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

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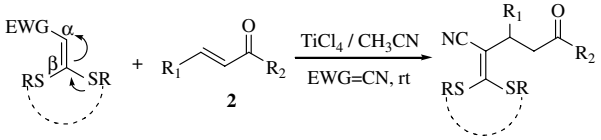
Abstract—Titanium tetrachloride promoted Michael addition reactions of α-cyanoketene-*S*,*S*-acetals **1** with enones **2** have been developed. The polyfunctionalized 2-[1,3]dithiolan-2-ylidene-3-substituted-5-oxo-5-substituted-pentanenitriles **3** were obtained in good to high yields and the corresponding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



1a: R,R=$(CH_2)_2$ EWG=CN
1b: R=CH_2CH_3 EWG=CN
1c: R,R=$(CH_2)_2$ EWG=CH_3CO

3aa-3ah: R,R=$(CH_2)_2$
3ba-3bd: R=CH_2CH_3

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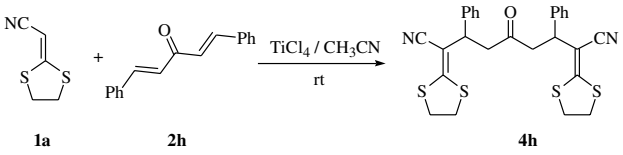
Table 1. Experimental results of $TiCl_4$ mediated michael addition of **1a** to enone **2b**

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.