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ORGANOCOPPER CONJUGATE ADDITION REACTION IN THE PRESENCE OF TRIMETHYLCHLOROSILANE

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Abstract - In the presence of TMSCl, the conjugate addition of organocuprates to various α,β-unsaturated esters, amides, ketones and nitriles is greatly improved. The reaction is faster, the yields are very high and the reaction is very clean.

A recent communication[1] on the use of the combined organocuprate-trimethylchlorosilane reagent for conjugate addition reaction to α,β-unsaturated ketones, prompts us to report our own results concerning α,β-unsaturated ketones, esters, amides and nitriles. Organocuprates are known, for years now, to be the reagents of choice for the efficient 1,4-transfer of an alkyl (aryl or vinyl) group to an α,β-unsaturated carbonyl substrate[2]. In the classical procedure, the carbonyl compound is added to a cuprate solution and the resulting intermediate enolate is often trapped, as trimethylsilyl enol ether, by subsequent addition of trimethylchlorosilane[3]. However, in many instances, this procedure does not avoid side reactions of the enolate, such as Michael or aldol reactions, which lower the overall yield of the 1,4-addition product[2].

In 1980, in a study of the conjugate addition of organocuprates to unsaturated aldehydes, Normant et al.[4] proposed an alternative procedure, in which trimethylchlorosilane is added before the enal in order to immediately trap the resulting enolate. This idea was based on the observation that the reaction between TMSCl (trimethylchlorosilane) and R_2CuLi was very slow[5], while the 1,4-addition of R_2CuLi to an enal and the O-silylation of the resulting enolate were fast processes. In addition, it was observed that the presence of TMSCl enhances the rate of the conjugate addition reaction. Using this procedure the yield of the conjugate adduct of Bu_2CuLi to acrolein jumped from 25% to 60%.[4a]

To try to extend this concept to other carbonyl systems, we have undertaken a screening of various unsaturated carbonyl compounds using this new procedure and we compared these results with the ones obtained by the more classical conjugate addition reaction in the absence of TMSCl. Our studies were mainly directed to the improvement of the yield obtained with α,β-ethylenic esters and amides, particularly in their reaction with Me_2CuLi and Ph_2CuLi, the less reactive homocuprates but among the most useful ones. Indeed, Me_2CuLi has been claimed to be unreactive towards α,β-unsaturated amides[6], although N-tosyl amides were shown recently to readily react with organocopper reagents[7]. On the other hand, competitive 1,2-addition or more complex side-reactions were observed with unsaturated esters[8]. These difficulties were only partly overcome by the use of $RCu\text{-}BF_3$[9] system or the use of higher order cuprates $R_2CuCNLi$.[10,11]

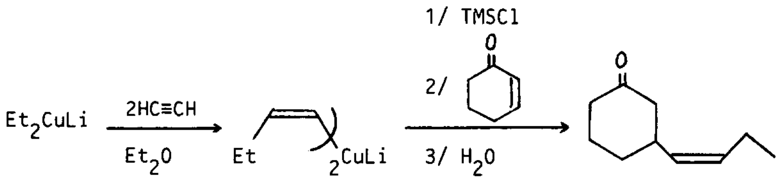
The original procedure of Normant et al.[4] requires, along with TMSCl, one equivalent of NEt_3 and/or one equivalent of hexamethylphosphotriamide (HMPT). These two latter reagents accelerate the O-silylation of the resulting enolate. In their absence almost no silylation occurs, but the presence of TMSCl still accelerates the reaction rate and permits a very clean reaction.

Some of our most significant results are shown in the table.

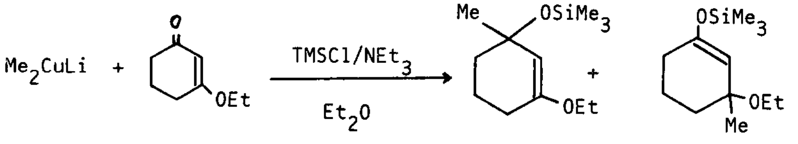
Esters : In most cases, the reaction without TMSCl does not afford the expected 1,4-adduct in significant yield (except for nBu_2CuLi) although the starting material is totally consumed to unidentified high molecular weight products. In contrast, with TMSCl present, quantitative glc yields (75-95% isolated) of 1,4-adducts are obtained and no side-products were detected. These experiments are extremely clean, as they lead through the whole reaction process, only to the starting material and the final 1,4-adduct. Together with these high yields, we note a significant enhancement of the reaction rate, particularly with Me_2CuLi and Ph_2CuLi. More importantly, these results were obtained with only a slight excess (20%) of the organometallic reagent.

Amides : The results obtained with amides are most noteworthy since it was known that cuprates do not react under the classical reaction conditions. Grignard[13] or organolithium[6,14] reagents also undergo conjugate addition but large excesses of the organometallic reagents are required. Here again, when the reaction is run in the presence of TMSCl, excellent yields of the 1,4-adduct are obtained, in total contrast to the experiments where TMSCl is omitted.

Ketones : The results obtained with enones are not as clearcut as with esters and amides, although the same trend is noted : i/ improved yields, ii/ enhanced reactivity, iii/ absence of any by-products. This is illustrated by the following two examples :

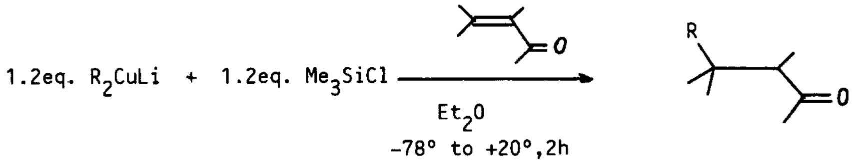


86%
(66% without TMSCl)[15]



95%

2 : 1 (no reaction without TMSCl)[16]

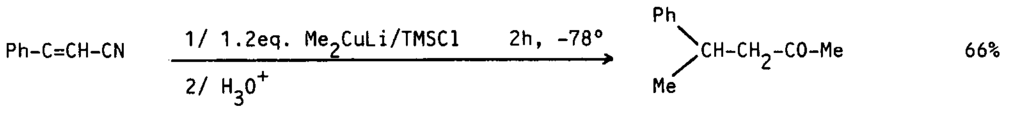


Carbonyl compound	R_2CuLi	Isolated yield[a]	
		with TMSCl %	without TMSCl %
Ph-CH=CH-COOEt	Me_2CuLi	97	38
Ph-CH=CH-COOtBu	Me_2CuLi	95	21
Me-CH=CH-COOEt	Me_2CuLi	94	67
	Ph_2CuLi	95[b]	29
	nBu_2CuLi	97	89
CH_2=CH-COOMe	Me_2CuLi	87a	64
	Ph_2CuLi	75[b]	18
	nBu_2CuLi	83	78
Ph-CH=CH-CO-NMe_2	Me_2CuLi	95	0
Me-CH=CH-CO-NMe_2	Ph_2CuLi	86	0
Ph-CH=CH-CO-NH-COMe	Me_2CuLi	93	0
Me-CH=CH-CO-NH-COMe	Ph_2CuLi	88	0

a. Identical reaction conditions were used with or without TMSCl
b. 48h at 20°C
c. 7h at 20°C

3-Alkoxy-cyclohexenone was reported to be unreactive due to high reduction potential (E_{red}:-2.43V)[16]. In the presence of TMSCl the reaction does occur although a mixture of 1,2-and 1,4-adducts was obtained.

Nitriles : α,β-unsaturated nitriles were also investigated. While, in the absence of TMSCl, only polymeric materials are obtained, a clean reaction takes place with TMSCl. However, the isolated product is the dialkylated ketone.



$$\text{Ph-C=CH-CN} \xrightarrow[\text{2/ } H_3O^+]{\text{1/ 1.2eq. } Me_2CuLi/TMSCl \quad \text{2h, -78°}} \begin{matrix}\text{Ph}\\ \\ \text{Me}\end{matrix}\!\!>\!\text{CH-CH}_2\text{-CO-Me} \qquad 66\%$$

$$\text{Me-CH=CH-CN} \xrightarrow{\quad '' \quad} Me_2CH\text{-}CH_2\text{-CO-Me} \qquad 72\%$$

$$CH_2\text{=CH-CN} \xrightarrow{\quad '' \quad} \text{Me-CH-}CH_2\text{-CO-Me} \qquad 69\%$$

Owing to the simplicity of the experimental procedure, this new methodology greatly enhances the synthetic applicability of the conjugate addition of organocopper reagents to α,β-unsaturated carbonyl compounds. We are currently investigating extension of this concept of trapping reactive intermediates with TMSCl in the addition of organometallic reagents to other substrates.

Typical procedure : To a solution of lithium diorganocuprate (12mmol) in 50ml Et_2O are added, at -78°C, successively 12mmol of TMSCl in 5ml Et_2O and 10mmol of α,β-ethylenic ester or amide in 10ml Et_2O. The stirred mixture is allowed to warm slowly up to room temperature (1h). A yellow precipitate appears during this time. Stirring is continued at +20°C for 2h (unless otherwise stated), then hydrolyzed with aqueous NH_4Cl (20ml) or aqueous KCN and worked up as usual.

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