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Stereoselective Synthesis of Functionalized γ-Amino Esters: Azetidinium Salts and Epoxy Esters

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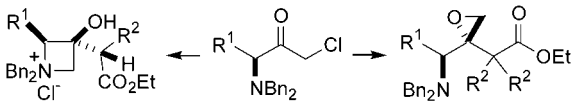
ABSTRACT



Addition of several lithium ester enolates to chiral 1-aminoalkyl chloromethyl ketones 1 affords enantiomerically pure 3-hydroxyazetidinium salts 3 or 3-(1′-aminoalkyl)-3,4-epoxy esters 4, depending on the reaction conditions.

γ-Amino acids represent an important class of compounds not only due to their biological activity[1] but also because they are present in the structure of natural products with antitumor activity.[2] Likewise, azetidines appear as substructures in natural products,[3] and homochiral azetidines have been used as ligands[4] and catalysts[5] in asymmetric synthesis.

Previously, we have described the synthesis of chiral α′-amino α-chloro ketones **1**[6] by treatment of easily available α-amino esters with in situ generated chloromethyllithium. We have also described some synthetic applications of these α-amino chloromethyl ketones, such as the preparation of enantiopure *threo* aminoalkyl epoxides,[6b] 3-azetidinols,[7] amino epihalohydrins,[8] α′-amino-α,β-epoxyketones,[9] and amino aziridines, from their ketimine derivatives.[10] The high diastereoselectivity of all these reactions, and the enantiopurity of the obtained compounds, prompted us to study new synthetic applications of chiral 1-aminoalkyl chloromethyl ketones **1** in the synthesis of enantiomerically pure building blocks. Herein, we report the addition of different lithium ester enolates to chiral 1-aminoalkyl chloromethyl ketones **1**, obtaining 3-hydroxyazetidinium salts **3** or 3-(1′-aminoalkyl)-3,4-epoxyesters **4**, depending on the reaction conditions, in enantiomerically pure form.

The reaction of 1-aminoalkyl chloromethyl ketones **1** with lithium enolates of different esters at −78 °C gave, after hydrolysis at the same temperature, the corresponding

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chlorohydrins **2**, despite of the formation of a quaternary center (Scheme 1). Compounds **2** were stable in tetrahydrofuran solution.[11] But, when the solvents were completely evaporated to dryness at room temperature, compounds **2** underwent an intramolecular heterocyclization, yielding azetidinium salt **3**[12] or epoxy ester **4**, with high yield and diastereoselectivity (Table 1).[13] The isolation of compound **3** or **4** depends on the substitution pattern in the ester enolate. Thus, in the case of ethyl acetate and ethyl 3-phenylpropionate enolates (Table 1, entries 1−4), the corresponding azetidinium salts **3** were isolated, whereas epoxy esters **4** were obtained when disubstituted ester enolates were used (Table 1, entries 5−7). Therefore, the use of bulky esters favors epoxidation instead of azetidinium salt formation.

Scheme 1. Addition of Ester Enolates to Ketones **1**

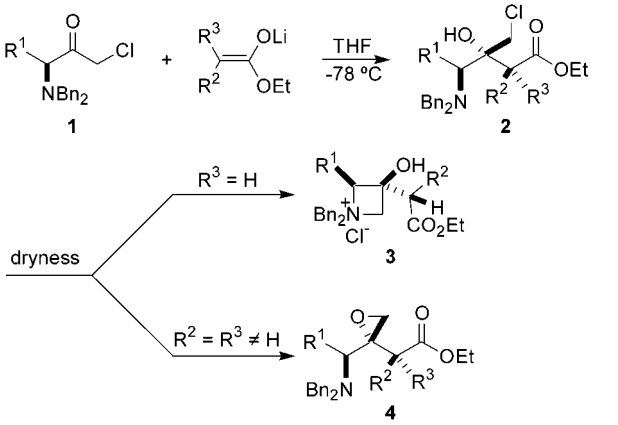


Table 1. Addition of Ester Enolates to Ketones **1**

entry	product	R^1	R^2	R^3	yield (%)[a]	de[b]
1	**3a**	Me	H	H	87	>95
2	**3b**	*i*-Bu	H	H	82	>95
3	**3c**	Bn	H	H	80	>95
4	**3d**	Me	Bn	H	68[c]	72
5	**4e**	Me	Me	Me	76	93
6	**4f**	*i*-Bu	Me	Me	72	>95
7	**4g**	Me	-$(CH_2)_5$-		73[c]	95

[a] Isolated yield based on the starting ketone **1**, after a 1 h reaction time. [b] Diastereoisomeric excess determined by 300 MHz ^{1}H and ^{13}C NMR analysis of the crude products **3** and **4**. [c] To complete the reaction, 8 h was required.

Although azetidinium salts **3a**−**c** were obtained when acetate enolate was used, we also prepared the corresponding epoxy esters **4a**−**c**, as shown in Scheme 2.[14] To do this, the reaction of α-amino ketone **1** with acetate enolate at −78 °C was followed by addition of a few drops of water at the same temperature. Then, without isolating the intermediate chlorohydrin, the reaction mixture was treated with an excess of sodium hydride at −40 °C. When this mixture was allowed to warm to room temperature, the epoxy esters **4a**−**c** were isolated in high yield (Table 2).[15]

Scheme 2. Synthesis of Epoxy Esters **4a**−**c**

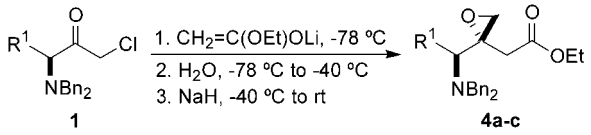


Table 2. Synthesis of Epoxy Esters **4a**−**c**

product	R^1	yield (%)[a]	de[b]
4a	Me	80	>95
4b	*i*-Bu	76	>95
4c	Bn	70	>95

[a] Isolated yield based on the starting ketone **1**. [b] Diastereoisomeric excess determined by 300 MHz ^{1}H and ^{13}C NMR analysis of the crude products **4**.

Azetidinium salts **3** and epoxy esters **4** were isolated in enantiomerically pure form,[16] and with total or high diastereoselectivity. The degree of stereoselectivity was only moderately affected by the size of R^1 in the α-amino ketone and the substituents in the enolate ester (see Tables 1 and 2). In the case of product **3d**, two new chiral centers were created in moderately diastereoisomeric excess (de = 72%).

(11) Compound **2a** with 20% of THF was characterized by ^{13}C NMR: δ 171.5, 139.2, 128.7, 127.9, 126.6, 75.9, 60.3, 55.6, 55.0, 49.5, 38.9, 13.6, 6.0.

(12) Formation of azetidinium salts starting from halohydrins has been also observed in similar substrates: (a) Reference 7. (b) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *J. Org. Chem.* **1997**, *62*, 8902−8906.

(13) **Representative procedure for the enolate ester addition to ketones 1:** To a −85 °C stirred solution of lithium diisopropylamide (5.5 mL of solution 0.3 M in THF, 1.65 mmol) was added dropwise a solution of the corresponding ester (1.5 mmol) in dry THF (1 mL). After stirring for 15 min, a solution of 1-aminoalkyl chloromethyl ketone **1** (1 mmol) in dry THF (2 mL) was added dropwise at −78 °C. When the reaction was complete (see Table 1), the mixture was quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Crude azetidinium salts **3** was recrystallized from CH_2Cl_2/EtOAc to give pure compounds **3**. When epoxy esters **4** were isolated, flash column chromatography over silica gel (hexane:triethylamine = 50:1) provided pure compounds **4e**−**g**.

(14) **Representative procedure for the synthesis of epoxy esters 4a-c:** To a −85 °C stirred solution of lithium diisopropylamide (5.5 mL of solution 0.3 M in THF, 1.65 mmol) was added dropwise a solution of ethyl acetate (0.14 mL, 1.5 mmol) in dry THF (1 mL). After stirring for 10 min, a solution of the corresponding 1-aminoalkyl chloromethyl ketone **1** (1 mmol) in dry THF (2 mL) was added dropwise at −78 °C. The reaction mixture was stirred at the same temperature for 1 h, and then water (4 drops) was added. After stirring for 15 min at −40 °C, NaH (0.24 g, 10 mmol) was added, and the mixture was allowed to warm to room temperature for 20 min and carefully quenched with water (10 mL). Usual workup provided crude compound **4a**−**c**. Flash column chromatography over silica gel (hexane:ethyl acetate = 15:1) afforded pure compounds **4a**−**c**.

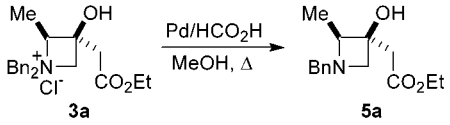
(15) When the aldol reaction was hydrolyzed at room temperature, a mixture of **4** and an α,β-unsaturated lactone derived from **4** was isolated. See: Concellón, J. M.; Riego, E.; Bernad, P. L. *Org. Lett.* **2002**, *4*, 1303.

(16) The optical purity was determined by chiral HPLC analysis of the α,β-unsaturated lactone derived from **4c**. See ref 15.

Since the reactions with disubstituted ester enolates take place with high or total diastereoselectivity (Table 1, entries 5−7), the lower de observed in this product could be due to the stereogenic center formed from the ester enolate.

Azetidinium salts **3** can be precursors of azetidines via a hydrogenolysis process. In this way, compound **3a** was monodebenzylated by treatment with formic acid in the presence of palladium in refluxing methanol, to afford the azetidine **5a** in quantitative yield (Scheme 3).[17]

Scheme 3. Hydrogenolysis of the Azetidinium Salt **3a**



3a **5a**

Configurational assignments of the condensation products were made by NOESY experiment with azetidine **5a**. As shown in Figure 1, NOE effects were observed between the

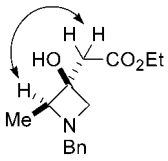


Figure 1. NOE effects observed in azetidine **5a**.

H-2 proton at the heterocycle and α-hydrogens at the carbonyl position, showing the *cis* relationship of these protons.[18] Therefore, addition of ester enolate to ketone **1** took place under nonchelation control, in agreement with the previously reported aldol addition to dibenzylated amino aldehydes[19] and reduction and addition of organometallic compounds to amino ketones.[6b,7]

In conclusion, we have developed new synthetic applications of chiral 1-aminoalkyl chloromethyl ketones **1** by reaction with ester enolates, affording different enantiopure γ-amino esters, such as azetidinium salts and epoxy esters, with high yield and diastereoselectivity. This method is simple, and the starting materials are readily available.

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Supporting Information Available: Spectroscopic data for all new compounds **3**, **4**, and **5a**, ^{13}C NMR spectra of **2a**, **3**, **4**, and **5a**, and NOESY ^{1}H NMR spectrum of **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) **Representative procedure for the synthesis of 5a:** A solution of **3a** (0.3 g) in 5% formic acid−methanol (30 mL) containing palladium black catalyst (0.3 g) was stirred at reflux temperature overnight. Then, the reaction mixture was filtered through a pad of Celite and evaporated to dryness. The residue was dissolved in CH_2Cl_2 and washed with saturated K_2CO_3. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to provide compound **5a**.

(18) The relative configuration of the chiral center formed from the enolate in the major diastereoisomer **3d** was determined by an NOESY experiment on a **3d** derivative. See ref 15.

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