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FLUORIDE CATALYZED MICHAEL REACTION OF α-ISOCYANOESTERS WITH α,β-UNSATURATED CARBONYL COMPOUNDS

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Summary: The Michael reaction of α-isocyanoesters with α,β-unsaturated carbonyl compounds was efficiently promoted by a catalytic amount of tetrabutylammonium fluoride to produce α-isocyano-δ-ketoesters or silyl ethers of their enols in high yields.

The carbon-carbon bond formation at the α-carbon of α-isocyanoester has been conveniently achieved by the reaction with carbon-electrophiles under basic conditions, which provides a facile and useful preparative method for a variety of derivatives of α-amino acids.[1] Thus, glutamic acid derivatives could be synthesized by the Michael reaction of α-isocyanoesters with α,β-unsaturated esters followed by hydrolysis of the isocyano group into amino group. However, the base induced Michael reaction of α-isocyanoesters has not been widely utilized, because of low yields and low selectivities of the reaction.[2] Herein, we wish to describe the fluoride catalyzed Michael reaction of α-isocyanoesters with α,β-unsaturated carbonyl compounds giving the corresponding Michael products in high yields.[3]

α-Isocyanoesters (**2**) were treated with α,β-unsaturated carbonyl compounds (**1**) in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) to afford only Michael products (**3**) in good yields (Table 1). Not only α,β-unsaturated esters (entry 1-3) but also α,β-unsaturated ketones (entry 4-10) can be used as an acceptor. α-Isocyanoesters prepared from glycine and alanine reacted smoothly with **2** (entry 4,5,7-9), whereas the reaction of α-isocyanoester having bulky substituent at the α-carbon required longer time (entry 6). α-Isocyanocarboxamide also underwent the fluoride catalyzed Michael reaction with **1** (entry 10). Diastereoselectivities of the present Michael reaction were not generally satisfactory.

Next, the Michael reaction was conducted at -78 °C in the presence of various silylating reagents in order to trap an intermediary enolate (**4**) of the Michael product as its trimethylsilyl ether (**5**).[4] As shown in Table 2, trimethylsilyl enol ether (**5**) was obtained in the best yield (93%) by employment of N,O-bis(trimethylsilyl)acetamide (BSA). Of interest was that the use

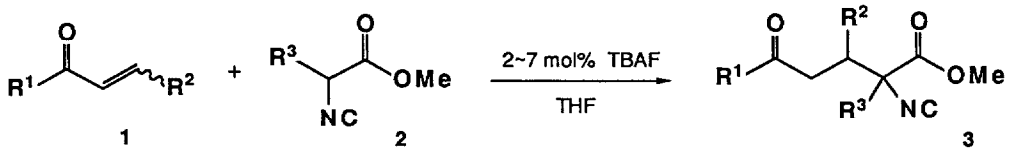


Table 1. The Fluoride Catalyzed Michael Reaction of α-Isocyanoesters

entry	1	R^3 of 2	conditions	yield (%)	diastereomers ratio[a]
1	$MeO_2CCH{=}CH_2$ (**1a**)	Me	rt, 2 h	94	–
2	$MeO_2CCH{=}CHMe$ (**1b**)	H	rt, 2 h	91	59 : 41
3	**1 b**	Me	rt, 3.5 h	93	70 : 30
4	Me-C(=O)-CH=CHMe (**1c**)	H	0 °C, 2 h	83	61 : 39
5	**1 c**	Me	rt, 3 h	93	70 : 30
6	**1 c**	*i*-Pr	rt, 2 d	72	75 : 25
7	 (**1d**)	H	0 °C, 1 h	83	50 : 50
8	**1 d**	Me	0 °C, 1 h	88	50 : 50
9	 (**1e**)	Me	-78 °C, 4 h	85	56 : 44
10	**1 c**	H[b]	rt, 3 h	91	63 : 37

a) The relative stereochemistry was not assigned. b) α-Isocyanocarboxamide ($CNCH_2C(=O)N$ ) was used.

of BSA or N-(trimethylsilyl)acetamide resulted in remarkable acceleration of the Michael reaction, *i.e.* the Michael reaction of **1d** with methyl 2-isocyanopropionate was completed in 40 min at -78 °C in the presence of BSA, whereas no Michael product was obtained at all under the same conditions in the absence of BSA.

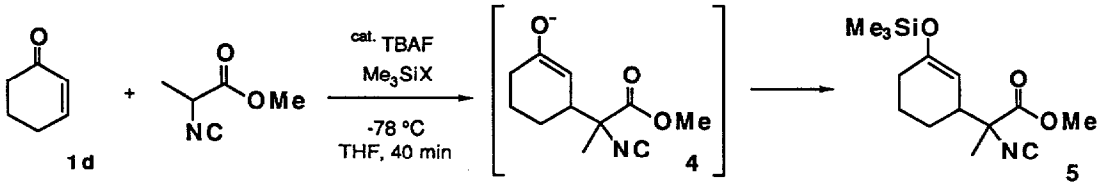
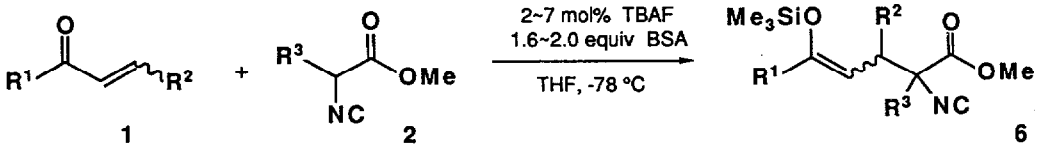


Table 2. Effect of Silylating Reagents in the Michael Reaction

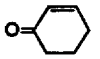
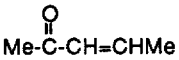
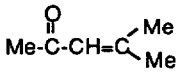
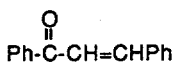
Me_3SiX	None	$ClSiMe_3$		Me-C(=O)-NH-$SiMe_3$	Me-C(OSiMe_3)=N-$SiMe_3$	CF_3-C(OSiMe_3)=N-$SiMe_3$
yield of 5 (%)	0	0	2	87	93	10

The Michael reactions of α-isocyanoesters (**2**) with α,β-unsaturated ketones (**1**) in the presence of BSA are shown in Table 3. Silyl enol ethers of the Michael products (**6**) were obtained in high yields. Even β-disubstituted α,β-unsaturated ketone gave **6**, though an elevated temperature (0 °C) was required (entry 7). Typical experimental procedure is as follows: To a stirred THF solution (2 ml) of 2-cyclohexenone (62 mg, 0.64 mmol), methyl 2-isocyanopropionate (54 mg, 0.48 mmol) and BSA (162 mg, 0.80 mmol) was added a THF solution (25 μl) of TBAF (0.025 mmol) at -78 °C under nitrogen. After stirring for 40 min at that temperature, tributyltin chloride (15 μl, 0.055 mmol) was added. The resulting solution was subjected to column chromatography on Florisil to afford the corresponding silyl enol ether of the Michael product (oil, 126 mg, 93%).



1 **2** **6**

Table 3. Synthesis of Silyl Enol Ether (**6**)

entry	**1**	R^3	time (min)	yield (%)	diastereomers ratio
1	 (**1d**)	H	40	97	50 : 50
2	**1 d**	Me	40	93	50 : 50
3	**1 d**	Et	70	85	57 : 43
4	**1 d**	*i*-Pr	110	94	75 : 25
5	 (**1f**)	Me	20	81	—
6		Me	30	91	70 : 30[a]
7		Me	180	66[b]	—
8		Me	75	80	82 : 18[a]
9		Me	90	91	65 : 35[a]

a) The ratio was determined after hydrolysis of **6** to **3**. b) reaction temperature: 0 °C.

Reductive de-isocyanation of trimethylsilyl ethers of the Michael products (**6**) thus prepared was performed by organotin hydride with triethylborane[5] or 2,2'-azobis(isobutyronitrile) (AIBN)[6] to give the corresponding silyl enol ethers (**7**) selectively (Table 4). The present reactions provide useful and regioselective preparation of silyl enol ethers of δ-ketoesters.

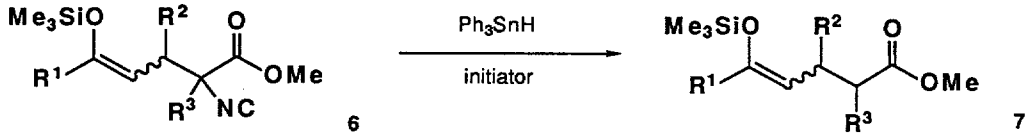
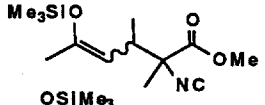
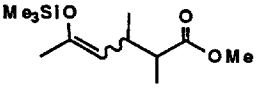
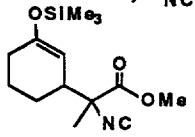
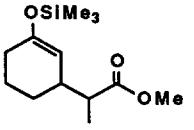
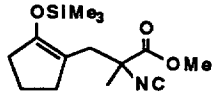
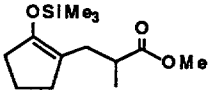
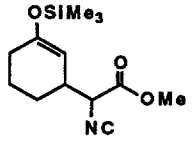
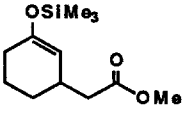


Table 4. Reductive De-isocyanation of Silyl Enol Ethers (**6**) with Ph_3SnH

entry	6	initiator	conditions	7	yield (%)
1		Et_3B	toluene, r t, 40 min		76
2		Et_3B	toluene, r t, 30 min		77
3		Et_3B	toluene, r t, 90 min		83
4		AIBN	benzene, reflux, 5 min		74

Further study on synthetic utilization of **6** is now in progress in our laboratory.

References and Notes.

1) D. Hoppe, Angew. Chem., Int. Ed. Engl., 13, 789 (1974).
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