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One-pot synthesis of aza-Morita–Baylis–Hillman adducts from α-oxo ketene-*S*,*S*-acetals, arylaldehydes and nitriles

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Abstract—Promoted by $TiCl_4$, a series of α-(1,3-dithiolan-2-ylidene)-β-amino carbonyl derivatives—the aza-Morita–Baylis–Hillman adducts, have been synthesized from α-oxo cyclic ketene-*S*,*S*-acetals, arylaldehydes, and nitriles in good to excellent yields. A mechanism involving sequential Morita–Baylis–Hillman and Ritter reactions for this novel one-pot, three-component reaction is described.

Based on the C–C coupling of an activated alkene with a carbon electrophile, the Morita–Baylis–Hillman (MBH) reaction[1,2] can provide various polyfunctionalized molecules in an atom-economic fashion[3] and has been applied to the synthesis of various biologically active compounds and natural products.[4] Accordingly, the related α-methylene-β-amino carbonyls can be prepared typically via amine substitution of the alcohol functionality in MBH adducts[5] or via the aza version of the MBH reaction with imines as electrophiles.[6] However, the former reaction requires a two- or three-step procedure and is often accompanied by undesired side reactions, for example, S_N2'-substitution or Michael addition;[5c–h] and the latter one usually requires the aldimine to be preformed and isolated prior to the aza-MBH reaction.[6] As an alternative route, the three-component aza version of the MBH reaction is an attractive method for the formation of α-methylene-β-amino carbonyls although such reactions are not well-developed and have been performed mainly with the tosyl group as the protecting and activating group of ammonia[6,7] or carried out with large excess of arylaldehydes (5 equiv) and methyl acrylate (5 equiv) to drive the reaction to completion, as in the case of the SES group functioning as the protecting group.[8]

In the past few decades, functionalized ketene-*S*,*S*-acetals are emerged as versatile intermediates in organic synthesis.[9] During the course of our studies on the chemistry of α-oxo ketene-*S*,*S*-acetals, some useful methodologies and transformations have been achieved,[10–12] and the nucleophilicity of the α-carbon atom in α-oxo ketene-*S*,*S*-acetals has been recognized.[13] One of our recent reports[14] showed that α-acetyl ketene-*S*,*S*-acetals, such as compound **1a** (Scheme 1, R = Me), could be taken as a kind of activated alkenes as those used in the MBH reaction.[1,2] When the reaction of **1a** with an arylaldehyde was carried out in dichloromethane in the presence of $TiCl_4$, the double MBH type product **3** (Scheme 1) was produced and a carbocation intermediate **5**, stabilized by the adjacent sulfur atoms, was proposed to be the key intermediate.[14] In order to broaden the synthetic utility of α-oxo ketene-*S*,*S*-acetals and find a facile and efficient synthetic route to the aza-MBH type products, in our continuing research, nitriles were chosen as the nitrogen nucleophiles for the capture of carbocation **5** according to the Ritter reaction.[15] In this communication, with α-oxo cyclic ketene-*S*,*S*-acetals **1** as the activated alkenes, arylaldehydes as the electrophilic species, and nitriles as the nitrogen nucleophiles, the synthesis of the aza-MBH type products **4** via a novel one-pot, three-component reaction was described (Scheme 1).

In the initial experiments, when **1a** (1.0 mmol) was reacted with 4-nitrobenzaldehyde **2a** (1.1 mmol) in acetonitrile (4 mL) in the presence of $TiCl_4$ (1.2 mmol) at

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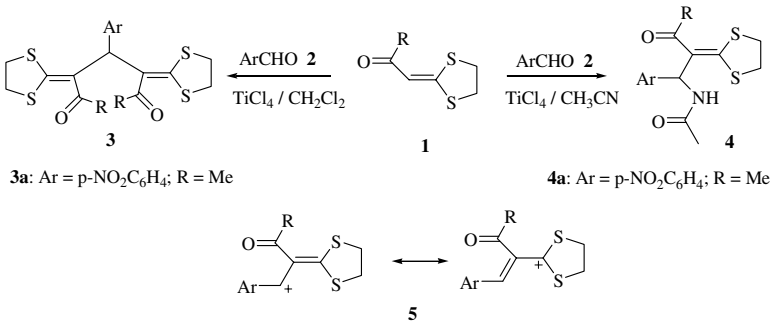


Scheme 1.

room temperature for 10 h, compound **4a**, an aza-MBH type product, assembled by the simultaneous MBH and Ritter reactions, could be obtained up to 93% isolated yield.[16] However, when the reaction proceeded in dichloromethane (4 mL) and acetonitrile was added in 5- to 10-fold excess to **1a**, the double MBH type product **3a** was obtained dominantly (Scheme 1). Also in acetonitrile, with the increasing of the ratio of **1a**:**2a**, compound **3a** became the main product and was dominant when the ratio of **1a**:**2a** reached to 3:1. These results might indicate that α-acetyl ketene-*S*,*S*-acetal **1a** was a much stronger nucleophile than acetonitrile toward carbocation **5**. According to the above results, nitriles were chosen as both nucleophiles and the solvent for this simultaneous MBH and Ritter reactions.

To extend the scope of this new procedure for the synthesis of aza-MBH type products, a variety of arylaldehydes were then examined by reacting with ketene-*S*,*S*-acetal **1a** under the optimized conditions and the results were summarized in Table 1. Arylaldehydes bearing electron-withdrawing groups on the phenyl ring led to good to excellent yields (Table 1, entries 1–7), whereas benzaldehyde and arylaldehydes bearing electron-donating groups, such as methyl or methoxy group, on the phenyl ring, gave sluggish or nearly no reactions under the identical conditions (Table 1, entries 8–10). Furthermore, the ketene-*S*,*S*-acetals, ethyl 2-(1,3-dithiolan-2-ylidene)acetate **1b**, and 2-(1,3-dithiolan-2-ylidene)-1-phenylethanone **1c**, were subsequently tested as the activated alkenes. We were pleased to find that the desired aza-MBH type products were also prepared in high yields under the under the same conditions as those of **1a** after a relatively long reaction time (Table 1, entries 11–14).

Table 1. Synthesis of the aza-MBH type products **4a**–**n**[a]

Entry	Product **4**	R	Ar	Time (h)	Yield[b] (%)
1	**4a**	CH_3	*p*-$NO_2C_6H_4$	10	93
2	**4b**	CH_3	*m*-$NO_2C_6H_4$	10	85
3	**4c**	CH_3	*o*-$NO_2C_6H_4$	12	78
4	**4d**	CH_3	*o*-FC_6H_4	24	72
5	**4e**	CH_3	*p*-FC_6H_4	24	76
6	**4f**	CH_3	*p*-ClC_6H_4	24	78
7	**4g**	CH_3	*P*-$CHOC_6H_4$	18	75
8	**4h**	CH_3	C_6H_5	72	55
9	**4i**	CH_3	*p*-$CH_3C_6H_4$	72	48
10	**4j**	CH_3	*p*-$CH_3OC_6H_4$	72	Trace[c]
11	**4k**	Ph	*p*-$NO_2C_6H_4$	72	84
12	**4l**	Ph	*m*-$NO_2C_6H_4$	72	80
13	**4m**	EtO	*p*-$NO_2C_6H_4$	12	88
14	**4n**	EtO	*m*-$NO_2C_6H_4$	10	85

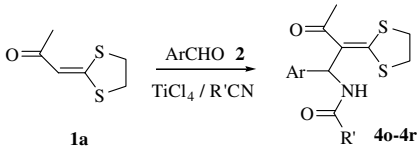
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.1 mmol), $TiCl_4$ (1.2 mmol), CH_3CN (4 mL), rt.
[b] Isolated yields.
[c] Based on the ^1H NMR spectrum of the reaction mixture.

On the other hand, to investigate the effects of nitriles on the sequential MBH and Ritter reactions as mentioned above, two other nitriles, propiononitrile, and 2-phenylacetonitrile, were then examined (Table 2). Similar to acetonitrile, the aza-MBH type products **4o**–**r** were obtained in high to excellent yields when 4-nitrobenzaldehyde **2a** and 3-nitrobenzaldehyde **2b** were selected as the electrophilic species and the structure of **4o** was established by the X-ray single crystal analysis (Fig. 1).[17]

Interestingly, when **3a** (1.0 mmol) was treated with $TiCl_4$ (1.2 mmol) in acetonitrile (4 mL) at room temperature for 24 h, compound **4a** and **1a** were isolated in 77% and 65% yields, respectively. This result might suggest that the double MBH product **3** was not stable in acetonitrile in the presence of $TiCl_4$ and a reversible process between **3** and intermediate **5** existed, which led to the formation of **4**.

Based on the experimental results mentioned above, a mechanism for this three-component reaction and related transformations was proposed as shown in

Table 2. Synthesis of the aza-MBH type products **4o**–**r**[a]



Entry	Product **4**	Ar	R′	Time (h)	Yield[b] (%)
1	**4o**	*p*-$NO_2C_6H_4$	$PhCH_2$	10	92
2	**4p**	*m*-$NO_2C_6H_4$	$PhCH_2$	12	87
3	**4q**	*p*-$NO_2C_6H_4$	Et	5	87
4	**4r**	*m*-$NO_2C_6H_4$	Et	6	83

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.1 mmol), $TiCl_4$ (1.2 mmol), RCN (4 mL), rt.
[b] Isolated yields.

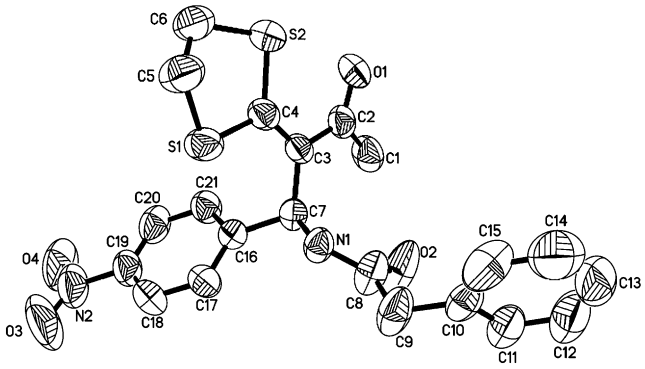


Figure 1. ORTEP drawing of X-ray structure of **4o**.

Scheme 2. It was clear that promoted by $TiCl_4$, a MBH type adduct was first formed and then converted to the carbocation intermediate **5**. At this stage, either the double MBH type product **3** or the aza-MBH product **4** could be formed depending on the reaction conditions. When a nitrile was used as the solvent (large excess), the reaction might favor the formation of aza-MBH type product **4** via the trapping of carbocation **5** by the nitrile as in the Ritter reaction.[15]

In summary, a novel one-pot three component coupling reaction of α-oxo cyclic ketene-*S*,*S*-acetals, arylaldehydes and nitriles, promoted by $TiCl_4$, was described. This methodology extended the synthetic potential of the versatile α-oxo ketene-*S*,*S*-acetals[9–14] and provided a preparative method for aza-MBH products without the use of very stable protecting group–the tosyl group.[6–8,18] Moreover, the transformation proceeded in the atom economic fashion in one step starting from the easily available or cheap materials under very mild reaction conditions. Further investigation is in progress.

Acknowledgements

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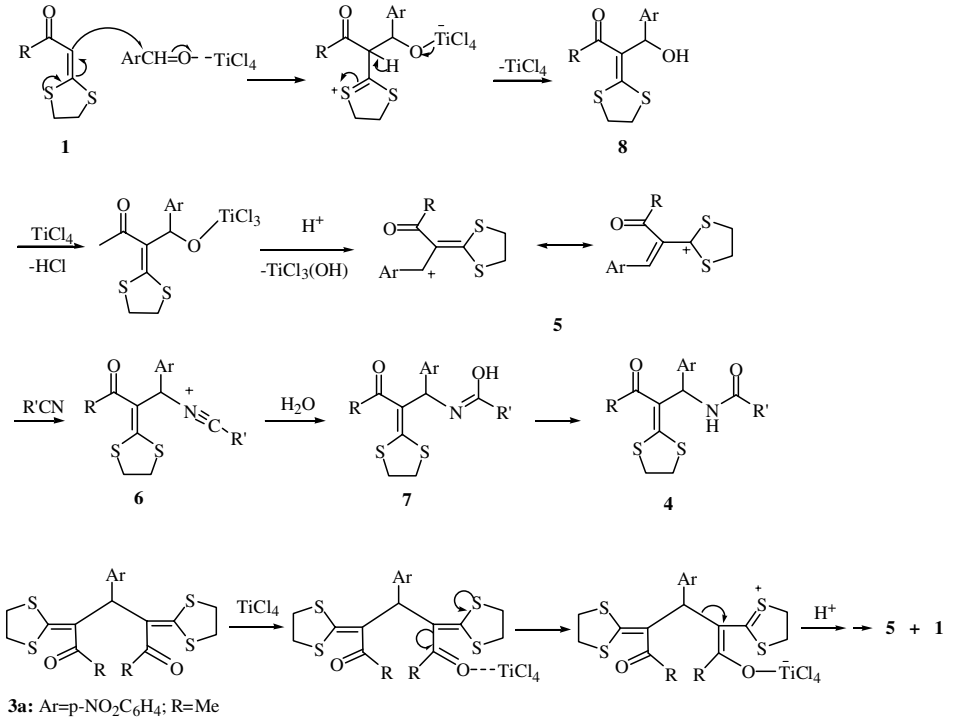

Scheme 2. Proposed mechanism for MBH and Rittert reactions.

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16. General procedure for the synthesis of aza-Morita–Baylis–Hillman adduct **4a**: To a solution of substrate **1a** (160.0 mg, 1.0 mmol) and **2a** (4-nitrobenzaldehyde) (166.0 mg, 1.1 mmol) in acetonitrile (4.0 mL) with ice-water bath was added titanium tetrachloride (0.13 mL, 1.2 mmol). The reaction mixture was stirred for 10 h, monitored by TLC, and the above mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution. After filtration, the filtrate was extracted with dichloromethane (5.0 mL × 2), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to give compound **4a** (328.0 mg, 93%) as a yellowish solid (eluent: ethyl acetate–petroleum ether = 3/1). Compound **4a**: yellowish solid, mp 98–100 °C; IR (KBr) 3416, 2920, 1657, 1632, 1518, 1348, 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.13 (s, 3H), 2.43 (s, 3H), 3.39–3.55 (m, 4H), 6.61 (d, $J = 9.0$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 1H), 7.10 (d, $J = 9.0$ Hz, 2H), 8.16 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.32, 30.06, 36.97, 39.35, 55.14, 123.78, 125.54, 126.85, 147.00, 147.61, 166.01, 169.66, 194.68; MS (*m*/*z*): 384.0 $[(M+1)]^+$. Anal. Calcd for $C_{15}H_{16}N_2O_4S_2$: C, 51.12; H, 4.58; N, 7.95. Found C, 51.33; H, 4.63; N, 7.86.
17. Crystal data for **4o**: $C_{21}H_{20}N_2O_4S_2$, yellowish, $M = 428.51$, monoclinic, space group $P2(1)/n$, $a = 10.825(2)$, $b = 11.232(2)$, $c = 17.885(4)$ Å, $V = 2143.1(7)$ Å^3, $\mu = 0.451$ mm^{-1}, $Z = 4$, $T = 293(2)$ K, $F_{000} = 896$, $R = 0.0498$, $wR^2 = 0.0905$. The CCDC deposition number: 268411.
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