H) have been already prepared by an other way (8-11) and reacted with some electrophiles : α , β ethylenic ketones, allylic halides and allylic epoxides (8-11).

This talk is concerned with the preparation, and synthetic use, of such vinylic cuprates bearing an acetal moiety geminated to copper.

ADDITION OF ORGANO COPPER REAGENTS TO UNSUBSTITUTED ACETALS

The regioselectivity observed in the addition of organocopper derivatives to α -acetylenic acetals is highly dependent on the nature of the organometallic precursor (RMgX or RLi), on the nature of the organo copper reagent (RCu, MX or R_2CuM) and on the nature of the solvent.

Two isomers can be obtained via carbocupration of 1,1-diethoxy propyne :

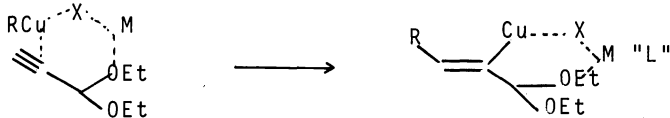


The linear "L" isomer can also decompose, by β -elimination, to the corresponding alkoxy allene

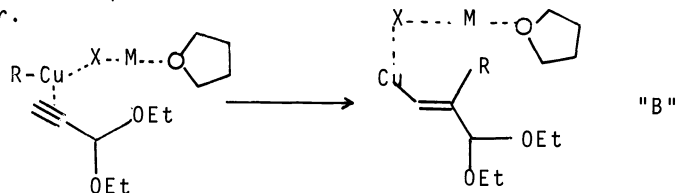


Organo copper and cuprate reagents derived from Grignards are prone to give this β -elimination even at -45° for the former, whereas those derived from lithium reagents are much more stable with regard to allene formation : at $-20^\circ C$ in ether or even $0^\circ C$ in THF, this reaction is still avoided.

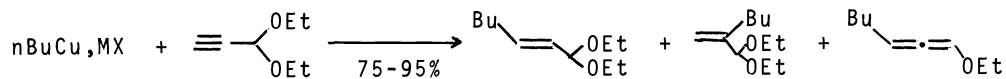
The branched isomer corresponds to the normal addition scheme of organo copper (cuprate) reagents towards terminal alkynes (non functionalised) (13,14). Chelation of the cluster by the oxygen atom of the acetal is assumed, to explain the reverse regiochemistry (15,16)



which is less operative, when a more basic solvent like THF is used instead of ether.

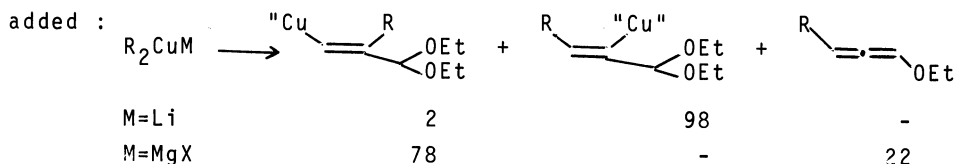


The organo copper reagents RCu, MX(Li, Mg) are not very sensitive to the nature of the solvent :



MX	Solvent	"L" %	"B" %	3 %
LiX	ether	24	76	0
	THF	53	47	0
MgX ₂	ether	22	64	14
	THF	59	38	3

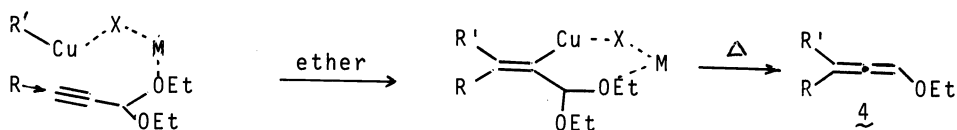
but high regiochemical control is observed with the cuprate reagents : the "L" regio isomer is obtained almost pure in ether, with the lithium cuprate, and the "B" isomer is obtained from the magnesium cuprate in THF : in this later case, the L isomer has, in fact, decomposed to the non metallated allenic ether 3, which remains unaffected when any further electrophile is



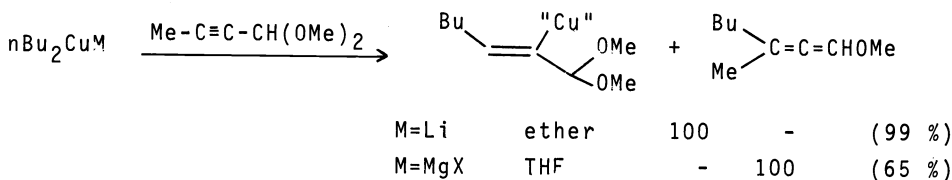
ADDITION TO SUBSTITUTED ACETALS

The triple bond is now less reactive, and a higher temperature has to be applied, so that β elimination from the "L" isomer is favored.

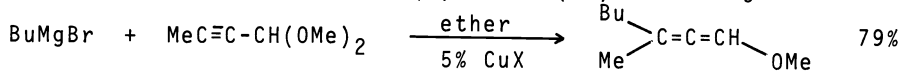
The electron donating substituent tends to favor the sense of the addition in the same way as does the chelating ability of the acetal moiety



Organo copper, or cuprate reagents derived from magnesium, only afford the allene derivative 4. The organo copper species derived from lithium reagents also lead to some allene, but lithium dialkyl cuprates are sufficiently reactive, at a lower temperature, to yield the pure linear addition product.

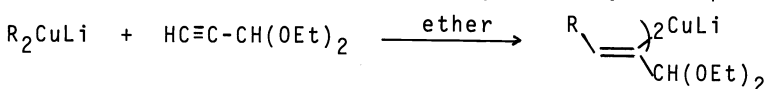


in each case, both alkyl groups of the cuprate are consumed. The latter alkoxy allene may be obtained, even more conveniently by use of a Grignard and a catalytic amount of Cu(I) salts (17) according to :



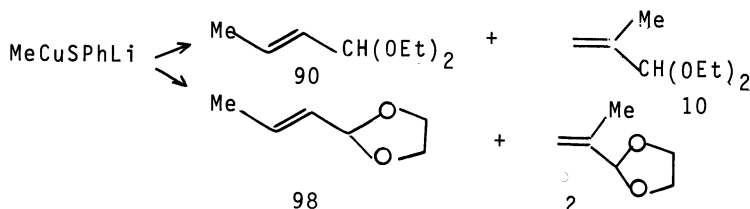
GENERALIZATION

The regioselective addition of dithium dialkyl cuprates to propiolaldehyde acetal has been extended to a large variety of cuprates

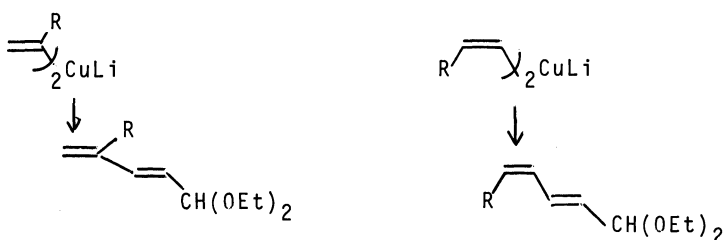


R =	Me	Et	n.Bu	sec Bu	ter Bu	Phenyl	Vinyl
Yields %	67	92	94	89	76	65	70-80

Only in the case of a ditertiaryalkyl cuprate, are observed regio (25%) and stereo (5%) isomers. The well known inability of methyl copper to add smoothly to alkynes, as compared with its higher homologs, can be circumvented here. Whereas the addition of Me_2CuLi to the diethylacetal gives a 90/10 ratio of L/B isomers, use of a dióxolan raises the regio selectivity to 98/2. Lithium dimethyl cuprate is not as convenient as methyl thiophenyl cuprate, and the latter transfers the methyl moiety to the acetylenic cyclic acetal with high regioselectivity

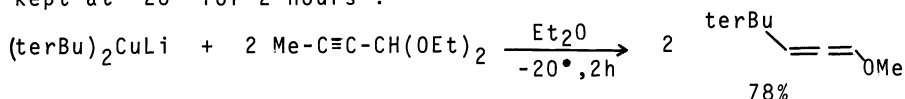


Divinyl cuprates also add regio- and stereo-selectively: the Z divinyl cuprates, obtained by carbocupration of acetylene, are more sluggish and are best used in a 1/1 ratio towards the acetal.

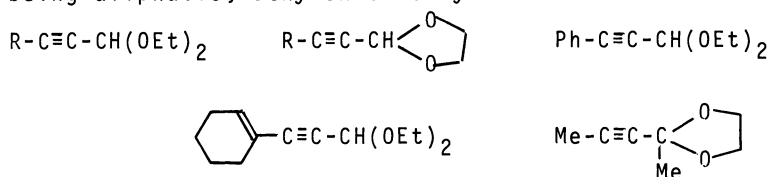


The dienic acetals, thus prepared, are useful synthons for Diels Alder reactions, or for natural product synthesis (pear ester (18) 1-3-5-undecatrienes (19)).

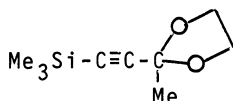
As for disubstituted acetals and ketals, they are much less reactive, and only primary or secondary dialkyl cuprates can be used (80-90%). Di tertio-butyl cuprate adds one tertbutyl group readily. By raising the temperature to -30° , the second one may be also added, but β -elimination now occurs, and the alkoxy allene may be the only isolated product if the reaction is kept at -20° for 2 hours:



Various acetylenic acetals or dioxolans may be used also, the organic chain being aliphatic, ethylenic acetylenic or aromatic:

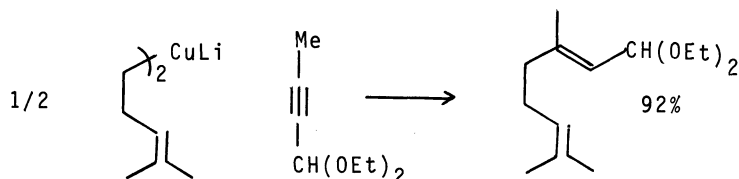


The addition does not take place on the silyl substituted acetal:

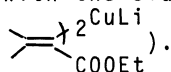


SYNTHETIC USE OF THE GEM DIALKOXY VINYL CUPRATES

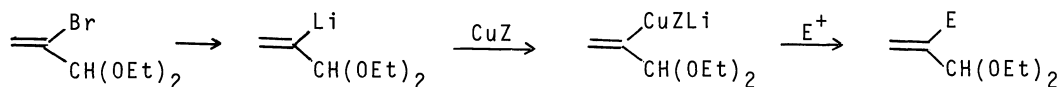
The simple hydrolysis in buffered medium yields the corresponding acetal. The following example shows the synthesis of geranial acetal, which can be further hydrolyzed to pure (>99%) E Geranial:



For further synthetic use, the metallated species may be treated with a large array of electrophiles. Worth of note is the fact that these cuprates, on an average, are more reactive than non functionalized vinyl cuprates, and are able to transfer both vinylic moieties in most cases (compare also with the sluggishness of the corresponding carbethoxy vinyl cuprates

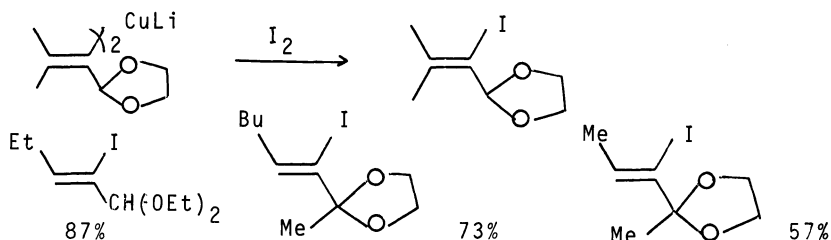


Several authors have already used the unsubstituted acetal, prepared via: (8-11)



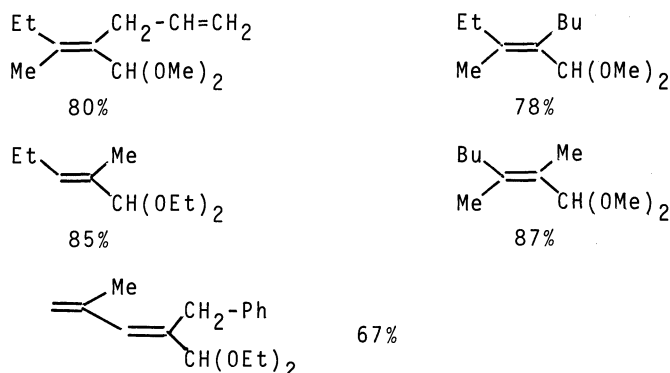
for conjugate addition to enones, opening of α -ethylenic epoxides, or coupling with allylic halides, but not with alkyl, alkenyl, aryl or benzylic ones.

Iodination is performed readily and gives the iodoacetals

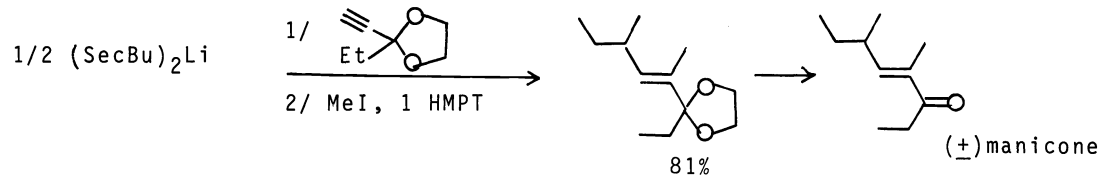


These iodo compounds may be in turn metallated to the corresponding lithio derivatives (20), for reactions where the cuprate itself is not convenient: addition to ketones, esters ...

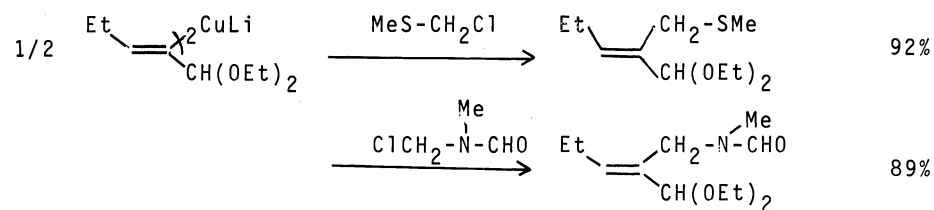
Alkylation is also possible. In the presence of THF, methyl iodide reacts smoothly ($\approx 80\%$). The addition of one equivalent of HMPT improves the yield. For higher primary alkyl iodides, use of 4 equivalents of HMPT is better. Allylic bromide reacts without this addend, whereas benzyl bromide requires one equivalent of it. In all cases, the two vinylic groups of the cuprate are transferred.



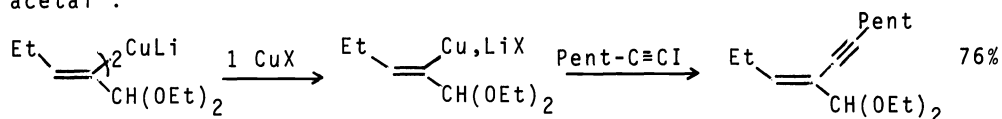
For an illustration, we have synthesized the alarm pheromone of *Manica mutica* (21) according to



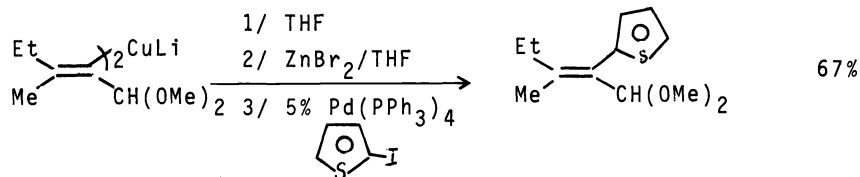
Methyl chloromethyl sulfide (22) leads to the corresponding allylic thioether, whereas N-Methyl chloromethyl formamide (22) affords the allylic formamide:



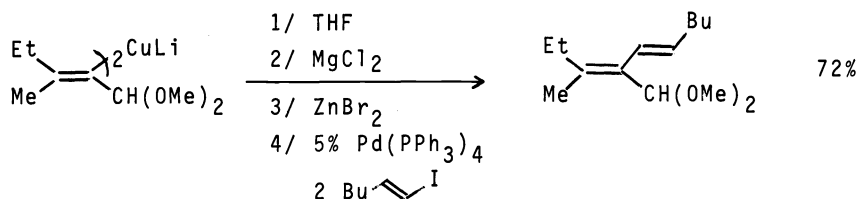
Coupling with less reactive halides is also possible : with 1-halo-1-alkynes, the divinyl cuprates are not suitable, as already described (23), but reverting to the vinyl copper reagent allows coupling to the desired enynal acetal :



Vinylic or aryl halides have also been coupled successfully, according to previous studies performed in our laboratory (24,25) which showed that transmetalation and palladium catalysis led to the desired coupling.

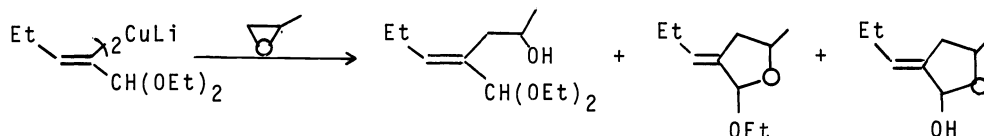


Both vinylic groups are consumed if the following procedure is followed :

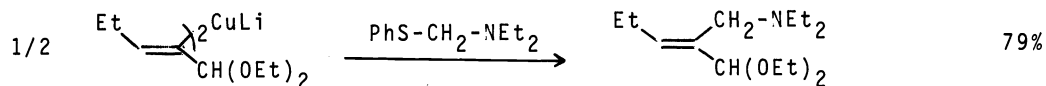


α - β unsaturated epoxides are known to react with alkenyl cuprates bearing an α acetal group (11). Simple epoxides also react with our alkenyl cuprates, but only one alkenyl group is transferred in this case.

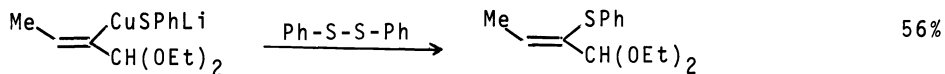
The reaction proceeds smoothly, but the desired alcoholic acetal suffers from hemiacetalization



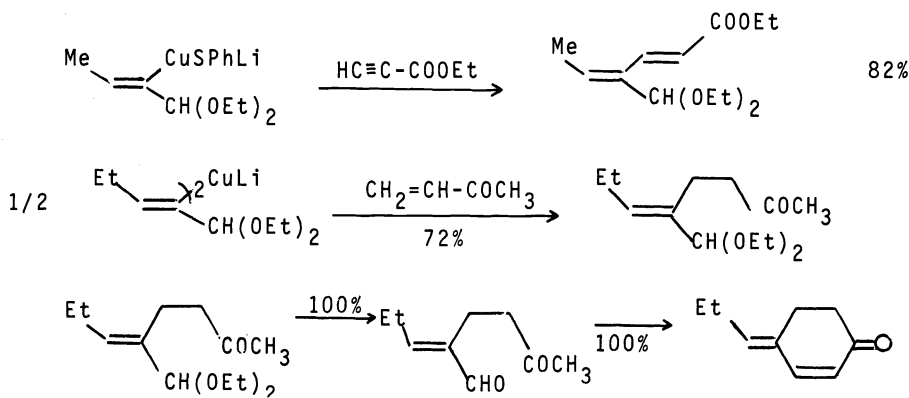
Aminomethylation can also be performed, by use of thioaminals (26) :



and the vinylic cuprates can be derivatized to vinyl thio ethers, according to (27) :

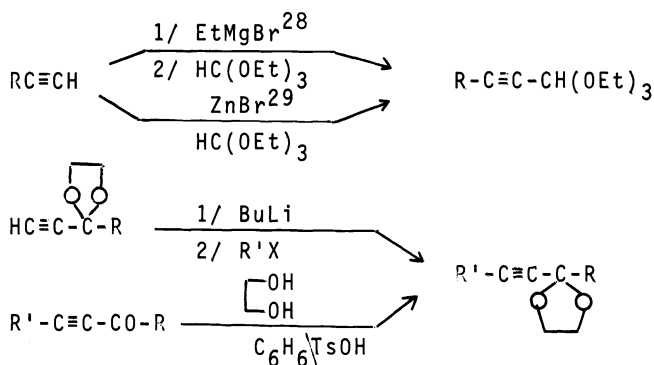


Addition to α , β -unsaturated carbonyl derivatives (8-10) is readily obtained in the case of propiolic esters, or α , β -ethylenic ketones

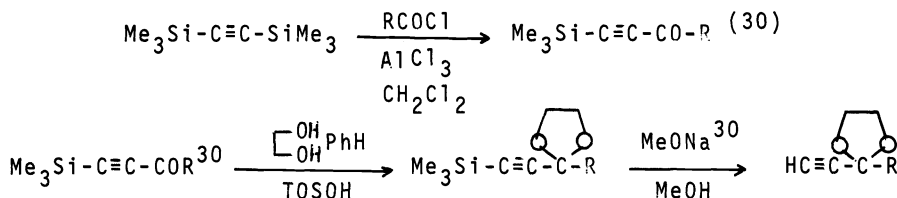


In the latter case, further hydrolysis and crotonisation leads quantitatively to 4-vinyliden-cyclohex-2-enones with a given geometry.

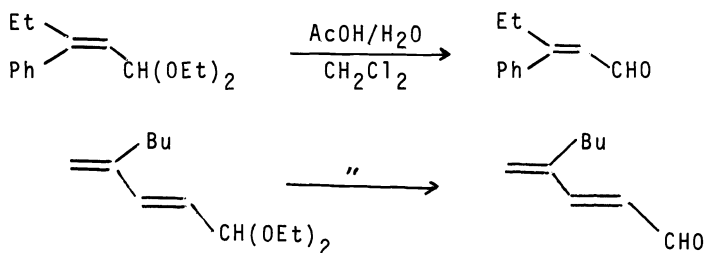
In this study, the starting acetylenic acetals have been prepared according to conventional routes :



But terminal acetylenic ketone acetals cannot be prepared conveniently by direct ketalization with glycol, and we used the following efficient pathway:



Finally we have checked, on several of the preceding ethylenic ketals or acetals, that mild hydrolysis by acetic acid/water, or the milder Bestmann's procedure(28) leads to the corresponding carbonyl compound without isomerisation :



CONCLUSION

The carbocupration of acetylenic acetals is a very competitive methodology as compared to the carbocupration of acetylenic esters, ketones or aldehydes. Although the former substrates are less reactive, they permit the obtention of highly pure products as far as the stereochemistry of the double bond is considered. The obtained alkenyl cuprates are also much more reactive than those obtained by the carbocupration of acetylenic esters. Hence an easy access to very elaborated synthon for further use in multistep synthesis.

This general method may also be used for the synthesis of many natural product such as geranial, (+) Manicone and variously substituted 2,4(E,Z)-dienals.

ACKNOWLEDGEMENTS

We acknowledge for the financial help from C.N.R.S. (ERA 825) and we thank Mrs Mathé for typing the manuscript.

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