Pergamon

Tetrahedron Letters, Vol. 35, No. 4, pp. 569-571, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0310-G

Synthesis of Chiral N-Protected β–Amino Alcohols by the Use of UNCAs

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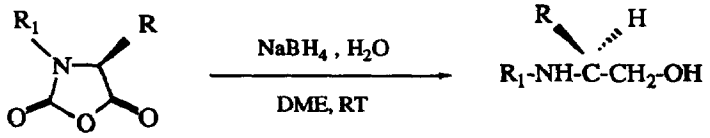
Abstract: A facile synthesis of a wide variety of N-protected β-amino alcohol derivatives under mild conditions is described. N-urethane protected amino acid N-carboxyanhydrides (UNCAs) were used as starting material and reduced into the corresponding alcohols with the appropriate hydride, sodium borohydride. The reaction is simple, unexpensive, easily scaled up, and proceeds without observable racemization.

N-protected β-amino alcohols are of great interest in the synthesis of peptide bond surrogates because they are key intermediates for the obtention of α-amino aldehydes by oxydation[1] which are potent inhibitors of proteases or for the preparation of stereochemically defined "methylene-oxy" dipeptides[2]. They can also be incorporated at the C-terminal end of hormones like in the case of enkephalins to achieve receptor selectivity[3]. N-protected β-amino alcohols are prepared by reduction of alkyl esters of amino acids[4,5], and active esters of amino acids[6] with sodium borohydride. Recently we and others described an efficient synthesis of N-protected β-amino-alcohols via the reduction of mixed anhydrides by sodium borohydride[7,8]. We present here a convenient and attractive one-pot synthesis of β-amino alcohols by chemoselective reduction of N-protected amino acids N-carboxyanhydrides (UNCAs) with sodium borohydride.

Scheme 1. Synthesis of β-amino-alcohols from UNCAs.



R_1 = Boc, Fmoc, Z

The synthesis of UNCAs and their use in peptide synthesis were described by Fuller et al.[9]. More recently Savrda and Wakselman described another attractive method of synthesis of UNCAs (Z and Boc) by reacting N,N-bis(alkoxycarbonyl) amino acid derivatives with the $SOCl_2$/DMF Vilsmeier reagent[10]. UNCAs are crystalline compounds, stable when stored in anhydrous conditions; they are commercially available. UNCAs were reduced by sodium borohydride into N-protected β-amino alcohols in 1,2-dimethoxyethane as solvent, rapidly (in a few minutes) at room temperature in good to high yields with retention of optical purity and with high homogeneity (Scheme 1). Different reaction conditions were investigated, all of them leading to the expected β-amino alcohols in satisfactory yields (Table 1).

Table 1. Synthesis of Boc-L-phenylalaninol from Boc-L-Phe-NCA under different reaction conditions.

Experimental conditions	$[\alpha]^{20}_D$ (c = 1, MeOH)	Yield (%)	mp (C°) *
A	- 24	81	98-100
B	- 23	87	96
C	- 23	91	96
D	- 26	91	96

* mp = 93-95°C (from reference 8).Conditions A : as described in reference 8; B : solvent THF, H-LiAl(OtBu)$_3$ 4 molar equivalents added portionwise; C : solvent THF, $NaBH_4$ 1 molar equivalent added portionwise; D : solvent 1,2-dimethoxyethane, $NaBH_4$ 1.5 molar equivalent in water added in one portion.

The usefulness of this method was demonstrated by the synthesis of various N-protected β-amino alcohols (Z, Boc, Fmoc) (Table 2). The tert-butyl-ester or the benzyl ether used for the protection of carboxylic acid side chain of glutamic acid and of the phenol of tyrosine remains unaffected under the described reaction conditions.

In a typical experiment, the UNCA derivative (Z, Boc or Fmoc) (10 mmoles) was dissolved in 1,2-dimethoxyethane (20 ml) and stirred at room temperature. A solution of sodium borohydride (15 mmol) in water (5ml) was added in one portion. A strong evolution of gas was produced and after 5 to 10 minutes the reaction was quenched by addition of water (200 ml). In some cases, the expected alcohol precipitated (entries **3**, **5**, **7**, and **8**, Table 2); it was collected by filtration, washed with water and hexane. When the expected compound did not precipitate as a solid, the reaction mixture was extracted with ethyl acetate (entries **1**, **2**, **4** and **6**), and the organic layer washed with water, dried over sodium sulfate and concentrated *in vacuo*.

All N-protected β-amino alcohols that were synthesized were homogeneous by TLC and reversed phase HPLC on a C_{18} analytical column. They were identified by mass spectrometry. No racemization could be detected as indicated by comparaison of their $[\alpha]_D$ with those reported in the literature.

The use of UNCAs and their reduction allowed us to obtain in a one step synthesis the desired β-amino alcohols in good yields (80 to 96%). The reaction proceeds without racemization and with a very simplified procedure (room temperature, no need to prepare the anhydride, easy recovery of the compound). This method seems to be valuable for the preparation of β-amino alcohols from Boc, Z or Fmoc N-carboxyanhydrides and is compatible with various side-chain protecting groups as revealed by the syntheses of β-amino alcohol derivatives of Fmoc-Glu(OtBu) **4** and Boc-Tyr(Bzl) **8** (Table 2).

Table 2. Preparation of β-amino alcohols from urethane-protected amino N-carboxyanhydrides

N-protected β–amino alcohols	Yield (%)	mp (°C)	$[\alpha]^{20}_D$ (c=1, MeOH)	Rf_A	Rf_B
1 Z-Leu	80	oil	-21	0.57	0.64
2 Z-Ile	96	64	-14	0.57	0.60
3 Fmoc-Leu	90	130	-17	0.52	0.59
4 Fmoc-Glu(OtBu)	83	55-57	-10	0.42	0.59
5 Fmoc-Ile	89	108-110	-12	0.50	0.70
6 Fmoc-Trp	80	86-90	-26	0.21	0.44
7 Boc-Phe	91	96	-26	0.48	0.58
8 Boc-Tyr(Bzl)	87	108	-17	0.34	0.60

(A) Ethyl acetate/hexane 1:1; (B) dichloromethane/methanol 95:5.

In conclusion, the present synthesis of N-protected β-amino alcohols from UNCAs is a rapid and convenient method which can be applied to Z, Boc and Fmoc amino acids. This method permits a selective conversion of their carboxyl group into a hydroxymethyl group in the presence of other functional side chain protecting groups under mild conditions and without racemization.

REFERENCES

1. Stanfield, C. F.; Parker, J. E. & Kanellis, P. *J. Org. Chem.*, **1981**, *46*, 4797-4798.
2. TenBrink, R. E. *J. Org. Chem.*, **1987**, *52*, 418-422.
3. Handa, B. K.; Lane, A. C.; Lorn, J. A. H.; Morgan, B. A.; Rance, M. J. & Smith, C. F. C. *Eur. J. Pharmacol.*, **1981**, *70*, 531-540.
4. Soai, K.; Oyamada, H. & Takase, M. *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 2327-2328.
5. Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S. & Shioiri, T. *J. Org. Chem.*, **1987**, *52*, 1252-1255.
6. Nitakawa, J.& Shiba, T. *Chem. Lett.*, **1979**, 981-982.
7. Kokotos, G. *Synthesis*, **1990**, 299-301.
8. Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A. & Martinez, J. *Tetrahedron Lett.*, **1991**, *32*,923-926.
9. Fuller, W. D.; Cohen, M. P.; Shabankareh, M.; Blair, R. K.; Miller, T. A.; Goodman, M.; & Naider, F. R. *J. Am. Chem. Soc.*, **1990**, *112*, 7414-7416. All UNCAs are available from Propeptide, BP 12, 91710 Vert-Le Petit, France.
10. Savrda, J. & Wakselman, M. *IIIème Forum Peptides and Proteins*, Biarritz, France, **1993**, Abstract C18.

(*Received in France* 15 *October* 1993; *accepted* 16 *November* 1993)