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ALKENYL-COPPER DERIVATIVES 24[1]

STEREOSPECIFIC SYNTHESIS OF ENONES BY PALLADIUM CATALYSED ACYLATION OF ALKENYL-COPPER REAGENTS

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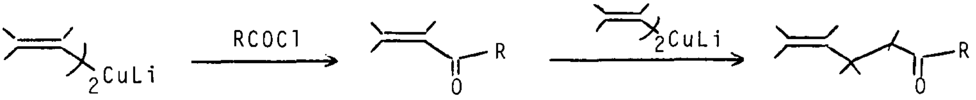
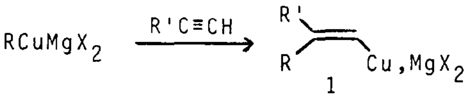
Summary :

α,β-ethylenic ketones and α,β , α',β' diethylenic ketones with a stereodefined substitution pattern are easily prepared by coupling of alkenyl copper and cuprate reagents, directly obtained by carbocupration of alkynes, with acid chlorides and anhydrides in the presence of a catalytic amount of Pd° complex.

Acylation of organocopper derivatives is considered as one of the best methods for the synthesis of ketones[2]. In the case of alkenyl copper or cuprate reagents, however, this method suffers from a serious drawback : the conjugate addition of the cuprate to the newly formed ketone[3] :



It was our goal to use the alkenyl copper 1 and cuprate reagents 2, obtained by carbocupration of alkynes[4], to the synthesis of α,β-ethylenic ketones with a stereodefined substitution pattern.



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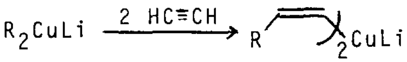
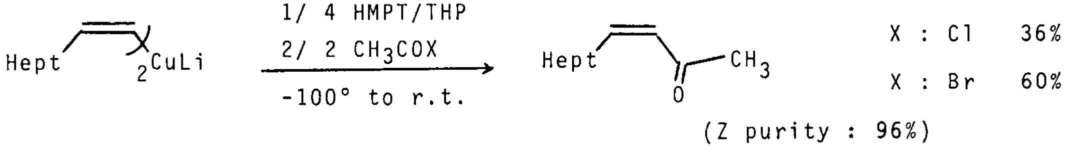


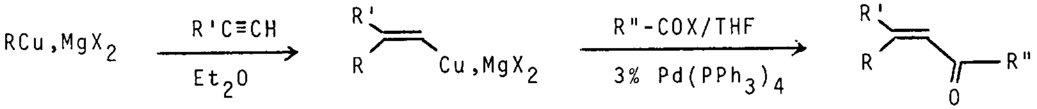
2

Alkenyl copper reagents 1 are not very reactive towards acyl halides and a 25-35% yield of isomerised ketone is usually obtained[5]. No conjugate addition to the strongly hindered enone is either observed. On the other hand, cuprates 2 are very reactive, and when the reaction is performed with a strongly polar cosolvent, such as HMPT, in order to enhance the rate of acylation and slow down the rate of the undesired conjugate addition[6], a moderate to good yield (based on the use of both alkenyl groups of the cuprate) of non-isomerised ketone is obtained



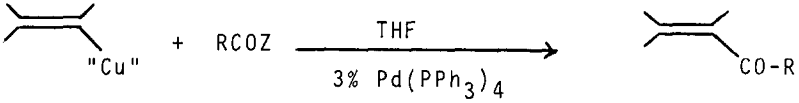
Among the various acylation methods, the Pd° catalysed ones attracted[7] our attention, since we knew from previous studies that alkenyl copper derivatives undergo Pd° catalysed reactions, such as the coupling with alkenyl and aryl halides[8].

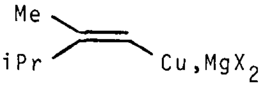
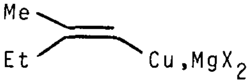
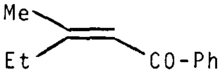
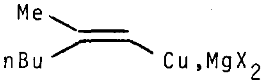
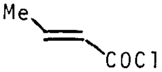
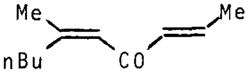
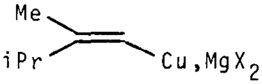
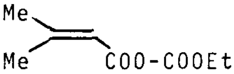
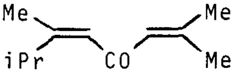
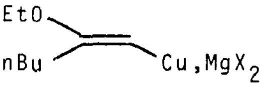
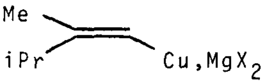
We found that alkenyl copper reagents, associated with magnesium salts **1** are also acylated in the presence of Pd° catalyst to afford the desired α,β-ethylenic ketone with a stereodefined substitution pattern :



In the case of lithium dialkenyl cuprates **2**, many alternatives are possible to accomplish succesfully this acylation. One of them consists in the transmetallation of this organometallic reagent into the zinc species[8] which is known to be efficiently acylated under Pd° catalysis[7i] (entry 1). Another possibility, which has the advantage of using both alkenyl groups of the Z dialkenyl cuprate, is to transform this species into two equivalents of Z alkenyl copper reagent, associated with magnesium salt by addition to the lithium cuprate of two equivalents of magnesium halide followed by addition of one equivalent of copper halide (entry 2). The Z α,β-ethylenic ketones, thus obtained, are of high stereoisomeric purity ($>$ 99%). They may be easily isomerised into the pure E ones by treating them with dilute acid. Thus, our method may afford either the Z or E ethylenic ketone in high yield.

Alkenyl copper reagents **1** react with a great variety of acyl chlorides (entries 3-9), to produce monoethylenic or di-ethylenic ketones (entries 4-6) in high yield. The substitution pattern of the alkenyl copper reagent is fully retained as judged by capillary glass chromatography. Indeed, it is very easy to isomerise these ketones by dilute acid and, thus, to have both isomers for comparative purposes. Ethyl chloroformate also reacts (entry 9) with reagents **1** although in this case the yield is somewhat lower. Noteworthy is also the possibility to use mixed carbonic-carboxylic anhydrides in this acylation reaction (entries 5,7). These anhydrides are



Entry	Copper reagent	Acyl derivative	Product[a]	Isolated yield[b]
1		MeCOCl (+ $ZnBr_2$)	 [c]	80%
2		nBuCOCl (+ 2 $MgCl_2$) (+ 1 CuBr)	 [d]	76%
3		tBuCOCl		84%
4		PhCOCl		73%
5	"	PhCOO-COOEt	"	80%
6				85%
7				58%
8		MeCOCl		74%
9		Cl-COOEt		56%

a. All spectroscopic data agree with the proposed structures
b. Isolated by distillation
c. Only one alkenyl group of the cuprate is used
d. Both alkenyl groups of the cuprate react

a useful alternative for the cases where the acid chloride cannot be prepared from the corresponding acid. This is the first report on acylation with these anhydrides under Pd° catalysis.

Finally we should also note that even functionalised alkenyl copper reagents are acylated, such as the one bearing an enol ether functionality (entry 9).

The synthesis of natural products using this method is underway and will be reported elsewhere.

Acknowledgements -

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