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Tetrahedron Letters 44 (2003) 4265–4266

TETRAHEDRON LETTERS

'$Me_2CuLi·TMSCl$ in CH_2Cl_2'. The most powerful methylating agent for sterically congested α,β-enoates

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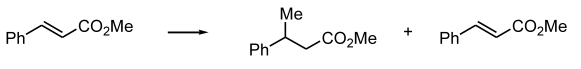
Received 30 October 2002; revised 4 April 2003; accepted 4 April 2003

Abstract—The reaction of Me_2CuLi with sterically congested α,β-unsaturated esters in the presence of TMSCl in CH_2Cl_2 proceeded very smoothly to produce the conjugate addition products in high yields. © 2003 Elsevier Science Ltd. All rights reserved.

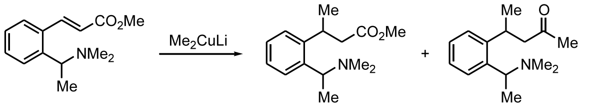
Conjugate addition using organocopper reagents to α,β-unsaturated esters is one of the most practical and important methods for C–C bond formation in organic synthesis.[1] In 1978, we found that when RCu was treated with Lewis acids, such as $BF_3·OEt_2$, at lower temperatures, the combined reagent exhibited an enhanced reactivity toward enoates in comparison with RCu itself or even with R_2CuLi.[2] For example, the conjugate addition of $BuCu·BF_3$ to ethyl tiglate gave the conjugate adduct in 96% yield, although the addition with Bu_2CuLi afforded the desired product only in 16% yield.[2b] In contrast, the reactivity of $MeCu·BF_3$ was relatively lower than alkylcoppers·BF_3, such as $BuCu·BF_3$, and in certain cases the conjugate addition to sterically hindered enoates did not give a satisfactory result. Later on, it was reported that the addition of TMSX (X = Cl or I) to MeCu or Me_2CuLi dramatically improved the yield of the conjugate adducts in additions to α,β-unsaturated esters.[3–5]

Nilsson and co-workers reported that the addition of MeCu·TMSI to enoates in CH_2Cl_2 gave the conjugate adducts in much higher yields than that in diethyl ether (for example, Eq. (1)).[5]



$MeCu·TMSI/CH_2Cl_2$	92 %	-	(1)
$MeCu·TMSI/Et_2O$	39 %	56 %	
$Me(Th)CuLi·TMSCl/Et_2O$	75 %	-	

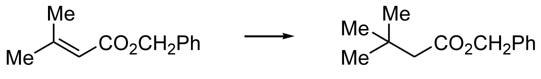
They also reported that the reagent system, MeCu·TMSI in CH_2Cl_2, was more efficient than Me(Th)CuLi·TMSCl in diethyl ether.[6] Ullenius and co-workers reported that the diastereoselectivities in the conjugate addition of Me_2CuLi to the enoate shown in Eq. (2) were higher in the non-coordinating solvents, such as CH_2Cl_2 and toluene, than in Et_2O, and even higher chemical yields of the conjugate adducts were obtained in the non-coordinating solvents (Eq. (2)).[4]



(2)

THF	<1 %	-
Et_2O	18 % (68 %de)	17 %
CH_2Cl_2	94 % (79 %de)	-
toluene	91 % (82 %de)	-

Based on the above results, it occurred to us that MeCu or Me_2CuLi in the presence of TMSX in a non-coordinating solvent would become an efficient methylating agent for conjugate addition to sterically congested enoates. This idea was tested in conjugate additions to **1a** (Eq. (3)).



1a **2a**

$Me_2CuLi·TMSCl/Et_2O$	0 %[a]	
$Me(Th)CuLi·TMSCl/Et_2O$	0 %[a]	(3)
$Me_2CuLi·TMSCl$/toluene	0 %[a]	
Me_2CuLi only/CH_2Cl_2	0 %[a]	
$MeCu·TMSCl/CH_2Cl_2$	75 %	
$Me_2CuLi·TMSCl/CH_2Cl_2$	96 %	

[a] The starting material was recovered.

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0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00891-8

Table 1. Conjugate addition reaction of '$Me_2CuLi{\cdot}TMSCl/CH_2Cl_2$' to **1**[a]

Entry	Substrate **1**					Time (h)	**2**	Yield (%)[b]
	R^1	R^2	R^3	R				
1	Me	n-C_6H_{13}	H	Et	**1b**	6	**2b**	100
2	Me	*i*Pr	H	Et	**1c**	6	**2c**	94
3	$(CH_2)_5$		H	Et	**1d**	2.5	**2d**	99
4	Me	Ph	H	Et	**1e**	3	**2e**	98
5	H	Me	Me	$PhCH_2$	**1f**	3.5	**2f**	63
6[c]	H	Me	Me	$PhCH_2$	**1f**	13	**2f**	87
7[c]	Me	n-C_6H_{13}	Me	Et	**1g**	2	**2g**	97

[a] The reaction was carried out using **1** (1 equiv.), Me_2CuLi (2 equiv.), and TMSCl (2 equiv.) in CH_2Cl_2 at −78 to 0°C unless otherwise noted.

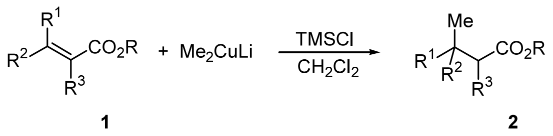
[b] Isolated yield.

[c] Reaction was carried out using Me_2CuLi (3 equiv.) and TMSCl (3 equiv.).

As shown in Eq. (3), '$Me_2CuLi{\cdot}TMSCl/CH_2Cl_2$' is the most efficient methylating agent. The use of ether or toluene as a solvent gave no conjugate adduct at all. The absence of TMSCl did not afford the desired product at all even if CH_2Cl_2 was used as a solvent. '$Me_2CuLi{\cdot}TMSCl/CH_2Cl_2$' was better than '$MeCu{\cdot}TMSCl/CH_2Cl_2$'.

The preparation of **2a** is representative. To a suspension of CuI (380 mg, 2 mmol) in ether (2 mL) was added MeLi (4 mmol, 1.04 M in ether) at 0°C and the mixture was stirred for 10 min. The solvent was removed under reduced pressure at 0°C and then CH_2Cl_2 (2 mL) was added. The mixture was stirred for 5 min at 0°C, and then the solvent was removed again in vacuo at 0°C. To the residue was added pre-cooled CH_2Cl_2 (15 mL) and the mixture was cooled to −78°C. To the mixture were added TMSCl (0.25 mL, 2 mmol) and a solution of **1a** (190 mg, 1 mmol) in CH_2Cl_2 (2 mL), successively. The mixture was allowed to warm to 0°C gradually and the reaction was quenched by addition of a mixture of aqueous saturated NH_4Cl and 28% NH_4OH (1:1). The mixture was extracted with ether three times and the combined extracts were dried (Na_2SO_4) and evaporated to leave the crude product, which was purified by a silica gel column, and the product was isolated using hexane/EtOAc = 3/1 as eluent; **2a** was obtained as a pale yellow oil (197 mg, 0.96 mmol) in 96% yield.

We next examined the conjugate addition of other sterically congested α,β-unsaturated esters **1b–g** using '$Me_2CuLi{\cdot}TMSCl/CH_2Cl_2$' (Eq. (4)) and the results are summarized in Table 1. In the reactions of the β,β-disubstituted substrates **1b–e**, the corresponding conjugate adducts were obtained in more than 90% yields (entries 1–4). While the reaction of the α,β-disubstituted substrate **1f** afforded **2f** in a moderate yield (entry 5), the chemical yield was increased to 87% when the equivalents of both Me_2CuLi and TMSCl were increased from two to three (entry 6). Finally, we examined the reaction of the α,β,β-trisubstituted substrate **1g**. To our surprise, the reaction proceeded smoothly and the conjugate addition product **2g** was obtained in 97% yield (entry 7).



(4)

We are now in a position to carry out effectively the conjugate addition of a methyl group to sterically congested enoates using the '$Me_2CuLi{\cdot}TMSCl/CH_2Cl_2$' reagent system. We also investigated whether or not $Bu_2CuLi{\cdot}TMSCl/CH_2Cl_2$ and $Ph_2CuLi{\cdot}TMSCl/CH_2Cl_2$ can be used as powerful agents for the conjugate addition, however, we found that these reagent systems are not useful.

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