Letter

Direct Synthesis of β,γ -Unsaturated α -Keto Esters from Aldehydes and Pyruvates

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atom-economic, step-economic, mild conditions

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Abstract Herein, we describe two practical methods to synthesize β , γ unsaturated α -keto esters directly from aldehydes and pyruvates promoted by BF₃ • Et₂O in the presence of Ac₂O or by Ti(OEt)₄ under mild conditions. A variety of aromatic aldehydes was tolerated to afford the desired products in moderate to excellent yield. Moreover, aliphatic aldehydes and Isatin were also employed to give the γ -alkyl β , γ -unsaturated α -keto esters in moderate yield with use of the Ti(OEt)₄ system.

Key words α -keto esters, step economy, pyruvates, aldehydes, aldol condensation

Because of their diverse reactivities, β , γ -unsaturated α keto esters¹ are synthetically useful building blocks, which have been widely applied in a variety of reactions, such as reduction,² Diels-Alder reaction,³ inverse-electron-demand hetero-Diels-Alder reaction,⁴ Friedel-Crafts reaction,⁵ aldol reaction (or nitro-aldol reaction),⁶ Michael addition,⁷ multicomponent reaction,⁸ and other cascade reactions⁹ to construct more complex compounds. Generally, β,γ-unsaturated α -keto esters could be prepared by aldol condensation of pyruvic acid with aromatic aldehydes under strong caustic conditions, followed by acidification and esterification (Scheme 1, path a).¹⁰ However, this method needs three steps with low overall yield and is limited to aromatic aldehydes. Sugimura's group¹¹ developed a Mukayaima-aldol reaction of 2-(trimethylsiloxy) acrylate with acetal promoted by BF_3 •Et₂O at very low temperature, and subsequent β elimination in the presence of silica gel in benzene heated to reflux (path b). Although versatile aldehydes could be employed with moderate to good yields in this process, it is a long journey under harsh conditions. The Wittig reaction has also been applied to synthesize β , γ -unsaturated α -keto esters with moderate yield (path c),¹² but it takes three

steps to prepare the ylide from pyruvate. These methods above lack atom economy¹³ and step economy.¹⁴ Although Dujardin et al.¹⁵ reported that copper(II)triflate catalyzed the direct synthesis of β , γ -unsaturated α -keto esters from aldehydes with pyruvate (path d), this method is limited to aromatic aldehydes, and aliphatic aldehydes are not suitable. This seems to be just a simple aldol condensation reaction; however, there are still challenges to synthesize β , γ unsaturated α -keto esters directly not only from aromatic aldehydes but also from aliphatic aldehydes with pyruvate.





As a continuation of our studies on exploring the reactivity of β , γ -unsaturated α -keto esters,¹⁶ we would like to establish a direct and practical procedure to prepare β , γ unsaturated α -keto esters efficiently. Herein, we document two direct methods to synthesize β , γ -unsaturated α -keto esters from aldehydes with pyruvates promoted by BF₃-Et₂O in the presence of acetic anhydride or by titanium ethoxide as dehydrate. As Dujardin reported that the dehydrate played an important role in improving the yield, we investigated the catalysis of various Lewis acids with acetic anhydride as the dehydrating agent in the cross-condensation

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reaction of benzaldehyde with ethyl pyruvate. As shown in Table 1, several common Lewis acids were examined. ZnCl₂, $Cu(OAc)_2$, and BiCl₃ did not work at all (Table 1, entries 1–3), but FeCl₃ or TiCl₄ could give the desired product **1a** in low yields (Table 1, entries 4, 5). BF₃•Et₂O, however, afforded the product in 30% yield (Table 1, entry 6) at room temperature in toluene after 72 hours. The yield could be greatly increased to 65% by increasing the reaction temperature to 40 °C (Table 1, entry 7). The yield was reduced to 44% (Table 1, entry 8) when the reaction temperature was raised to 100 °C. Further improvement was realized by increasing the catalyst loading to 50% (Table 1, entry 9) and 96% yield was achieved. When one equivalent of BF₃•Et₂O was used, the reaction could be shortened to one day with the yield slightly lowered to 75% (Table 1, entry 10). Control experiments demonstrated that both BF₃•Et₂O and acetic anhydride played a very important role in the reaction (Table 1, entries 11, 12). A solvent screening showed that this condensation reaction could be carried out in other common solvents, such as dichloromethane, chloroform, 1,2-dichloroethane, whereas the yield slightly dropped compared with the reaction in toluene (Table 1, entries 13-15). Notably, only the *E* isomer was detected in the ¹H NMR spectrum of the crude product. Finally, the best conditions were obtained: 50% BF₃•Et₂O as the catalyst with 1.5 equivalents of acetic anhydride as the dehydrator in toluene at 40 °C for 48 hours.

Table 1 Optimization of the Direct Aldol Condensati	iona
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(1 m	+ CHO 0 + CO ₂ Et 1.2 mmol) (1.2 mmol)	Ac ₂ O (1.5 equi	iv)	1a	CO ₂ Et
Entry	Lewis acid	Solvent	Temperat (°C)	ure Time (h)	Yield (%) ^b
1	ZnCl ₂ (20%)	toluene	rt	72	0
2	Cu(OAc) ₂ (20%)	toluene	rt	72	0
3	BiCl ₃ (20%)	toluene	rt	72	0
4	FeCl ₃ (20%)	toluene	rt	72	8
5	TiCl ₄ (20%)	toluene	rt	72	12
6	BF ₃ • Et ₂ O (20%)	toluene	rt	72	30
7	BF ₃ •Et ₂ O (20%)	toluene	40	72	65
8	BF ₃ •Et ₂ O (20%)	toluene	100	24	44
9^{d}	BF ₃ •Et ₂ O (50%)	toluene	40	48	96
10 ^d	BF ₃ •Et ₂ O (100%)	toluene	40	24	75
11	-	toluene	40	48	0
12 ^c	BF ₃ • Et ₂ O (50%)	toluene	40	48	0
13 ^d	BF ₃ •Et ₂ O (50%)	CH_2Cl_2	40	48	88

Entry	Lewis acid	Solvent	Temperatı (°C)	ure Time (h)	Yield (%) ^b
14 ^d	BF ₃ •Et ₂ O (50%)	$CHCI_3$	40	48	78
15 ^d	BF ₃ •Et ₂ O (50%)	(CH ₂ Cl) ₂	40	48	87

^a Reaction conditions: Benzaldehyde (1 mmol, 102 µL), ethyl pyruvate (1.2 mmol, 131 µL), and acetic anhydride (1.5 mmol, 142 µL) in solvent (5 mL). ^b Isolated yield after column chromatography.

^c Without acetic anhydride.

^d E/Z ratio > 19:1 from ¹H NMR spectrum of the crude product.

Having the optimized reaction conditions in hand, we applied this method to other substrates. As shown in Table 2,¹⁷ other pyruvates were tested and could afford the corresponding products in high yield with high E/Z selectivity (Table 2, entries 1–3). Furthermore, a variety of substituted benzaldehydes were investigated. All worked well to give the target products in good to excellent yield (Table 2, en-

Table 2 Substrate Scope^a



Entry	R	\mathbb{R}^1	Product 1	E/Z ratio ^b	Yield (%)
1	Ph	Et	1a	> 19:1	95
2	Ph	Me	1b	16:1	91
3	Ph	<i>i</i> -Pr	1c	> 19:1	89
4	2-MeC ₆ H ₄	Et	1d	6.5:1	78
5	3-MeC ₆ H ₄	Et	1e	6.4:1	77
6	$4-MeC_6H_4$	Et	1f	7:1	74
7	$4-MeOC_6H_4$	Et	1g	5.8:1	58
8	$4-FC_6H_4$	Et	1h	> 19:1	91
9	$2-CIC_6H_4$	Et	1i	9:1	75
10	3-CIC ₆ H ₄	Et	1j	15:1	81
11	$2,4-Cl_2C_6H_3$	Et	1k	> 19:1	77
12	$2-BrC_6H_4$	Et	11	> 19:1	91
13	$4-BrC_6H_4$	Et	1m	> 19:1	92
14	$3-NO_2C_6H_4$	Et	1n	> 19:1	87
15	$4-NO_2C_6H_4$	Et	10	> 19:1	96
16	1-naphthyl	Et	1р	> 19:1	53
17	2-furyl	Et	1q	> 19:1	31
18	2-thienyl	Et	1r	> 19:1	27
19	<i>n</i> -Pr	Et	1s	-	trace
20	<i>i-</i> Pr	Et	1t	> 19:1	35
21	Су	Et	1u	> 19:1	42

^a Reaction conditions: aldehyde (2 mmol), pyruvate (2.4 mmol), BF₃ • Et₂O (1 mmol), and acetic anhydride (3 mmol) in toluene (10 mL) at 40 °C for 48 h. ^b The *E*/*Z* ratio was detected by ¹H NMR analysis of the crude product. ^c Isolated yield after column chromatography.

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tries 4-15), and the benzaldehydes substituted with electron-donating groups showed lower yields with moderate selectivity than those with electro-withdrawing groups. 1-Naphthaldehyde can also be employed in this reaction to afford product 1p in 53% yield (Table 2, entry 16). Because of their low stability, 2-furyl-substituted 1q and 2-thienylsubstituted 1r were isolated in 31 and 27% yield, respectively (Table 2, entries 17, 18). Encouraged by the good results of the aromatic aldehydes, we wanted to apply this method to aliphatic aldehydes. Unfortunately, the linear butyraldehyde only afforded a low amount of product (Table 2, entry 19). However, the branched isobutvraldehvde and cvclohexane carboxaldehyde could be involved in this method to form the y-alkyl β , y-unsaturated α -keto esters **1t** and **1u**, respectively, in moderate yields (Table 2, entries 20, 21). Notably, a large scale reaction of 20 mmol benzaldehyde was carried out and 3.92 g (96% yield) of 1a could be separated (Scheme 2).



So far, the direct synthesis of γ -alkyl substituent β , γ -unsaturated α -keto esters still remained a challenge. To address this problem, a lot of conditions were investigated and Ti(OEt)₄ was found to be a good choice, working as a Lewis acid and dehydrating agent.¹⁸ After simple optimization, 1s from butyraldehyde was obtained in 36% yield in the presence of 1.2 equiv of Ti(OEt)₄ in toluene at 40 °C after three days (Table 3, entry 1).¹⁹ 3-Phenylpropionaldehyde could also be employed in this system to achieve the desired product 1v in 32% yield. The yields of 1t and 1u obtained from branched aldehydes were slightly increased compared with those obtained with the method employing BF₃•Et₂O. Aromatic aldehydes performed well in this Ti(OEt)₄ process. Even cinnamaldehyde tolerated those conditions to provide the target compound 1w in 68% yield (Table 3, entry 11).

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R-CHO + CO2Et		Ti(OEt) ₄ (1.2 equiv) toluene, 40 °C, 3 d		CO ₂ Et	
Entry	R	Product 1	E/Z ratio ^b	Yield (%)℃	
1	<i>n</i> -Pr	1s	> 19:1	36	
2	PhCH ₂ CH ₂	1v	> 19:1	32	
3	<i>i</i> -Pr	1t	> 19:1	39	
4	Су	1u	> 19:1	51	
5	Ph	1a	> 19:1	86	
6	$4-MeOC_6H_4$	1g	6.3:1	51	
7	$4-FC_6H_4$	1h	> 19:1	84	
8	$4-NO_2C_6H_4$	10	> 19:1	63	
9	2-furyl	1q	> 19:1	47	
10	2-thienyl	1r	> 19:1	29	
11	styryl	1w	> 19:1	68	

^a Reaction conditions: aldehyde (2 mmol), ethyl pyruvate (2.4 mmol),

Ti(OEt)₄ (2.4 mmol) in toluene (10 mL) at 40 °C for 3 d.

^b The *E*/*Z* ratio was detected by ¹H NMR analysis of the crude product. ^c Isolated vield after column chromatography.

What's more, activated ketone N-benzyl isatin was chosen to expand the application of these two methods. To our delight, the target product 1x was obtained in 33% yield with the Ti(OEt)₄ system (Scheme 3). In the previous report, it was prepared only by Wittig reaction in a similar yield.²⁰

In summary, we have developed two practical methods to synthesize β , γ -unsaturated α -keto esters directly from aldehydes and pyruvates through aldol condensation promoted by BF₃•Et₂O in the presence of Ac₂O or by Ti(OEt)₄ under mild conditions. Both methods could be applied in most of aromatic aldehydes to afford the target products in moderate to excellent yields. Moreover, aliphatic aldehydes also were employed in this process to give γ -alkyl β , γ -unsaturated α -keto esters in moderate yield with use of the Ti(OEt)₄ system.



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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612255.

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(17) β,γ-Unsaturated α-Keto Esters (1a–u); General Procedure A

To the solution of aldehyde (2 mmol) and pyruvate (2.4 mmol) in toluene (10 mL) were added BF₃•Et₂O (1 mmol) and Ac₂O (3 mmol). After stirring for 48 h at 40 °C, the mixture was poured into saturated NaHCO₃ (aq) solution (20 mL). The separated aqueous phase was extracted with ethyl acetate (20 mL) and the combined organic phases were washed by brine (20 mL), dried with Na₂SO₄, filtered, and concentrated in vacuum. The residue was filtered through a short pad of silica gel with petroleum ether/ethyl acetate (10:1) as the eluent to obtain a crude product, which was analyzed by ¹H NMR spectroscopy to calculate the *E*/*Z* ratio. Further purification was carried out by column chromatography on silica gel with petroleum ether/ethyl acetate (20:1) as the eluent to afford the products **1**.

Ethyl (E)-4-Cyclohexyl-2-oxobut-3-enoate (1t)

Pale yellow oil; yield: 176 mg (42%). ¹H NMR spectrum of the crude product shows an *E*/*Z* ratio of >19:1. ¹H NMR (400 MHz CDCl₃): δ = 7.09 (dd, *J* = 16.0, 6.8 Hz, 1 H), 6.57 (dd, *J* = 16.0, 1.1 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 2.29–2.13 (m, 1 H), 1.78–1.64 (m, 5 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.31–1.08 (m, 5 H). ¹³C NMR (101 MHz, CDCl₃): δ = 183.8, 162.5, 159.6, 122.7, 62.2, 41.2, 31.4, 25.8, 25.6, 14.0.

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(19) Ti(OEt)₄ System; General Procedure B

To the solution of aldehyde (2 mmol) and pyruvate (2.4 mmol) in toluene (10 mL) was added Ti(OEt)₄ (2.4 mmol). After stirring for 72 h at 40 °C, the mixture was diluted with ethyl acetate (40 mL) and quenched with water (1 mL). After stirring for 0.5 h at rt, the mixture was dried with Na₂SO₄, filtered, and concentrated in vacuum. The residue was filtered through a short pad of silica gel with petroleum ether/ethyl acetate (10:1) as the eluent to obtain a crude product, which was analyzed by ¹H NMR spectroscopy to calculate the *E*/*Z* ratio. Further purification was carried out by column chromatography on silica gel with petroleum ether/ethyl acetate (20:1) as the eluent to afford the products **1**.

Ethyl (E)-2-Oxohept-3-enoate (1s)

Pale yellow oil; yield: 122 mg (36%). ¹H NMR spectrum of the crude product shows an *E/Z* ratio of >19:1. ¹H NMR (400 MHz, CDCl₃): δ = 7.18 (dt, *J* = 15.8, 6.9 Hz, 1 H), 6.64 (d, *J* = 15.9 Hz, 1 H), 6.64 (d, *J* = 15.9 Hz, 1 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 2.29 (td, *J* = 8.0, 1.0 Hz, 2 H), 1.59–1.47 (m, 2 H), 1.37 (t, *J* = 7.1 Hz, 3 H), 0.95 (t, *J* = 7.4 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 183.5, 162.4, 154.9, 125.3, 62.30, 35.1, 21.1, 14.0, 13.7.

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