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Synthesis of N-protected γ-amino-β-keto-esters from Urethane N-carboxyanhydrides (UNCAs)

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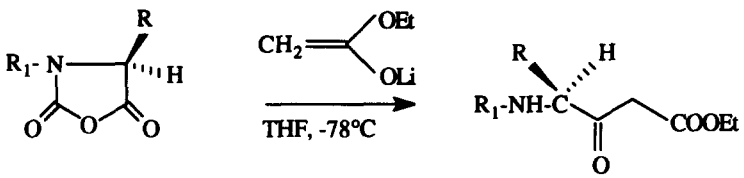
Abstract: N-protected γ-amino-β-keto-esters were synthesized from the corresponding N-protected N-carboxyanhydride (UNCAs) by reaction with the lithium enolate of ethyl acetate in good yields. These compounds are precursors of statine derivatives. Copyright © 1996 Elsevier Science Ltd

Our laboratory is involved in the study of the reactivity of urethane N-protected carboxyanhydrides (UNCAs) in peptide synthesis and in several reactions leading to aminoacid derivatives. UNCAs are very reactive aminoacid derivatives. They were used with success in solid phase peptide synthesis (SPPS)[1] and we have shown their usefulness in the synthesis of peptides in solution.[2] We have also shown that UNCAs can be considered as starting material for the synthesis of various aminoacid derivatives such as β-amino alcohols[3], statine derivatives[4], α-amino-aldehydes[5] and vicinal tricarbonyl compounds[6] in good yields. Recently we showed that UNCAs are reactive enough to yield to the corresponding tert-butyl esters when tert-butanol is used as solvent, in the presence of potassium bicarbonate at 45°C.[7] However, the use of UNCAs in the presence of tertiary amines has to be controlled, since 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) or triethylamine (TEA) in dimethylformamide solutions can lead to the formation of pyrrolidine-2,4-dione derivatives[8] that should be avoided in the synthesis of peptides. N-methylmorpholine is highly recommended when UNCAs are used in peptide synthesis. All the reactions involving UNCAs are characterized by their simplicity, efficiency and mild conditions and can be performed from readily available commercially materials.[9]

Statine derivatives have been widely used for the synthesis of aspartyl protease inhibitors such as renin or more recently HIV proteases. These γ-amino-β-hydroxy acids are recognized to mimic the transition state analog of the substrate when interacting with the enzyme. Many stereoselective or non stereoselective syntheses of *syn* and *anti*-statine derivatives have been reported, including acylation of ester enolates with amino aldehyde derivatives[10,11] or diastereoselective reduction of the corresponding β-oxo esters.[12] These β-oxo esters can also be useful intermediates for the synthesis of amino-acid and pyrrazole derivatives. We report herein a simple and efficient preparation of N-protected γ-amino-β-keto-esters from the corresponding UNCAs. These N-protected γ-amino-β-keto-esters are precursors of N-protected γ-amino-β-hydroxy-esters or statines derivatives which can be obtained as a mixture of diastereoisomers by reduction with non chiral reducing agents or as pure diastereoisomers by chiral reduction of the corresponding ketones as described by Nishi et al.[13] in the presence of Wilkinson catalyst. However, they can be used as chiral building blocks in combinatorial chemistry.

We have shown that in the presence of the lithium enolate of ethyl acetate in THF at - 78°C, UNCAs led to the corresponding N-protected γ-amino-β-keto-ester derivatives (scheme 1).



R_1 = benzyloxycarbonyl; tert-butyloxycarbonyl.

Scheme 1. Synthesis of N-protected γ-amino-β-keto-esters from UNCAs.

The synthesis of a series of various N-protected γ-amino-β-keto-ester (Boc or Z) from the corresponding UNCAs (Table 1) showed the usefulness of this method. As shown in Table I, the condensation of the lithium enolate is compatible with various protecting groups used in peptide synthesis such as tert-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Z) groups.

UNCA	Yield (%)	M+H+	$[\alpha]_D$ (c=1, MeOH)	m.p. (°C)
Boc-Leu	50	302	-39	oil
Boc-Ala	60	260	-24	oil
Boc-Met	64	320	-35	oil
Boc-Ile	60	302	-23	oil
Boc-Ser(Bzl)	60	366	-1	oil
Boc-Asp(OBzl)	55	394	-40	54-57
Boc-Phe	70a	336	-44	61-62
Z-Phe	60	370	-39	57-61
Z-Ala	52	294	-10	oil
Z-Lys(Boc)	60b	451	-14	69-71
Z-Glu(OBzl)	55c	442	-24	71-74

Table 1. Physical properties of N-protected γ-amino-β-keto-esters obtained from UNCAs. Yields are given after purification. a: crystallized from hexane; b: crystallized from ether/hexane; c: crystallized from hexane.

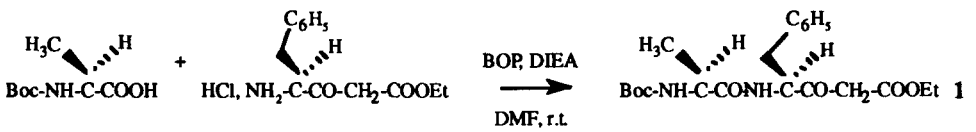
In a typical experiment, the lithium enolate of ethyl acetate was prepared under argon atmosphere at - 78°C from 1 eq. of ethyl acetate in THF (1 mmole/10 ml) and 2 eq. of LDA (2M in THF/heptane/ethylbenzene, purchased from Aldrich). After 1 h, the UNCA (1 eq.) was added (1mmole/10 ml THF) and stirred during 10

min. Hydrolysis was performed with 3 eq. of acetic acid. The reaction mixture was then allowed to reach room temperature and the solvent was concentrated *in vacuo*. The desired compound was extracted with diethyl ether, the organic layer was washed with aqueous solutions of potassium hydrogenosulfate (1M), sodium hydrogenocarbonate (saturated) and with brine. It was then dried over sodium sulfate and concentrated *in vacuo*. The product was purified by silica gel chromatography with an ethyl acetate/hexane system as eluent or crystallized when possible.

UNCA	ratio *syn/anti*	temperature (°C), solvent	NH (*syn*) ppm(δ)	NH(*anti*) ppm(δ)
Z-Ala	2.2/1	0, EtOH	4.03	3.96
Boc-Phe	1/5	0, EtOH	4.85	4.52
Boc-Phe	1/5.5	-20, MeOH	4.85	4.52

Table 2. N-protected γ-amino-β-hydroxy-esters obtained by reduction of the corresponding γ-amino-β-keto-esters synthesized from Z-L-Ala-NCA and Boc-L-Phe-NCA; The ^1H NMR studies were performed in $CDCl_3$ on a 360 MHz Bruker instrument.

All the N-protected γ-amino-β-keto-esters that were synthesized were homogeneous on TLC on silica gel in various solvent systems and reversed phase HPLC on a C18 analytical column. They were identified by ^1H NMR and mass spectrometry. The reduction of two γ-amino-β-keto-ester corresponding to lithium enolate condensation with Z-L-Ala-NCA and Boc-L-Phe-NCA was performed with sodium borohydride (4 molar eq.) at 0°C in ethanol or at -20°C in methanol as described by Reetz and al.[12] In these two cases, the mixture of stereoisomers was studied by ^1H NMR and quantified by the distinguishable signals (Table 2); the assignment of the *syn/anti* conformation was performed according to Rich et al.[10] The ^1H NMR study of the corresponding γ-amino-β-hydroxy-esters revealed the presence of only two stereoisomers, suggesting that no racemization occurred at the α carbon.



Scheme 2. Synthesis of the dipeptide **1**.

To verify that the stereochemistry of the α carbon was conserved, the dipeptide Boc-Ala-Phe-CH2COOEt **1** was prepared by condensation of Boc-Ala-OH with the γ-amino-β-keto-ester derivative obtained by reaction of Z-Phe-NCA with the lithium enolate of ethyl acetate, according to the scheme 2. The ^1H NMR analysis of compound **1** revealed the presence of only one diastereoisomer[14], within the ^1H NMR detection limit.

In this study, we have shown that N-protected γ-amino-β-keto-ester derivatives can be easily obtained from commercially available UNCAs.[9] These reactions proceed smoothly, rapidly, yielding a variety of N-protected γ-amino-β-keto-ester derivatives in acceptable yields. This study points out again the superb reactivity of UNCAs and their usefulness in the synthesis of aminoacid derivatives.

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14. Compound 1 : HPLC, C18 Lichrosorb, flow 1 ml min., detection 220 nm, gradient water/acetonitrile 0 to 100% in 50 min., single peak, Rt = 31.76 min. ^{1}H NMR (Bruker 360 Mhz), δ ppm, 1.10 d, 3H, Ala; 1.20 t, CH_3; 1.37 s, 9H, Boc; 2.8 m, 1H, Hβ Phe; 3.15 m, 1H, Hβ Phe; 3.60 s, 2H, CO-CH_2-CO; 3.87 m, 1H, Hα Ala; 4.10 q, 2H, CH2; 4.42 m, 1H, Hα Phe; 6.90 d, 1H, NH Ala; 7.2-7.3 m, 5H, arom. Phe; 8.25 d, 1H, NH Phe.

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