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COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMAGNESIUM REAGENTS TO α, β-ETHYLENIC ESTERS: A SIMPLE HIGH YIELD PROCEDURE.

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Abstract : *The conjugate addition of organomagnesium reagents to α, β-ethylenic esters is performed in THF, at room temperature (30 min to 1.5 h), in the presence of CuCl (3%) and Me_3SiCl (1.2 eq.). Good yields of 1,4-addition products are obtained according to this very simple procedure.*

Conjugate addition of organocopper or cuprate reagents to α, β-ethylenic esters is not easy to perform and very often requires both the use of various additives and low temperatures[1]. In addition, the yields based on the starting organometallic reagents remain moderate since they range from 10 to 40%[2]. These features represent a serious drawback for large scale preparative applications.

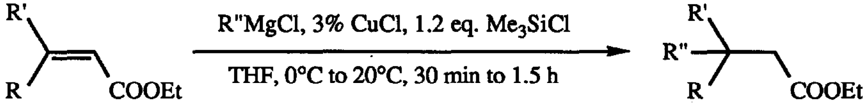
In theory, the copper-catalyzed conjugate addition of organomagnesium reagents to α, β-ethylenic esters appears more attractive. In fact, Munch-Petersen has shown that, in ether (0°C, 1 to 1.5 h), this reaction effectively leads to the 1,4-addition products in good yields (50 to 90%)[3]. However, the α, β-ethylenic esters must bear a large alkoxy group (e.g. s- or t-butyl ester) to avoid the competing Michael addition process and the reaction requires an important excess of the organomagnesium reagent (1.5 to 10 eq.)[4]. On the other hand, one example of copper-catalyzed addition has also been performed in THF, at -80°C, in the presence of 10% $CuBr.Me_2S$, Me_3SiCl (2eq.) and HMPT (3eq.)[5]. These reaction conditions are not suitable for preparative applications; moreover, no successful extention to the less reactive β-bisubstituted α, β-ethylenic esters, has been reported to our knowledge[6].

Finally, two cases of conjugate addition in good yields of organomagnesium reagents to enoates in the presence of Cu^{II} salts (1 to 5% Cu^{II} salt, 1.5 eq. RMgBr) have been recently reported[7] (yields of crude product: 99%). The reaction takes place in a mixture ether/THF at -46°C (1 h) in the presence of Me_3SiCl (3 eq.) or Me_3SiCl/HMPT (3eq./3eq.).

The course of our study on the organomanganese chemistry[8] has induced us to reinvestigate the copper-catalyzed addition of organomagnesium reagents to α, β-ethylenic esters. We now report that good yields of 1,4-addition products are obtained in many cases by adding an organomagnesium reagent to an α, β-ethylenic ester, in THF at room temperature, in the presence of 3% CuCl and Me_3SiCl (1.2 eq.). Some examples are listed in Table I.

This reaction allows to perform in good yields the 1,4-transfer of primary, secondary and tertiary alkyl groups to various β-monosubstituted α, β-ethylenic esters (entries 1 to 4 and 8 to 12). Even the β, β-bisubstituted α, β-ethylenic esters can be used successfully (entries 13 and 14) in spite of their well known poor ability to react with organocopper reagents to give the 1,4-addition products (e.g. with lithium dibutylcuprate the 1,2-addition occurs mainly)[9].

Table I

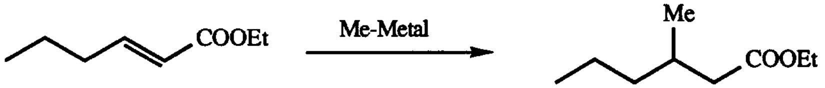


Entry	R	R'	R" ($R"MgCl$)	Yield (%) of Isolated Product[a]
1	H	Me	Me	83
2	H	Me	Bu	94
3	H	Me	iPr	86
4	H	Me	tBu	86
5	H	Me	Ph	20 (62)[b]
6	H	Me	$CH_3CH=CH$	34 (45)[c]
7	H	Pr	$CH_2=CHCH_2$	0[d]
8	H	Pr	Bu	95
9	H	Pr	iPr	95
10	H	Pr	tBu	91
11	H	iPr	Bu	82
12	H	Ph	Bu	88
13	Me	Me	Bu	82
14	Me	Me	iPr	73[e]
15	Me	Me	Me	16[f]

a) All products have been isolated by distillation. **b)** 62% in the presence of 2 eq. of DMAP[10]. **c)** 43% in the presence of 2 eq. of DMAP[10]. **d)** Under the conditions described above, allylmagnesium chloride reacted with Me_3SiCl. In the absence of Me_3SiCl (only 3% CuCl), a mixture of the starting methyl crotonate with the 1,2-addition product was obtained (76% yield based on $CH_2=CHCH_2MgCl$). **e)** 16% of recovered enoate. **f)** 80% of recovered enoate.

The conjugate addition of methyl cuprates to enoates is also known to occur with difficulty. As an example, with methyl magnesium bromide, the afore-mentioned Cu^{II} catalyzed reaction fails when $CuBr_2$ is used as a catalyst and it is necessary to replace it by $Cu(N\text{-}iPr\text{-}Sal)_2$[11] (cf Table II) to obtain a good yield[7]. As illustrated below, Cu^{I} halides are more efficient than Cu^{II} halides since the 1, 4-transfer of a methyl group to enoates takes place easily under our conditions. Moreover the reaction has been performed at room temperature with only stoichiometric amounts of methyl magnesium chloride and Me_3SiCl.

Table II



Reaction Conditions	Yield
1.5 eq.MeMgBr, 1% CuBr$_2$; 3 eq. Me$_3$SiCl ether/THF (1/5), -46°C, 1 h	trace[7]
1.5 eq.MeMgBr, 1% Cu(N-iPr-Sal)$_2$[10]; 3 eq. Me$_3$SiCl ether/THF (1/5), -46°C, 1 h	99% (crude product)[7]
1.04 eq. MeMgCl, 3% CuCl[a]; 1.2 eq. Me$_3$SiCl THF, 20°C, 1 h	92% (isolated product)

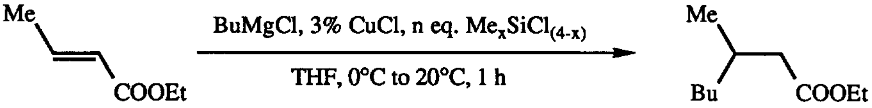
a) CuCl can be replaced by CuCN (3%), the 1,4 addition product is then obtained in 88% yield.

Nevertheless, it should be noted that with the β, β-bisubstituted α, β-ethylenic esters, the addition of a methyl group occurs only in low yields and the starting esters are recovered in a large extent (Table I, entry 15).

With the β-monosubstituted α, β-ethylenic esters, the main limitation of our procedure concerns the conjugate addition of aryl and alkenylmagnesium halides which gave poor yields (e.g. entries 5 and 6). Allylmagnesium halides react with Me$_3$SiCl. In the presence of 3%CuCl, they give only, as expected, the 1,2-addition product (entry 7)[12].

Interestingly we show below that Me$_3$SiCl can be replaced by MeSiCl$_3$ (cf Table III). This is the first time, to our knowledge, that this compound is used in place of Me$_3$SiCl for a conjugate addition. It is interesting to note that the three chlorine atoms participate in the reaction (compare entries 17 and 18). Accordingly, this activating/trapping reagent[13] is more economical than Me$_3$SiCl[14].

Table III



Entry	Me$_x$SiCl$_{(4-x)}$	Yield of Isolated Product (%)
16	1.2 eq. Me$_3$SiCl	95
17	1.2 eq. MeSiCl$_3$	94
18	0.45 eq. MeSiCl$_3$	89

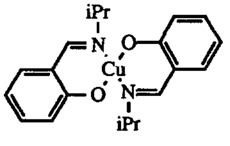
Our procedure offers the following advantages over the previous ones:

- the use of both low temperatures and additives such as BF$_3$;Et$_2$O or hazardous HMPT is avoided,
- the reaction occurs with methyl or ethyl esters,
- the copper chloride used as catalyst is a very common copper salt,
- only stoichiometric amounts of organomagnesium reagents are necessary,
- organomagnesium reagents prepared in ether or in THF can be used.

General Procedure : To 50 mmol of an α, β-ethylenic ester in 70 ml of THF are successively added CuCl (1.5 mmol, 3%), Me_3SiCl (60 mmol, 1.2 eq.) and then, at 0°C, RMgX (52 mmol, 1.04 eq., X= Cl or Br) as a THF or ether solution. After stirring for 30 min to 1.5 h at room temperature, the reaction mixture is hydrolyzed with a NH_4Cl solution (ca 80 ml) and, after decantation, the aqueous layer is extracted with ether.The organic layer is dried over $MgSO_4$ and, after removal of the solvents in vacuo, the product is isolated by distillation.

Notes and References.

1. For instance, with RCu, it is necessary to prepare $RCu{\cdot}BF_3$. Moreover,the reaction must be performed in ether at -78°C and requires important excesses of reagents (e.g. 2 to 3 eq. for R= Bu and 10 eq. for R=Me): Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, J. Org. Chem. 1982, 47, 119. With R_2CuLi, it is necessary to add 1.2 eq. Me_3SiCl, the reaction takes place in ether at -78°C and only one of the two R groups is transfered: A. Alexakis, J. Berlan and Y. Besace, Tetrahedron Lett. 1986, 27, 1047. With the higher order cyanocuprates $R_2Cu(CN)Li_2$, the reaction does not require any stabilizing or activating additives but they must be used at low temperature and only one of the two R groups reacts: B.H. Lipshutz, Tetrahedron Lett. 1983, 24, 127.
2. See ref 1. As mentioned above, only one of the two R groups is transfered with R_2CuLi or $R_2Cu(CN)Li_2$. With a valuable R group, the use of mixed higher order cyanocuprates such as R(2-thienyl)$Cu(CN)Li_2$, at -78°C, allows to circumvent this drawback since only the starting 2-thienyl lithium is lost: B.H. Lipshutz, J. Kozlowski, D. Parker, S. Nguyen and K. McCarthy, J. Organomet. Chem. 1985, 285, 437.
3. J. Munch-Petersen, J. Org. Chem. 1957, 22, 170. See also J. Munch-Petersen, Bull. Soc. Chim. France 1966, 471 and the references 24 to 30 quoted herein.
4. In most cases, 2 to 2.5 eq are necessary.
5. Y. Horiguchi, S. Matsuzawa, E. Nakamura and I. Kuwajima, Tetrahedron Lett. 1986, 27, 4025.
6. T. Kint-Larsen, V. Bitsch, I. Andersen, A. Jart and J. Munch-Petersen, Acta Chem. Scand. 1963, 17, 1426.
7. H. Sakata, Y. Aoki and I. Kuwajima, Tetrahedron Lett. 1990, 31,1161.
8. See, for instance, G. Cahiez and M. Alami, Tetrahedron Lett. 1989, 30, 7365. See also the following communication in this journal.
9. Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara and K. Maruyama, J. Org. Chem. 1982, 47, 119. See also H. House and M. Umen, J. Am. Chem. Soc. 1972, 94, 5495 and ref. 6 quoted above.
10. DMAP (4-dimethylaminopyridine) is known to be as efficient as HMPA to improve the conjugate addition of an organocuprate to an enoate in the presence of R_3SiCl. However, until now, such an effect had never been observed in the case of a copper-catalyzed organomagnesium reagent. See S. Matsuzawa, Y. Horiguchi, E. Nakamura and I. Kuwajima, Tetrahedron 1989, 45, 349.
11. The complex is:



12. With copper-catalyzed allylic Grignard reagents, in ether, the 1,2-addition is also the only reaction: J. Munch-Petersen, P. Jorgensen and S. Refn, Acta Chem. Scand. 1959, 13, 1955.
13. The role of Me_3SiCl is both to trap the enolate as soon as it is formed and to accelerate the addition reaction rate. See ref. 5 quoted above.
14. According to the Aldrich catalogue, 1.2 eq. Me_3SiCl is twice as expensive than 0.45 eq. $MeSiCl_3$. The influence of some monochlorosilanes has already been studied: E. Nakamura, S. Matsuzawa, Y. Horiguchi and I. Kuwajima, Tetrahedron Lett. 1986, 27, 4029. However, to our knowledge, the influence of polychlorosilanes has never been reported.

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