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$TiCl_4$ mediated Michael addition reactions of α-cyanoketene-*S*,*S*-acetals with enones

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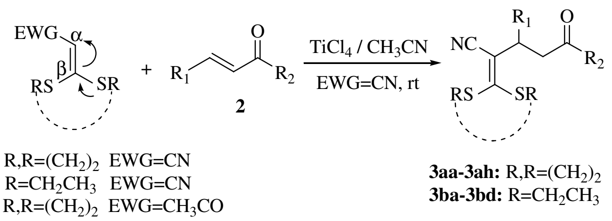
Abstract—Titanium tetrachloride promoted Michael addition reactions of α-cyanoketene-*S*,*S*-acetals **1** with enones **2** have been developed. The polyfunctionalized 2-[1,3]dithiolan-2-ylidene-3-substituted-5-oxo-5-substituted-pentanenitriles **3** were obtained in good to high yields and the corresponding mechanism was also described.

Carbon–carbon bond formation reaction is the most fundamental reaction for the construction of a molecular framework in organic chemistry.[1] In this context, the Baylis–Hillman (BH) reaction,[2,3] the C–C bond-forming reaction of activated alkenes with carbon electrophiles, has become the focus of intensive efforts in recent research since it provides a simple, convenient and atom-economical methodology for the synthesis of useful multifunctional molecules.[4] Although various carbon electrophiles, such as aldehydes, α-ketoesters, nonenolizable 1,2-diketones, aldimine derivatives, and fluoro ketones have been employed in the BH reaction, there are only few reports about taking enones as the electrophiles,[5–8] in which the intramolecular Michael cycloisomerization of bis(enones),[6] the intramolecular cyclizations of diactivated 1,5-hexadienes and 1,6-heptadienes[7] and the intermolecular BH reactions of β-aryl nitroethylenes to methyl vinyl ketone and ethyl acrylate[8] are the successful examples.

As versatile intermediates, α-oxoketene-*S*,*S*-acetals and their analogues have found wide applications in organic synthesis.[9] The push–pull interaction between the electron donating two alkylthio groups and the electron withdrawing group at the α-position makes the carbon–carbon double bond of α-EWG ketene-*S*,*S*-acetals (EWG = electron withdrawing group) highly polarized (compounds **1** in Scheme 1).[9,10] Thus, utilizing the electron rich α-carbon atom of α-EWG ketene-*S*,*S*-acetals, very recently, we successfully developed a novel BH type reaction between α-acetylketene cyclic-*S*,*S*-acetal **1c** and aldehydes to construct C–C bonds.[11] The results and our interest in the BH type reaction with enones as electrophiles prompt us to investigate the Michael addition reactions of α-EWG ketene-*S*,*S*-acetals with enones. To our knowledge, although enolsilanes and silyl ketene acetals have been widely used as nucleophiles in Mukaiyama–Michael reactions,[12] surprisingly, there were no reports of Michael addition reaction with α-EWG ketene-*S*,*S*-acetals as Michael donor. In this letter, we wish to report this kind of new reaction between α-cyanoketene-*S*,*S*-acetals **1a** or **1b** and enones.

The initial study was performed on the reaction between α-cyanoketene cyclic-*S*,*S*-acetal **1a**[13] and 3-phenyl-1-phenylprop-2-en-1-one **2b** in the presence of $TiCl_4$ in acetonitrile at room temperature (Scheme 1). To our



Scheme 1. Michael addition of **1a**, **1b** to enones **2**.

Keywords: α-Cyanoketene-*S*,*S*-acetal; Michael addition reaction; Enone; Titanium tetrachloride.

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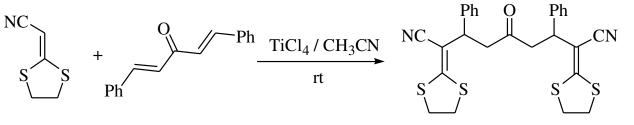
Table 1. Experimental results of $TiCl_4$ mediated michael addition of **1a** to enone **2b**

Entry	**1a** (mmol)	**2b** (mmol)	$TiCl_4$ (mmol)	Solvent	Time (h)	Yield[a] (%)
1	1.0	1.0	1.2	CH_3CN	13	78
2	1.5	1.0	1.2	CH_3CN	10	80
3	2.0	1.0	1.2	CH_3CN	8	85
4	3.0	1.0	1.2	CH_3CN	8	84
5	2.0	1.0	0.2	CH_3CN	48	81
6	2.0	1.0	0.5	CH_3CN	15	78
7	2.0	1.0	1.0	CH_3CN	9	84
8	2.0	1.0	1.5	CH_3CN	8	85
9	2.0	1.0	2.0	CH_3CN	7	86
10	2.0	1.0	1.2	MeOH	48	0
11	2.0	1.0	1.2	EtOH	48	0
12	2.0	1.0	1.2	CH_2Cl_2	30	75
13	2.0	1.0	1.2	THF	28	78

[a] Isolated yield.

delight, the desired Michael adduct, 2-[1,3]dithiolan-2-ylidene-3,5-diphenyl-5-oxo-pentanenitrile **3ab**, was obtained in 78% isolated yield (Table 1, entry 1). The reaction was then carried out under various conditions (the ratio of **1a**:**2b**, the amount of $TiCl_4$ and the reaction media) to optimize the yield. As shown in Table 1, when the ratio of **1a**:**2b** was increased to 2:1, **3ab**[14] was obtained in 85% isolated yield within 8 h (Table 1, entry 3). It was found that there was no significant difference for the product yield with increasing ratios of **1a**:**2b** beyond 2:1. When 0.2 equiv of $TiCl_4$ was used, **3ab** could be obtained in 81% isolated yield with a prolonged reaction time (two days, Table 1, entry 5). In addition, the reaction was found to be solvent dependent. It proceeded smoothly in dichloromethane and THF with a relatively longer reaction time (Table 1, entries 12 and 13) than in acetonitrile, but failed in methanol and ethanol (Table 1, entries 10 and 11); therefore, acetonitrile was proven to be the best solvent and was selected for the following investigations.

Subsequently, the scope of the Michael addition reaction was investigated by employing various Michael acceptors **2a**, **2c**–**2h** under the optimized conditions (Table 1, entry 3) and the corresponding Michael adducts **3aa** and **3ac**–**3ah** were obtained in good to high yields (Table 2, entries 1–8).[15] It is worth noting that double Michael acceptor **2h** could also undergo this Michael addition reaction to selectively afford the mono-Michael or double-Michael adduct. For example, the mono-Michael adduct **3ah** was obtained in a 76% isolated yield when the reaction was performed with the ratio 2:1 for **1a**:**2h**; while the ratio of **1a**:**2h** was increased to 4:1, the double-Michael adduct **4h** was obtained in 64% isolated yield (Eq. 1). Furthermore, it was observed that under the same optimized conditions, α-cyanoketene catenulate *S*,*S*-acetals **1b**[13] could also perform the Michael addition reaction with enones. As shown in Table 2, the reactions of **1b** with selected enones proceeded smoothly to afford Michael addition products **3ba**–**3bd** in a moderate yield. All the above results indicate that α-cyanoketene *S*,*S*-acetals could be successfully used as nucleophiles to undergo Michael addition reactions. Although α-EWG ketene-*S*,*S*-acetals have been extensively investigated and widely applied in organic synthesis,[9–11] to the best of our knowledge, the carbon–carbon bond-forming reaction represents the first example of the Michael addition reactions[16] between α-EWG ketene-*S*,*S*-acetals and α,β-unsaturated carbonyl compounds.[17]



1a **2h** **4h**

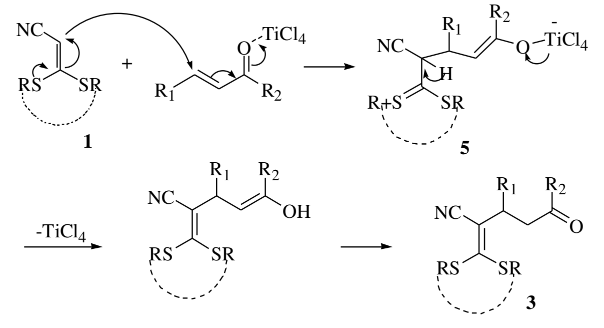
(1)

Compared with our previous reports,[11] the Michael addition reaction might follow a mechanism as depicted in Scheme 2. Initiated by the nucleophilic attack of the electron rich α-carbon atom of **1** to the β-carbon atom of a $TiCl_4$ activated enone, the thionium ion **5** would be formed at first. Then, through the proton transfer followed by the release of $TiCl_4$, the polyfunctionalized Michael adducts **3** were finally formed. Unlike the mechanism of the $TiCl_4$-mediated BH reaction[18] and our previous research on double BH type reaction,[11] in which excessive amounts of $TiCl_4$ should be required, a catalytic amount of $TiCl_4$ (0.2 mmol) could promote the present reaction since it would be regenerated during the reaction process.

Table 2. The $TiCl_4$ mediated Michael addition reaction of **1** with enones **2**[a]

Entry	1	2	R_1	R_2	Time (h)	Product 3	Yield[b] (%)
1	**1a**	**2a**	Cyclohexenone		5	**3aa**	82
2	**1a**	**2b**	Ph	Ph	8	**3ab**	85
3	**1a**	**2c**	*p*-ClPh	Ph	8	**3ac**	82
4	**1a**	**2d**	Ph	*p*-ClPh	9	**3ad**	77
5	**1a**	**2e**	Ph	CH_3	18	**3ae**	73
6	**1a**	**2f**	*p*-H_3CPh	CH_3	15	**3af**	75
7	**1a**	**2g**	*p*-H_3COPh	Ph	10	**3ag**	69
8	**1a**	**2h**	Ph	CHCHPh	9	**3ah**	76
9	**1b**	**2a**	Cyclohexenone		6	**3ba**	78
10	**1b**	**2b**	Ph	Ph	24	**3bb**	65
11	**1b**	**2c**	*p*-ClPh	Ph	18	**3bc**	71
12	**1b**	**2d**	Ph	*p*-ClPh	18	**3bd**	65

[a] Reaction conditions: **1** (2.0 mmol), **2** (1.0 mmol), $TiCl_4$ (1.2 mmol), CH_3CN (10 mL), room temperature.
[b] Isolated yields.



Scheme 2. Proposed mechanism for the Michael addition.

In summary, we have demonstrated a novel method for the C–C bond formation via the Michael addition of α-cyanoketene-*S*,*S*-acetals to α,β-unsaturated carbonyl compounds. By the reactions of α-cyanoketene-*S*,*S*-acetal **1** with enones, the polyfunctionalized Michael adducts **3** were obtained in good to high yields under mild reaction conditions. The investigations on extension of this type of Michael reaction and the synthetic applications of the polyfunctionalized Michael adducts are in progress.

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Supplementary data

Spectral data of compounds **3aa**–**3bd** and **4h**, preparation of α-cyanoketene-*S*,*S*-acetal **1a** are supplied in the supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.098.

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