Tetrahedron Letters, Vol 32, No 7, pp 923-926, 1991
Printed in Great Britain

0040-4039/91 $3.00 + 00
Pergamon Press plc

A FACILE SYNTHESIS OF CHIRAL N-PROTECTED β-AMINO ALCOHOLS.

Marc Rodriguez, Muriel Llinares, Sylvie Doulut, Annie Heitz & Jean Martinez*

Centre CNRS-INSERM de Pharmacologie-Endocrinologie

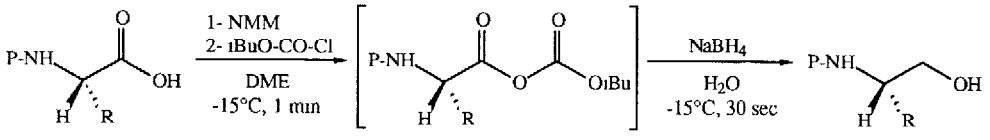
Rue de la Cardonille, 34094 Montpellier-Cédex 05, France.

Abstract: Chiral N-protected β-amino alcohols are easily obtained by $NaBH_4$ reduction of mixed anhydrides of N-protected α-amino acids in an organic/aqueous medium. The alcohols obtained from side chain or main chain reduction of N-protected aspartic acid are converted in good yields into lactones.

N-protected β-amino alcohols are key intermediates in the synthesis of peptide bond surrogates They lead to α-amino aldehydes by various oxydation procedures[1] (e.g. pyridinium dichromate), which can be used in the design of protease inhibitors[2], or in the synthesis of "reduced peptide bonds" [Ψ(CH_2-NH) peptide bond replacements][3]. On the other hand, β-amino alcohols have been utilized in the preparation of stereochemically defined "methylene-oxy" dipeptides [Ψ(CH_2-O) peptide bond replacements][4] and as C-terminal end of enkephalins to achieve receptor selectivity[5]

The most widely used synthesis of β-amino alcohols is the reduction of N-protected amino acids by borane-THF[1]. In 1987, Soai *et al* reported the chemoselective reduction of mixed carboxylic-carbonic anhydrides (generated from ethyl chloroformate) by sodium borohydride in tetrahydrofuran with dropwise addition of methanol[6]. We found this method very attractive for the conversion of N-protected α-amino acids into N-protected β-amino alcohols[7], although we were concerned with the possibility of side products formation (i.e. N-protected α-amino acids methyl or ethyl esters), due to the use of ethyl chloroformate and methanol

We found out that a mixed anhydride obtained from a N-protected α-amino acid by reaction with isobutyl chloroformate in 1,2-dimethoxyethane, cleanly reacted with 1.5 molar equivalent of aqueous sodium borohydride to lead to the corresponding alcohol in very good yields, according to Scheme 1. In our hands, the use of aqueous reagents with mixed carboxylic-carbonic anhydrides proved to be very efficient, as demonstrated in the synthesis of N-protected α-amino acid amides[8].



P: Boc, Z, Fmoc

Scheme 1

entry	alcohol	Yield (%)	mp (°C)		$[\alpha]_D$ (c, solvent)	
			found	reported	found	reported
1	Boc-Asp(OBzl)-ol	97	oil		- 6 (1.0, MeOH)	
2	Boc-D-Asp(ol)-OBzl	61	oil		+ 35 (1.0, MeOH)	
3	Boc-Arg(NO_2)-ol (a)	59	131-133		- 8 (1 0, MeOH)	
4	Boc-Gln-ol (a)	84	118-119		- 9 (1.05, MeOH)	
5	Boc-Lys(Z)-ol	94	64-67		- 9 (1.05, MeOH)	
6	Boc-Phe-ol	81	93-95	94.5 (b)	- 26 (1.05, MeOH)	
				90-91 (c)	- 26 (1.1, $CHCl_3$)	-2.16 (1.0, $CHCl_3$) (c)
7	Boc-Thr(Bzl)-ol	98	oil		+ 11 (1.4, MeOH)	
8	Boc-Trp-ol	82	111-113		- 28 (1 0, MeOH)	
9	Boc-Tyr(Bzl)-ol	98	104-106		- 19 (1.05, MeOH)	
10	Z-Asp(OBzl)-ol	84	73-75		- 3 (1.0, MeOH)	
11	Z-Asp(ol)-OBzl	84	oil		- 31 (0.65, MeOH)	
12	Z-Phe-ol	91	93-94	87-88 (c)	- 43 (1.05, MeOH)	-41.1 (2.0, MeOH) (c)
						-44.6 (2.0, MeOH) (d)
13	Z-Phe-ol (e)	83	93-94		- 46 (1.0, MeOH)	
14	Z-D-Phe-ol	90	93-94		+ 40 (1.1, MeOH)	
15	Z-Pro-ol	91	oil		- 48 (1.0, MeOH)	
16	Fmoc-Asp(OtBu)-ol (f)	87	96-97		- 7 (1.0, MeOH)	
17	Fmoc-Ile-ol	56	144-145		- 13 (1.0, MeOH)	
18	Fmoc-Met-ol	95	135-137		- 17 (1.0, DMF)	

(a): reaction run in DMF (b): See reference 6. (c): See reference 7 (d): See reference 9. (e): Without filtration of N-methyl morpholine hydrochloride, 3 molar equivalents of $NaBH_4$. (f): See note 10 for ^1H NMR data.

Table 1

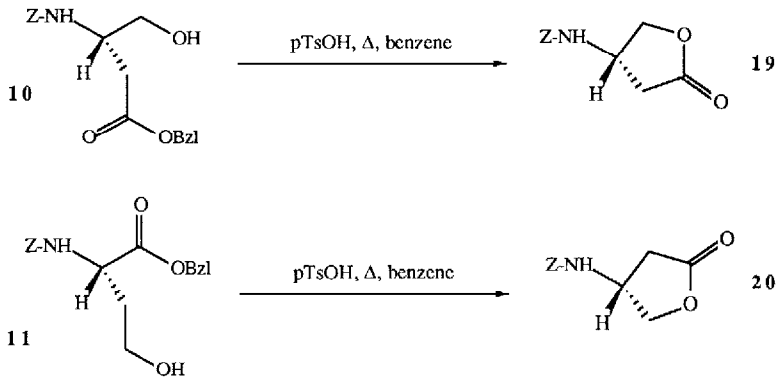
A typical procedure is as follows: To a cold (-15°C) solution of N-protected α-amino acid (10 mmol) in 1,2-dimethoxyethane (DME, 10 mL), were successively added N-methyl morpholine (1 11 mL, 10 mmol) and isobutyl chloroformate (1.36 mL, 10 mmol). After 1 min., the precipitated N-methyl morpholine hydrochloride was removed by filtration, washed with DME (5 x 2 mL) and the filtrate and washings were combined in a large flask in an ice-salt bath. A solution of sodium borohydride (570 mg, 15 mmol) in water (5 mL) was added at once, producing a strong evolution of gas, followed by water (250 mL) immediately afterwards. When the expected alcohol precipitated

(entries **5**, **6**, **8**, **9**, **10**, **12**, **13**, **14**, **17** and **18**, Table 1), it was collected, thoroughly washed with water and hexane In the other cases, the compound was extracted with the appropriate solvent (entries **1**, **2**, **3**, **7**, **11**, **15** and **16**: ethyl acetate, entry **4**: n-butanol, Table 1) and purified by classical aqueous work-up.

All crude compounds were homogenous by TLC When N-methylmorpholine hydrochloride was not removed from the reaction mixture, the amount of sodium borohydride had to be increased, as shown in entry **13**.

This methodology allowed us to obtain alcohols from highly functionalized α-amino acids, such as arginine (entry **3**, Table 1), lysine (entry **5**), tyrosine (entry **9**), etc., and to describe for the fisrt time the synthesis of alcohols from Fmoc N-protected α-amino acids. Analytical values are in good agreement with those of the litterature. As an example ^{1}H NMR data of Fmoc-Asp(OtBu)-ol are given[10].

Both compounds Z-Asp-(OBzl)-ol (**10**) and Z-Asp(ol)-OBzl (**11**)[11] led to the corresponding lactones (respectively **19**[12] and **20**[13]), as shown in Scheme 2, in refluxing benzene in the presence of a catalytic amount of p-toluene sulfonic acid.



Scheme 2

In summary, this procedure allowed the rapid obtention under very mild conditions of N-protected β-amino alcohols from a wide variety of α-amino acids, in combination with a large set of N or C-protecting groups.

References and notes:

1- C. Freeman Stanfield, J E. Parker & P Kanellis, *J. Org. Chem* , 1981, **46**, 4797-4798.

2- H. Umezawa, *Methods in Enzymology, Vol. XLV*, L. Lorand Ed., Academic Press, New York, 1976, P 678.

3- J. Martinez, J.P. Bali, M. Rodriguez, B. Castro, R. Magous, J. Laur & M.F Lignon, *J. Med. Chem* , 1985, **28**, 1874-1879.

4- R. E. TenBrinck, *J. Org Chem* , 1987, **52**, 418-422.

5- B.K. Handa, A.C. Lane, J A.H. Lorn, B.A. Morgan, M J. Rance & C.F.C. Smith, *Eur J Pharmacol.*, 1981, **70**, 531-540.

6- K Soai, H. Oyamada & M. Takase, *Bull. Chem. Soc Jpn* , 1984, **57**, 2327-2328.

7- By the time we carried out this work, a paper appeared in the litterature, describing the application of the method of Soai *et al.* to amino acids· G. Kokotos, *Synthesis*, 1990, 299-301.

8- C. Mendre, M. Rodriguez, J. Laur, A Aumelas & J. Martinez, *Tetrahedron*, 1988, **44**, 4415-4430

9- J. Zemlicka & M. Murata, *J. Org Chem* , 1976, **41**, 3317-3321.

10- ^{1}H nmr (DMSO-d_6) δ ppm: 7 88 (d, 2H, ^{3}J = 7 8 Hz, Ar), 7.68 (d, 2H, ^{3}J = 7.8 Hz, Ar), 7.41 (d, 2H, ^{3}J = 7.8 Hz, Ar), 7,31 (d, 2H, ^{3}J = 7.8 Hz, Ar), 7.13 (d, 1H, ^{3}J = 8.8 Hz, NH), 4.78 (t, 1H, J = 5.6 Hz, OH), 4.35-4.15 (m, 3H, CH-CH_2), 3.82 (m, 1H, Hα), 3 34 and 3.21 (m, 1H each, CH_2), 2 47 (dd, 1H, ^{3}J = 4.9 Hz, ^{2}J = 15.1 Hz, Hβ), 2.21 (dd, 1H, ^{3}J = 9.3 Hz, ^{2}J = 15.1 Hz, Hβ'), 1.36 (c, 9H, tBu).

11- Compound **11** can be refered to as N-benzyloxycarbonyl-homoserine benzyl ester.

12- Lactone **19**: Yield 86%; mp 102-103°C; $[\alpha]_D$ = -55.1 (1.4, DMF); ^{1}H nmr (DMSO-d_6) δ ppm: 7 87 (d, 1H, ^{3}J = 5.9 Hz, NH), 7.35 (m, 5H, Ar), 5.03 (s, 2H, CH_2), 4.42 and 4.10 (dd, 1H each, ^{3}J = 6.4 Hz and ^{3}J = 3.4 Hz respectively, ^{2}J = 8 8 Hz, CH_2-O), 2.85 and 2.38 (dd, 1H each, ^{3}J = 8.3 Hz and ^{3}J = 3.9 Hz respectively, ^{2}J = 15.1 Hz, Hββ').

13- Lactone **20**: Yield 78%; mp 124-125°C; $[\alpha]_D$ = -38.3 (1.05, DMF); ^{1}H nmr (DMSO-d_6) δ ppm: 7.80 (d, 1H, ^{3}J = 8.5 Hz, NH), 7.36 (m, 5H, Ar), 5.05 (s, 2H, CH_2), 4.44 (m, 1H , J = 9.0 Hz, 11.2 Hz, Hα), 4.32 and 4.20 (m, 1H each, J = 9.0 Hz, 1.2 Hz and J = 9.0 Hz, 6.4 Hz respectively, Hγγ'), 2.40 and 2 17 (m, 1H each, J = 6.4 Hz, 1 2 Hz and J = 9.0 Hz respectively, Hββ').

(Received in France 21 December 1990)