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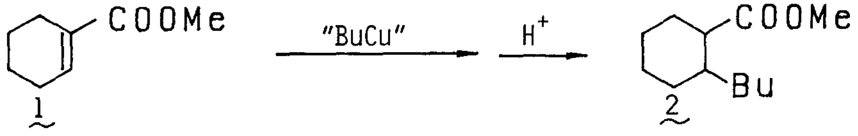
CONJUGATE ADDITION OF ORGANOCOPPER REAGENTS TO UNSATURATED ESTERS

Hiroshi Sakata and Isao Kuwajima*
Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Summary: A combination of copper(I) trimethylsilylacetylide and chlorotrimethylsilane accelerates the conjugate addition of an alkyllithium to α,β-unsaturated esters to give the 1,4-addition products in good yields.

In connection with our synthetic programs, it has been required to introduce alkyl moieties containing silyl group to β-position of α,β-unsaturated esters. Although reactions with organocopper reagents constitute an excellent methodology for conjugate addition to enones,[1] unsaturated esters are usually not sufficient as acceptors. Use of alkylcopper-boron trifluoride[2] complexes sometimes improves the product yields, but they are not so effective for conjugate addition to 1-cycloalkenecarboxylic esters.

We previously reported two methods to accelerate the conjugate addition to enone system; one is a use of copper(I) trimethylsilylacetylide (**A**) to prepare mixed cuprates,[3] and the other is the reaction in the presence of chlorotrimethylsilane (**B**).[4,5,6] It has now been found that a combined use of these two reagents (**A**) and (**B**) improves the conjugate addition of an alkyllithium to unsaturated esters. For comparison, we examined the reaction of methyl 1-cyclohexenecarboxylate **1** with several butylcopper reagents. As shown in the Table 1, most of the reagents gave the corresponding addition product **2** in less than 40% yields, whereas the conjugate addition has been remarkably accelerated in the presence of (**A**) and (**B**) to afford **2** in good yield. On using a Grignard reagent, however, the yield of **2** was greatly decreased accompanied with formation of butyl 2-butylcyclohexyl ketone 3 arising from a successive 1,2- and 1,4-addition reactions of butyl groups. In addition to effects of reagents (**A**) and (**B**), the yields of **2** were greatly dependent on the reaction solvent. On attempt for the addition reaction in ether or THF, the product 2 could not be obtained in synthetically acceptable yield, and use of a mixed solvent of ether and THF in an appropriate ratio (ca. 4:1) is preferable as can be seen in Fig 1. Ether appears to destabilize the mixed cuprate, whereas the addition reaction is very slow in THF.



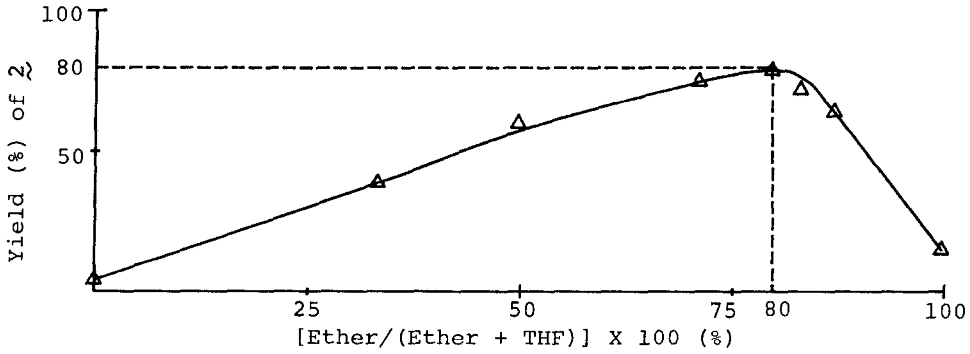
1 **2**

Table 1. Attempts for Conjugate Addition to 1.

Run	Reagents	Yield(%)		
		2	**3**	Recovered **1**
1	Bu_2CuLi^a	6	81	--
2	$BuCu/BF_3{}^a$	20	--	75
3	$BuCu/BF_3/TMS\text{-}Cl^b$	30	--	60
4	$BuLi/TMS\text{-}C{\equiv}C\text{-}Cu^c$	40	--	36
5	$BuLi/TMS\text{-}C{\equiv}C\text{-}Cu/TMS\text{-}Cl^d$	80 (92^e)	--	11(7e)
6	$BuMgBr/TMS\text{-}C{\equiv}C\text{-}Cu/TMS\text{-}Cl^d$	9	62	26
7	$BuMgBr/TMS\text{-}C{\equiv}C\text{-}Cu/TMS\text{-}Cl^{d,f}$	39	10	41

a) See ref 2. b) The reaction was performed with 2 equiv each of BuCu and BF_3 OEt_2. c) The reaction was performed with 2 equiv each of BuLi and TMS-C≡C-Cu. d) The reactions were performed with 2 equiv each of BuLi (or BuMgBr) and TMS-C≡C-Cu in the presence of TMS-Cl (3 equiv). e) The reaction was performed with 3 equiv each of BuLi and TMS-C≡C-Cu in the presence of TMS-Cl (4.5 equiv). f) The reaction was performed in the presence of HMPA (2 equiv). See ref 4.

Fig 1. Solvent Effects on Conjugate Addition to **1**.[a]



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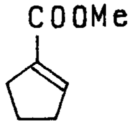
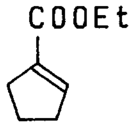
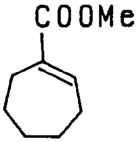
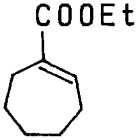
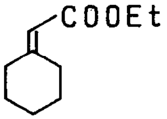
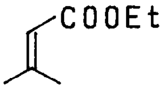
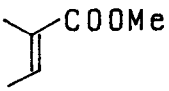
a) Reactions were performed with 2 equiv each of BuLi and TMS-C≡C-Cu in the presence of TMS-Cl (3 equiv).

Other unsaturated esters including β,β-disubstituted ones also undergo conjugate addition efficiently as shown in Table 2. The reaction with 3 equiv of butyllithium usually gave the corresponding addition product in ca. 90% yield in every case.

Table 2. Conjugate Addition of Butyllithium to α,β-Unsaturated Esters.^{a}

	Yield^b (%)	
	1,4-Addition Product	Recovery of Ester
	(62)	(28)
	60 93^c	(38) 0^c
	73(76)	(15)
	76(78) 88^c	(20) 6^c
	80(82) 51^d	(18)
	(76) 70^d	(22) 14^d
	(78)	(21)

a) Reactions were performed in a similar manner as described in the text. b) Isolated yields. Numbers in parentheses represent NMR yields based on 1,1,2,2-tetrachloroethane as internal standard. c) Reactions were performed with 3 equiv each of butyllithium and TMS-C≡C-Cu in the presence of 4.5 equiv of TMS-Cl. d) See ref 2.

The following procedures are representative. Trimethylsilylacetylene (0.715 mmol) in THF (0.36 ml) was treated with butyllithium (0.449 ml of 1.59 M hexane solution, 0.713 mmol) at 0 °C under nitrogen. The resulting solution was added to CuI (136 mg, 0.715 mmol) in ether (1.44 ml) at 0 °C. After stirring for 10 min, butyllithium (0.449 ml of 1.59 M solution, 0.713 mmol) was added at -78 °C, and it was stirred for 1 hr at that temperature. Then, methyl 1-cycloheptenecarboxylate (0.357 mmol) and chlorotrimethylsilane (1.07 mmol) were added to the solution and it was stirred for 1 hr at -78 °C. After it was gradually warmed up to room temperature during 4 hr under stirring, the reaction mixture was quenched with 1 N HCl and then with aq NH_4Cl-NH_4OH (4:1). Extraction with ether followed by drying and removal of the solvent gave an oil, which was purified by Merck Lobar column to afford methyl 2-butylcycloheptanecarboxylate in 73% yield.

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References and Notes

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5) On similar studies about the effect of the chlorosilane, see also; E. J. Corey and N. W. Boaz, Tetrahedron Lett., **26**, 6015, 6019 (1985). A. Alexakis, J. Berlan, Y. Besace, ibid., **27**, 1047 (1986).
6) Interestingly, the chlorosilane also improves the conjugate addition of alkylcopper-boron trifluoride complex. For example, on conjugate addition of trimethylsilylmethyllithium to 4-methyl-2-cycloheptenone, the Cu(I)-BF_3 complexes gave the corresponding addition product in 68% yield, whereas the same product was obtained in 96% yield with higher stereoselectivity in the presence of chlorotrimethylsilane. Unpublished observation by H. Sakata in our laboratory.

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