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An efficient synthesis of γ-amino β-ketoester by cross-Claisen condensation with α-amino acid derivatives

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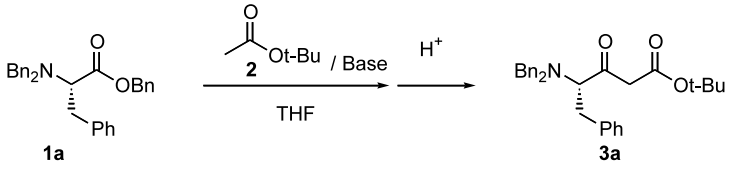
Abstract—Cross-ester condensation between *N*-protected amino acid ester and the lithium enolate prepared from alkyl acetate gave the corresponding β-ketoester in high yield without the formation of the tertiary alcohol that is commonly seen as by-product. This interesting reaction is applicable to the amino acid derivatives with suitable *N*-protecting groups, which can help to stabilize the reaction intermediates.

β-Ketoesters have for many years been widely used as versatile synthetic intermediates. The conversion of amino acids to their corresponding ketoesters, which can be used as chiral building blocks for various pharmaceutical intermediates, is an important technology.

Claisen condensation is a well-known method for the general synthesis of β-ketoesters. However, there have been very few reports of cross-condensation between different esters, and yields have mostly been quite low.[1,2] This is probably due to the presence of significant side reactions, such as self-condensation and the formation of tertiary alcohols. Successful results have been obtained in this reaction using hydroxyl esters as an electrophile with a large excess of base.[3] There have also been other examples with certain esters with strong electron-withdrawing groups adjacent to the carbonyl group such as alkyl fluoroalkanoate, and with methyl esters of γ-amino acid derivatives, but these have exhibited only moderate yields of at most 60%.[4] Ohta et al. overcame this problem by adding lithium alkoxide as an extra base to control the formation of tertiary alcohols.[1] Rather than cross-ester condensation, the approach that has most commonly been adopted has been to convert amino acid derivatives to their corresponding β-ketoesters by the nucleophilic addition of an enolate formed from alkyl acetate or a malonic acid half-ester to an activated carboxylic acid.[5] However, most of the methods used to activate carboxylic acids, e.g. mixed anhydride, acid chloride, activated ester, Weinreb amide, etc. have been reported to give only moderate yields.[6] While *N*-protected *N*-carboxy anhydride (NCA) is a reactive electrophile, it is not stable enough for widespread use.[7] Under such conditions, carbonyl imidazolide has often been efficiently applied and for many years it has been thought to be the only promising procedure for preparing β-ketoesters.[8,9] Rapid condensation with activated imidazolide can provide efficient conversion while avoiding the risk of racemization. In some reports, β-ketoesters have been formed using imidazolide which was prepared by means of the saponification of the corresponding alkyl ester even though cross-ester condensation could be expected to furnish the shortest path. Hoffman and Tao reported that the reaction with most *N*,*N*-dibenzyl amino acid methyl esters required several hours at a high tempera-



Scheme 1. Condensation reaction with *N*,*N*-dibenzyl L-phenylalanine benzyl ester.

Keywords: amino acid; γ-amino β-ketoester; Claisen condensation; cross-ester condensation; lithium enolate.
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ture to reach completion, and were accompanied by partial racemization.[8] It should also be noted that the use of imidazolide is rather expensive in an industrial setting. Therefore, we considered that the conversion of an amino acid to a β-ketoester using inexpensive and readily available intermediates would be an important technology for the pharmaceutical industry. We recently reported the synthesis of *N*-Cbz-α-aminoalkyl α′-halomethylketone in which cross-Claisen condensation was used as the key reaction.[10] This interesting result prompted us to investigate the cross-Claisen condensation of amino acid derivatives. We therefore studied the further application of this reaction as a general method for synthesizing β-ketoesters with various protecting groups other than Cbz, to determine its scope and limitations.

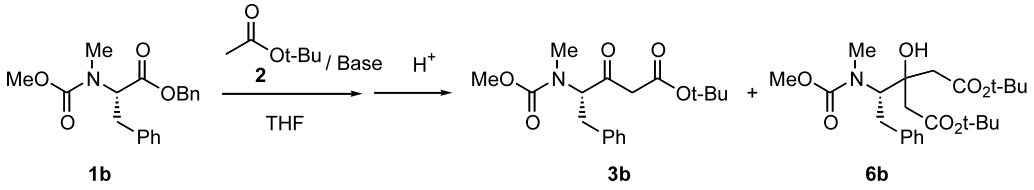
N,*N*-Dibenzyl L-phenylalanine benzyl ester **1a**,[11] which can be obtained by a one-step reaction from L-Phe, was reacted with *tert*-butyl lithioacetate prepared from *tert*-butyl acetate **2** and lithium diisopropylamide in tetrahydrofuran at −50°C (Scheme 1, Table 1);[12] the reaction selectively gave the corresponding β-ketoester **3a** without racemization (entry 1). The application of Claisen condensation to **1a** is an unusual example to avoid the formation of a tertiary alcohol, which is a common problem in cross-ester condensation. In contrast, condensation with *N*-methoxycarbonyl *N*-methyl derivative **1b**[13] gave a mixture of the desired β-ketoester and tertiary alcohol (entry 5) (Scheme 2). The unexpected success with **1a** could be due to the stabilized intermediate **8a**, obtained by the chelation of lithium with a dibenzylamino group[14] (Scheme 3, Path A). Regardless of the mechanism of this addition, the results show that the lithium in enolate **2a** can contribute to internal chelation with nitrogen to form **7a**, unaffected by the concentration of lithium ion (entries 1 and 4). On the other hand, the reaction with **1b** would be accompanied by the elimination of lithium since the *N*-methoxycarbonyl *N*-methylamino group of **1b** is a weaker Lewis base (Path B). In another possible path to establish selective condensation without the formation of a tertiary alcohol, lithium benzyloxide is not spontaneously eliminated from **7a** until the reaction mixture is quenched with acid (Path C). Path A is preferable because at least two equivalents of **2** were needed to complete the reaction (entries 2 and 3).

Application to other *N*-protected amino acid derivatives are also shown (Scheme 4, Table 2). *N*-Carbobenzyloxy L-phenylalanine methyl ester **2b** reacted with *tert*-butyl lithioacetate **2** to give β-ketoester **3b** quantitatively (entry 1). Lithium enolate prepared from a primary alkyl ester such as ethyl acetate as well as *tert*-butyl ester similarly gave a good result (entry 2). Although lithium hexamethyldisilazide also effectively gave the enolate at a high temperature, lithium *tert*-butoxide did not (entries 3 and 4). The examples in Table 2 show that this cross-ester condensation has a wide range of applications (entries 5–8). In the case of Claisen condensation to *N*-alkoxycarbonyl-protected amino acid ester, the negative charge of the nitrogen atom formed near the carbonyl group probably completely prevented the approach of the carbanion, as Ohta et al. previously noted in the reaction to the hydroxyl ester.[1] The reaction to Cbz-Cys(Ph)-OMe gave a considerable amount of tertiary alcohol, even though the desired ketoester was obtained as the major product (entry 8).

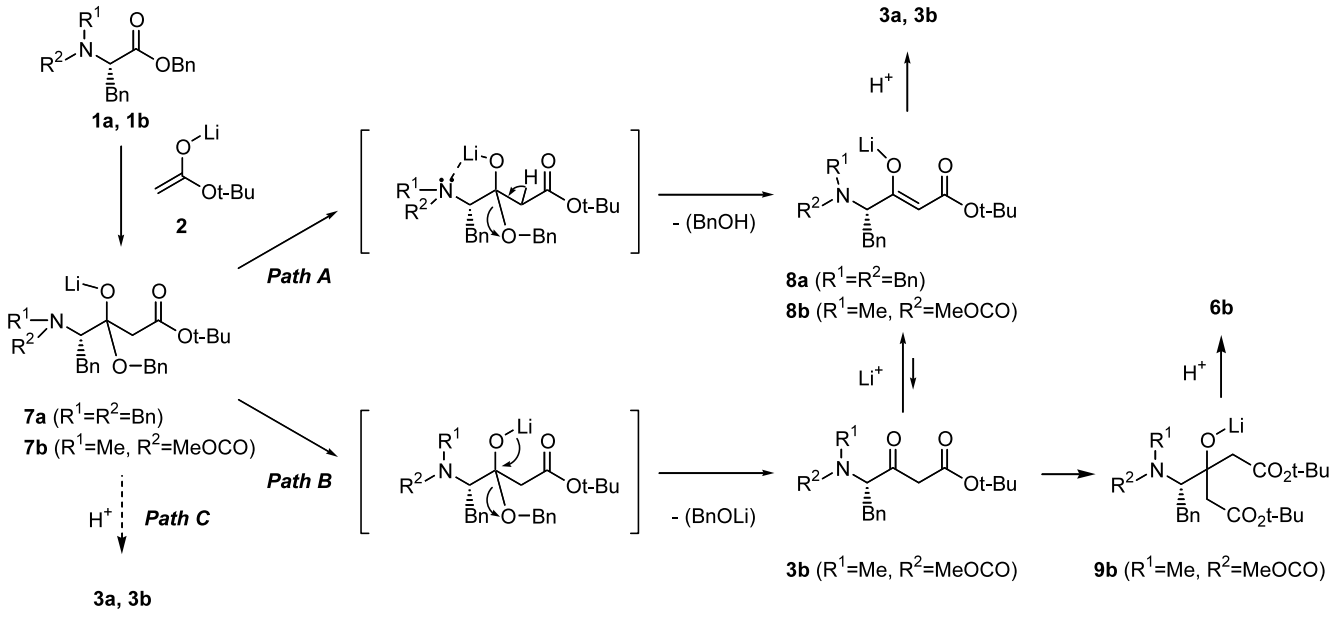
Table 1. Preparation of β-ketoester via cross-Claisen condensation between *N*-protected L-phenylalanine benzyl ester and *tert*-butyl acetate

Entry	Ester **1**	Enolate **2**		Temperature	Method[b]	Product HPLC peak ratio[c] **3**/**6**	Yield[d]
		t-BuOAc (equiv.)	Base (equiv.)	(1), (2)[a] (°C)			**3**[e] (%)
1	**1a**	3.3	LDA (2.9)	−45, −48	A	>99/1	90
2	**1a**	3.0	LDA (2.0)	−45, −50	A	>99/1	84
3	**1a**	1.0	LDA (1.0)	−45, −50	A	>99/1	30
4	**1a**	3.3	LDA (2.9)	−45, −50	B	>99/1	94
5	**1b**	3.3	LDA (2.9)	−45, −50	A	54/46	44

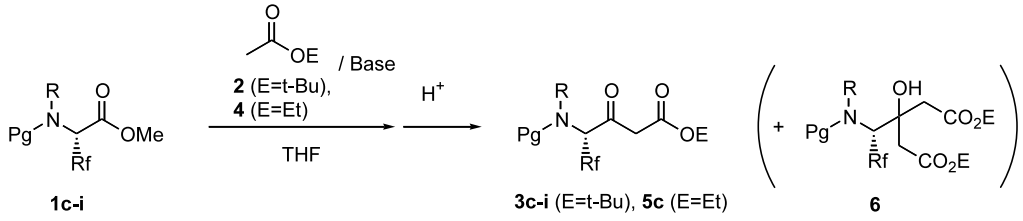
[a] Enolates were prepared at temperature (1), and condensation reactions were then carried out at temperature (2). The figure shows the maximum internal temperature during addition and reaction.
[b] Method A: The ester was added dropwise to the enolate. Method B: The enolate was added dropwise to the ester.
[c] The ratio of 'ketoester/tertiary alcohol' was indicated by peak area% (UV at 210 nm) in HPLC (Inertsil ODS-2, 0.03 M KH_2PO_4 aqueous buffer solution/acetonitrile).
[d] Ketoesters (**3a,b**) were isolated by preparative TLC.
[e] The optical purity of each compound was higher than 98% ee, as determined by chiral HPLC (Chiralcel OD-H, *n*-hexane/ethanol) at 210 nm.



Scheme 2. Condensation reaction with *N*-methoxycarbonyl *N*-methyl L-phenylalanine benzyl ester.



Scheme 3. Supposed mechanism of the reactions.



Scheme 4. Condensation reaction with *N*-protected amino acid methyl ester.

Table 2. Cross-Claisen condensation reaction between *N*-alkoxycarbonylamino acid methyl ester and acetic acid ester

Entry	Ester				Enolate		Temperature	Product HPLC peak ratio[b] **3** (**5**)/**6**	Yield (%)[c]	
		Rf	Pg	R	Ester (equiv.)	Base (equiv.)	(1), (2)[a] (°C)			
1	**1c**	Bn	Cbz	H	**2** (4.0)	LDA (3.5)	−45, −50	>99/1	**3c**	97
2	**1c**	Bn	Cbz	H	**4** (4.0)	LDA (4.0)	−50, −50	>99/1	**5c**	89
3	**1c**	Bn	Cbz	H	**2** (4.0)	LHMDS (3.5)	−25, −25	>99/1	**3c**	87
4	**1c**	Bn	Cbz	H	**2** (4.0)	LiOBu-*t* (3.5)	−20, −20	>99/1	**3c**	Trace
5	**1d**	*i*-Pr	Cbz	H	**2** (4.0)	LDA (3.6)	−50, −55	>99/1	**3d**	89
6	**1e**	*i*-Bu	Cbz	H	**2** (4.0)	LDA (3.6)	−50, −55	>99/1	**3e**	98
7	**1f**	4-OH-Bn	Cbz	H	**2** (4.0)	LDA (3.6)	−50, −55	>99/1	**3f**	65
8	**1g**	$PhSCH_2$-	Cbz	H	**2** (3.7)	LDA (3.6)	−65, −70	96/4	**3g**	87
9	**1h**	Bn	Boc	H	**2** (4.0)	LDA (3.5)	−45, −50	>99/1	**3h**	85
10	**1i**	Bn	Boc	Me	**2** (4.0)	LDA (3.5)	−50, −55	41/59	**3i**	29

[a] Enolates were prepared at temperature (1), and condensation reactions were then carried out at temperature (2). (Cf. footnote to Table 1).
[b] The ratio of 'ketoester/tertiary alcohol' was indicated by peak area% in HPLC. (Cf. footnote to Table 1).
[c] Ketoesters (**3c-i**, **5c**) were isolate by preparative TLC.

The participation of sulfur in the enolate may make the reaction less selective. In the absence of a carbamate anion, where acidic hydrogen is substituted by an alkyl group, a tertiary alcohol was obtained as the major product (entries 9 and 10).

In conclusion, the efficient application of cross-Claisen condensation between *N*-protected α-amino acid ester and alkyl acetate was achieved. This is an interesting reaction since an intermediate stabilized by the contribution of an amino functional group could overcome

the common problem of cross-ester condensation. This reaction may be useful as a versatile method for synthesizing γ-amino β-ketoesters.

Acknowledgements

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12. *Typical procedure* (Table 1, entry 1): A solution of *tert*-butyl acetate (5.8 g, 50 mmol) in THF (12 mL) was added dropwise to a mixture of dry THF (64 mL) and LDA (2 M solution in THF/heptane/ethylbenzene, 22 mL, 44 mmol) with stirring under an argon atmosphere over 15 min with cooling to under −45°C. After stirring at −45°C for 60 min, to this mixture at a temperature under −48°C was added dropwise over 15 min a solution of **1a** (purity 90%, 7.2 g, 15 mmol) in THF (8 mL). The resulting mixture was stirred at −48°C for 60 min and then poured into a solution of citric acid (16.5 g) in water (50 mL) to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 mL+50 mL). The combined organic layers were washed with 10% citric acid aqueous solution (20 mL), 5% $NaHCO_3$ aqueous solution (20 mL), and 25% NaCl aqueous solution (10 mL), and then dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by silica gel chromatography to give **3a** (6.1 g, 13.7 mmol, yield: 91.3%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.25$ (s, 9H), 2.93 (dd, 1H, $J = 3.9$, 13.5 Hz), 3.20 (dd, 1H, $J = 9.0$, 13.5 Hz), 3.40 (d, 2H, $J = 15.6$ Hz), 3.55 (m, 2H), 3.62 (dd, 1H, $J = 3.9$, 9.0 Hz), 3.82 (d, 2H, $J = 13.5$ Hz), 7.10–7.38 (m, 15H); FAB MASS m/z 444 (MH^+).
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