Pergamon

Tetrahedron Letters 39 (1998) 1569–1572

TETRAHEDRON LETTERS

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

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Received 30 October 1997; accepted 21 December 1997

Abstract: N-protected α-alkyl-γ-amino-β-keto-esters were synthesized from the corresponding N-urethane protected N-carboxyanhydride (UNCAs) by reaction with lithium enolates in fairly good yields. These compounds are candidates for mimicking the transition state analogue in enzyme inhibitors. They constitute, however, interesting and diverse building blocks for using in combinatorial chemistry.

We have a continuing interest in the design of potent enzyme inhibitors, particularly acid protease inhibitors. In this case, the most successful approach is based on the concept of the transition state analogues. As an example, the tetrahedral transition state involved in the proteolysis of angiotensinogen by renin at the scissible Leu-Val bond has been effectively mimicked by inhibitors containing hydroxyethylene isostere[1] or by incorporation of statine[2] derivatives. It was proposed that statine is a dipeptide isostere replacing the *P1-P'1* portion of the substrate[3] and that the 3*S*-hydroxyl group is a mimic of a hydroxyl group in the tetrahedral intermediate.[4] The low potency of statine containing inhibitors toward certain acid proteases could be explained at least in part by the lack of *P'1* side chain interaction. On the other hand, we have shown in the case of bombesin that mimics of statine could be incorporated into peptide chains to yield highly potent receptor antagonists.[5] N-urethane protected α-alkyl-γ-amino-β-keto-esters are potential precursors of «2-alkylated statine» derivatives and constitute however, interesting building blocks for using in combinatorial chemistry. A synthesis of these compounds has recently been reported from α-hydroxy-β-lactam derivatives, through prior formation of a N-carboxyanhydride obtained from the corresponding azetidine-2,3-dione followed by an ester enolate acylation protocol.[6] We describe here the synthesis of α-alkyl-γ-amino-β-keto-esters from N-urethane protected N-carboxyanhydrides (UNCAs).

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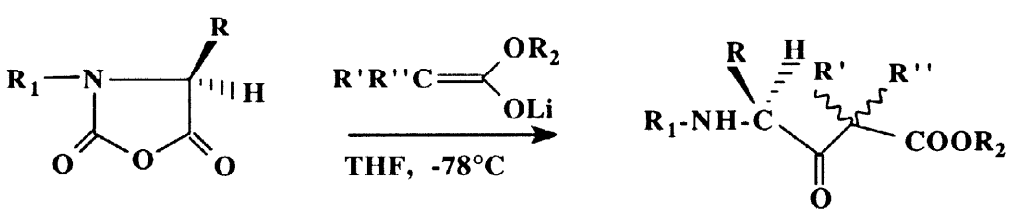
0040-4039/98/$19.00
PII: S0040-4039(98)00026-4

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 have been used with success in solid phase peptide synthesis (SPPS)[7] and we have shown their usefulness in the synthesis of peptides in solution.[8] We have also shown that UNCAs can be considered as starting material for the synthesis of various aminoacid derivatives such as β-amino alcohols[9], statine derivatives[10], α-amino-aldehydes[11] and vicinal tricarbonyl compounds[12] in fairly good conditions. We also demonstrated 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.[13] 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[14]. N-methylmorpholine is highly recommended when UNCAs are used in peptide synthesis. We recently published the synthesis of γ-amino- β-keto-esters from UNCAs.[15] All the reactions involving UNCAs are characterized by their simplicity, efficiency and mild conditions and can be performed from commercially available materials.[16]

We report herein a simple and efficient preparation of N-protected α-alkyl-γ-amino-β-keto-esters from the corresponding UNCAs. These compounds are precursors of N-protected α-alkyl-γ-amino-β-hydroxy-esters or statine derivatives which can be obtained as a mixture of diastereoisomers by reduction with non chiral reducting agents or as pure diastereoisomer by chiral reduction of the corresponding ketone as described by Nishi et al.[17] in the presence of Wilkinson catalyst.

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



R_1 = benzyloxycarbonyl; tert-butyloxycarbonyl.

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

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

UNCAs	Yield (%)/$[\alpha]_D$ (c=1,MeOH)/MP(°C)			
	R' = isopropyl R'' = H R_2 = Bzl	R' = isobutyl R'' = H R_2 = Bzl	R' = benzyl R'' = H R_2 = Bzl	R' = CH_3 R'' = CH_3 R_2 = Et
Boc-Ala	59/-41/oil	/	50/-36/69-71	50/-60/85-87
Boc-Phe	63/-27/84-86	50/-47/94-96	50/-32/oil	81/-49/68-71
Boc-Leu	50/-19/98-102	50/-43/75-76	43/-31/oil	/
Boc-Ile	/	56/-51/69-70	/	77/-85/oil
Boc-Met	/	32/-47/65-66	/	/
Boc-Ser(Bzl)	50/-9/oil	/	40/-1/oil	55/-29/oil
Boc-Asp(OBzl)	42/-45/oil	33/-29/oil	/	60/-54/oil
Boc-Glu(OBzl)	46/-19/oil	/	/	57/-42/oil
Z-Ala	43/-15/oil	48/-16/oil	30/-12/oil	48/-29/oil
Z-Phe	52/-43/68-72	40/-47/82-84	40/-48/83-85	70/-54/oil
Z-Val	40/-11/50-52	56/-30/oil	42/-22/oil	/
Z-Glu(OBzl)	/	25/-27/oil	40/-15/oil	37/-32/oil

Table 1. Physical properties of N-protected γ-amino-β-keto-esters obtained from UNCAs. Yields are reported for pure compounds after purification by chromatography on silica gel.

In a typical experiment, the lithium enolate was prepared from 1 eq of the alkylated ethyl acetate benzyl or ethyl ester under argon atmosphere at - 78°C in THF(1 mmole/10 ml) in the presence of 2 eq of LDA (2M in THF/heptane/ethylbenzene, Aldrich). After 1 h, the UNCA (1 eq) was added (1mmole/10 ml THF) and the reaction mixture was stirred for 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 a 1M potassium hydrogenosulfate solution, saturated sodium hydrogenocarbonate and with brine. The organic layer was dried over sodium sulfate and the solvent concentrated *in vacuo*. The crude material was purified by chromatography on silica gel using an ethyl acetate/hexane system as eluent or was crystallized when possible. After purification

or crystallization, the compounds were homogeneous on TLC in various solvent systems and reversed phase HPLC. They were identified by mass spectrometry and by ^{1}H NMR analysis (as exemplified[18]) that detected the presence of two compounds (1:1) corresponding to the two diastereoisomers (except from the compounds resulting from the condensation of the enolate of ethyl isobutyrate (R'= iPr) where only one component was obtained). However few amounts of pyrolidin-2,4-diones[14] could be detected by HPLC during the reaction (less than 10% of pyrolidin-2,4-dione was evidenced in the case of Z-Phe-NCA which is favorable to this formation).

In summary, we have shown in this piece of work that it was possible to obtain N-protected α-alkyl-γ-amino-β-keto-esters from UNCAs in fairly good conditions. This reaction shows again the usefulness of UNCAs for the synthesis of aminoacid derivatives.

Acknowledgements: The authors thank Isochem for financial support of this research and especially Dominique Gibert and Jean-Pierre Senet for helpfull discussions.

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18. As examples some physical characteristics are reported : ^{1}H NMR studies were performed on a 360 MHz Bruker AMX spectrometer. **N(*tert*-butyloxycarbonyl)-4-amino-2,2-dimethyl-3-keto-5-phenyl ethyl pentanoate**: ^{1}H NMR ($CDCl_3$) 7.21(s, 5H, ar), 4.8(d, 1H, NH), 4.7(m, 1H, H4), 4.1(q, 2H, CH_2-ester), 2.9(qd, 2H, H5), 1.3(s, 15H, Boc + 2xCH_3), 1.2(t, 3H, CH_3-ester); M.P. 68-71°C; $[\alpha]_D$ -49 (c=1, MeOH). **N(*tert*-butyloxycarbonyl)-4-amino-2-methyl-3-keto-5-phenyl benzyl pentanoate**: ^{1}H NMR ($DMSO_{d6}$) 7.38 and 7.36(2d, 1H, NH), 7.3(m, 10H, 2xar), 5.1(s, 2H, CH_2-benzyl ester), 4.4 and 4.33(m, 1H, H4), 4.07 and 4.0(q, 1H, H2), 3.08 and 2.6(m, 1H, H5), 2.72 and 3.02(m, 1H, H5), 1.4(s, 9H, Boc), 1.24 and 1.2(d, 3H, CH_3); M.P. 78-80°C; $[\alpha]_D$ -44 (c=1, MeOH).