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Synthesis of Optically Active α-Aminoalkyl α′-Halomethyl Ketone: A Cross-Claisen Condensation Approach

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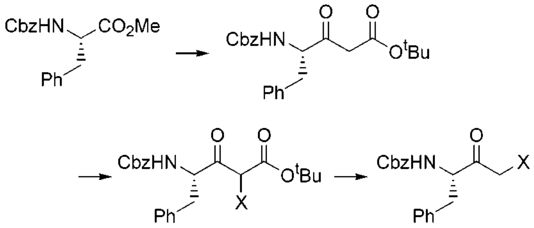
ABSTRACT



A simple and versatile method was developed for the synthesis of α-aminoalkyl α′-halomethyl ketone derivatives, which are useful intermediates of protease inhibitors. It involves selective halogenation of the α-position on a *β*-ketoester, which is prepared by cross-Claisen condensation using *N*-protected amino acid ester. The title compound is obtained in high yield after decarboxylation of the α-halo-*β*-ketoester.

Optically active α-aminoalkyl α′-halomethyl ketone derivatives are usually synthesized from the corresponding amino acids through multistep transformation. While conversion involving diazomethyl ketone and subsequent acidolysis with HX has been the classic approach in this area,[1] direct chloromethylation to *N*-protected amino acid ester has also been investigated to overcome the safety issue of using diazomethane.[2] Since α-aminoalkyl α′-halomethyl ketone can be readily converted into the amino epoxide, which is a key intermediate for several HIV protease inhibitors,[3] the use of phenylalanine as a starting material has been extensively studied with regard to industrially applicable synthesis. Recently, a method for synthesizing *N*-protected amino epoxide from the corresponding amino acids via *β*-ketoester was reported.[4] As the authors noted in their article, a similar synthetic approach had been previously reported by us in the patent literature.[5] Although they successfully extended our approach to other amino acids, their report prompted us to disclose our full results for comparison with their method. In addition, an elegant method (for α-aminoalkyl α′-halomethyl ketones) involving the condensation of L-phen-

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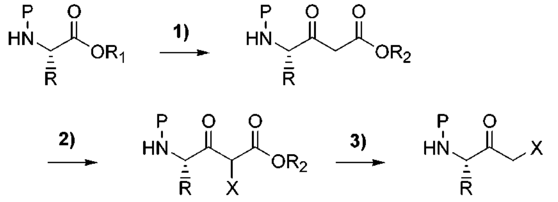
ylalanine derivatives with magnesium enolate of chloroacetic acid followed by one-pot decarboxylation during workup was reported in the course of our study.[6]

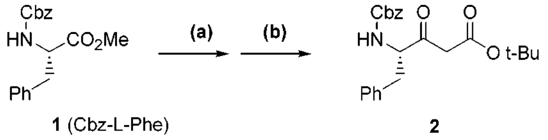
Our synthetic approach to α-aminoalkyl α′-halomethyl ketones consists of three steps, namely, (1) conversion of the *N*-protected amino acid ester to *β*-ketoester, (2) monohalogenation of the α-methylene, and (3) hydrolysis of the ester and decarboxylation to give the desired halomethyl ketones (Scheme 1). Our objective was to establish an industrially applicable process that would not require a hazardous reaction or chromatographic purification.

Scheme 1



Claisen condensation is a well-known method for the general synthesis of *β*-ketoesters. However, there have been very few reports on the application of cross-condensation between different esters,[7] and successful results were exceptionally obtained in the reaction using hydroxyl ester.[8] A nucleophilic reaction of ester enolate to acid imidazolide has been widely used as a common method for synthesizing *β*-ketoester,[9] but it can be rather expensive to use imidazolide or active ester in an industrial setting. Therefore, we considered that cross-Claisen condensation between two stable and readily available esters, i.e., *N*-protected amino acid alkyl ester and alkyl acetate, might be worth investigating. Thus, *N*-carbobenzyloxy L-phenylalanine methyl ester **1** was reacted with excess lithium enolate prepared from *tert*-butyl acetate and lithium diisopropylamide in tetrahydrofuran at −50 °C (Scheme 2); the reaction gave the corresponding *β*-ketoester **2** quantitatively without racemization.[10] To the best of our knowledge, this is the first successful cross-Claisen condensation with an alkyl ester of an α-amino acid derivative. Furthermore, we did not detect a tertiary alcohol formed by further attack of the enolate. The details of this method will be reported soon.

Scheme 2[a]



[a] (a) *t*-BuOAc (4.0 equiv), LDA (3.5 equiv), THF, −45 to −50 °C; (b) H^+ (97% from **1**).

Effective halogenation of the *β*-ketoester **2** is another important issue in this process (Scheme 3). Chloromethyl ketone is equivalent to bromomethyl ketone as a precursor of amino epoxide, since it has been reported that reduction with sodium borohydride proceeded with the same trend of selectivity.[11] The selectivity of this reduction could be influenced mainly by the reaction conditions, such as temperature or solvent, and less by the halogen at the α-position. Since the chloro ketone is more stable than the bromo derivative, chlorination seemed to be a good choice for halogenation. Therefore, the optimal conditions for chlorination were investigated. (Table 1) As noted by Hoffman et al., chlorination with *N*-chlorosuccinimide gave disappointing results. On the other hand, sulfuryl chloride, which is an effective reagent for chlorination at the α-position to a carbonyl group,[12] induced a selective reaction without dichlorination, and α-chloro-*β*-ketoester **3a** was produced in 95% yield.[13] The pure material could be isolated by recrystallization from toluene. Bromination was also studied

Scheme 3

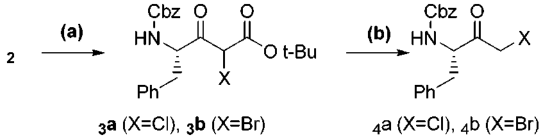


Table 1. Results of Halogenation at the α-Position of *β*-Ketoester **2** (Reaction (a))

product	reagent	conditions	yield (%)[a]
3a	NCS (1.0 equiv)	$CHCl_3$, 25 °C, 3.5 h	43
3a	SO_2Cl_2 (1.2 equiv)	CH_2Cl_2, 15 °C, 1.0 h	95
3b	NBS (1.0 equiv)	CH_2Cl_2, 25 °C, 2.0 h	40
3b	NBS (1.0 equiv)/DMAP	CH_2Cl_2, 25 °C, 2.0 h	56
3b	Br_2 (1.0 equiv)/$CaCO_3$ (1.0 equiv)	CH_2Cl_2, −10 °C, 2.0 h	93

[a] Reaction yield determined by HPLC.

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for comparison. Bromine induced a rapid reaction at low temperature, and **3b** was produced in 93% yield. Although *N*-bromosuccinimide worked more efficiently in the presence of an additive such as DMAP, the results were not promising. In the bromination studies, the results varied and were sometimes difficult to reproduce. This problem may have been due to the instability of **3b**.

Table 2. Results of Hydrolysis and Decarboxylation of **3a** and **3b** (Reaction (b))

reactant	product	reagent	conditions	yield (%)[a]
3a	**4a**	HCO_2H	80 °C, 20 min	60[a], 74[b]
3a	**4a**	4 M HCl (30 equiv) in AcOEt	25 °C, 15 h	30[a]
3b	**4b**	TFA (30 equiv) in AcOEt	60 °C, 17 h	42[a]
3b	**4b**	HCO_2H	25 °C, 15 h	53[a]

[a] Isolated yield purified on preparative TLC[a] with an eluent of *n*-hexane: AcOEt = 4:1, or purified by recrystallization from 2-propanol[b].

The α-halo-β-ketoesters **3a** and **3b** were converted into halomethyl ketones by acidic hydrolysis and subsequent decarboxylation (Table 2). Even though most of the reactions took place smoothly, the yields after isolation via TLC were rather low. On the other hand, **4a**, which was obtained quantitatively by reacting **3a** in formic acid, could be purified by recrystallization from 2-propanol with a satisfactory yield.[14] These halomethyl ketones might readily decompose on silica gel. We concluded that hydrolysis and decarboxylation proceed in formic acid and the pure product can be isolated by recrystallization. Thus, we obtained α-*N*-carbobenzyloxyaminobenzyl-α'-chloromethyl ketone in an overall yield of 65% from Cbz-L-phenylalanine methyl ester. We also converted **4a** into the corresponding Cbz-protected amino epoxide in 56% yield as a single stereoisomer.

In conclusion, a practical synthesis of α-aminoalkyl α'-halomethyl ketone derivatives via a β-ketoester was achieved. It involves efficient cross-Claisen condensation using amino acid derivatives and halogenation of the β-ketoester.

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(10) **Typical procedure:** A solution of *tert*-butyl acetate (4.0 equiv vs **1**) in THF was added dropwise to a mixture of dry THF and LDA (3.5 equiv in THF) with stirring at −45 °C. After stirring at −45 °C for 60 min, to the mixture at a temperature under −50 °C was added dropwise a solution of **1** in THF. The resulting mixture was stirred at −50 °C for 60 min and was then poured into 1 M HCl and extracted with toluene, washed with 5% $NaHCO_3$, and concentrated under reduced pressure to afford a crude product, which was purified by column chromatography to give **2** (96.6% from **1**) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.44$ (s, 9H), 2.99 (dd, 1H, $J = 7.1$, 14.1 Hz), 3.17 (dd, 1H, $J = 6.1$, 14.1 Hz), 3.38 (m, 2H), 4.68 (bq, 1H, $J =$ approximately 7 Hz), 5.07 (s, 2H), 5.38 (bd, 1H, $J = 7.9$ Hz), 7.12−7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 28.0$, 37.1, 48.2, 60.7, 67.0, 82.4, 127.1, 128.1, 128.2, 128.5, 128.7, 129.2, 135.8, 137.9, 165.8, 182.0, 201.7; mass (FAB) 398 (MH^+).

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(13) **Typical procedure:** Sulfuryl chloride (1.2 equiv) was added dropwise to a solution of **2** in dichloromethane in an ice bath with stirring at a temperature under 10 °C. After a reaction with stirring at 15 °C for 60 min, the resulting mixture was concentrated at 25−30 °C under reduced pressure to give crude **3a** as a pale yellowish crystal (95% determined by HPLC). The crude material was recrystallized from toluene to give a pure crystal (major isomer): ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.44$ (s, 9H), 2.99 (dd, 1H, $J = 7.5$, 14.1 Hz), 3.20 (dd, 1H, $J = 6.1$, 14.1 Hz), 4.85 (s, 1H), 4.97 (bq, 1H, $J = 8.4$ Hz), 5.06 (s, 2H), 5.25 (bd, 1H, $J = 8.4$ Hz), 7.14−7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 27.5$, 37.7, 59.5, 60.0, 67.2, 85.0, 127.3, 128.1, 128.3, 128.5, 128.9, 129.2, 135.3, 136.0, 155.6, 163.1, 197.4; mass (FAB) 432 (MH^+), 454 (MNa^+).

(14) **Typical procedure: 3a** was added to 90% formic acid at 25 °C and the suspended mixture was heated in an oil bath at 80 °C with stirring for 20 min. The resulting mixture was cooled to 25 °C and concentrated under reduced pressure at 30−35 °C. The residual crude material was recrystallized from 2-propanol to afford **4a** (70.3%): ^1H NMR (300 MHz, $CDCl_3$) $\delta = 3.00$ (dd, 1H, $J = 7.0$, 13.9 Hz), 3.09 (dd, 1H, $J = 6.9$, 13.9 Hz), 3.97 (d, 1H, $J = 16.2$ Hz), 4.14 (d, 1H, $J = 16.2$ Hz), 4.75 (bq, 1H, $J =$ approximately 7 Hz), 5.06 (s, 2H), 5.38 (bd, 1H, $J = 7.6$ Hz), 7.11−7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 37.6$, 47.3, 58.7, 67.2, 127.4, 128.1, 128.3, 128.5, 128.9, 129.0, 135.2, 135.9, 155.7, 200.8; mass (ESI) 332.2 (MH^+).