Tetrahedron Letters, Vol. 33, No. 30, pp. 4301-4302, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

SELECTIVE HYDROGENOLYSIS OF THE BENZYLOXYCARBONYL PROTECTING GROUP OF N^{ϵ}-LYSINE IN CYCLOPEPTIDES CONTAINING A BENZYLIC PHENYL ETHER FUNCTION. EVIDENCE FOR N^{ϵ}-METHYLATED LYSINE SIDE PRODUCTS.

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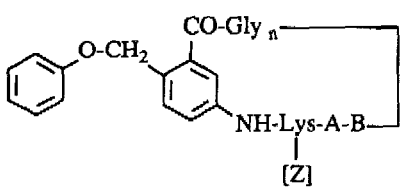
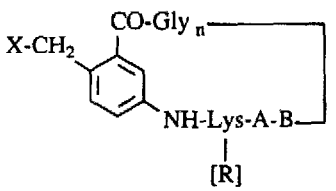
Abstract: Selective hydrogenolytic cleavage of the N^{ϵ}-Z protecting group of lysine in cyclopeptides c[-(Glycyl)$_n$-A-B-N^{ϵ}-Z-Lysyl-2-Phenoxymethyl-5-Aminobenzoyl-] (A = B = Glycyl, n = 2 or A = Phenylalanyl, B = Alanyl, n = 2 and 3) occured in both acidic (MeOH/aq.AcOH) and neutral (MeOH/DMF) solvents, with Pd/C catalyst. In the latter case, a N^{ϵ}-(bis)-methylated lysine side product was isolated.

The recent paper of Rocchi et *al* [1] concerning N-alkylation of aminoacids during hydrogenolytic deprotection prompts us to publish our results concerning hydrogenolytic cleavage of the Z protecting group of N^{ϵ}-lysine in cyclopeptides of type **1** (Fig. 1) incorporating a phenoxymethyl-substituted aminobenzoic residue. In the course of elaboration of new substrates/inhibitors of trypsin-like proteases,[2,3] we examined the hydrogenolytic deprotection conditions of the cyclopeptides **1a-c** and others, with the purpose of obtaining on one hand compounds of type **2** resulting from the selective deprotection of the N^{ϵ}-Lys Z group, and on the other hand compounds of type **3** resulting from hydrogenolysis of both the Z group and the benzylic phenoxy group





1 a : A = B= Gly ; n = 2
b : A = Phe ; B = Ala ; n= 2
c : A = Phe ; B = Ala ; n= 3

2 : X = C_6H_5O ; R = H
3 : X = H ; R = H
4 : X = C_6H_5O ; R = CH_3

Figure 1

Hydrogenations were conducted in a Parr apparatus, at pressures of 2-3 atmospheres and at room temperature, with always a large excess of palladium on charcoal as catalyst. Using the solvent mixture DMF/MeOH for solubility reasons, long reaction times had to be applied for reaction completion. A selective cleavage of the benzyloxycarbonyl (Z) protecting group of N^{ϵ}-lysine was always observed: compounds of type **2** highly predominated over compounds of type **3**. However, analytical t.l.c. (SiO_2; solvent system EtOAc/n-BuOH/AcOH/H_2O 1:1:1:1) presented spots (UV light), sometimes of quite high intensity, corresponding to side products of structure **4**. Typically, catalytic hydrogenation of **1b** [4] in DMF/MeOH 1:9 for

16 h gave **2b** (51 %) [4] with traces amounts of **3b** and **4b** (not isolated). From **1c**,[4] in DMF/MeOH 1:1 for 22 h, the cyclopeptides **2c**, **3c** and **4c** were isolated with 21 %, 7 % and 23 % yield,[4] respectively.

The structure of **4c** was evidenced by ^{1}H NMR analysis and FAB mass spectroscopy. In ^{1}H NMR (CD_3OD) (Fig.2), the main differences between **2c** and **4c** was for the latter a 0.1 ppm downfield shifting of the CH_2^{ϵ} multiplet and the presence of a singlet at 2.82 ppm (integrating for 6 protons), corresponding to N^{ϵ}-$[CH_3]_2$ (Lys). The signals for the aromatic protons of the phenoxy group and the AB quartet corresponding to C_6H_5O-CH_2-Ar (δ = 5.19 ppm ; J = 12.1 Hz) were present in **4c**, showing that N-(bis)-methylation had occurred faster than reductive cleavage of the benzyl ether.

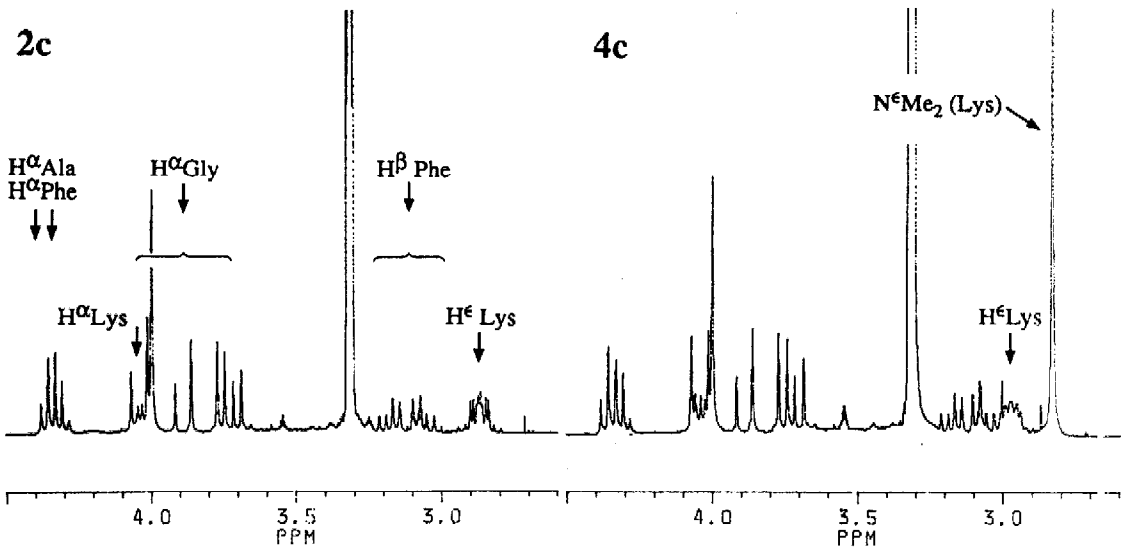


Figure 2

Cleaner reactions and still selective cleavage of the Z group were observed when hydrogenolysis was performed in the presence of water and acetic acid. The cyclopeptide **1a** [2,4] in MeOH/H_2O/AcOH 7:2:1 gave **2a** (70 %) [4] and traces of **3a** (not isolated) for 0.5 h reaction time, and **3a** (65 %) [4] after 24 h.

Thus, a selective cleavage of the N^{ϵ}-Z protecting group of lysine over a benzyl phenyl ether substituent in cyclopeptides **1** can be performed in both neutral (DMF/MeOH) and acidic solvent systems. In the former case however, longer reaction time results in the formation of N^{ϵ}-methylated lysine side products, resulting from reaction of $N^{\epsilon}H_2$ or $N^{\epsilon}HCH_3$ with formaldehyde, followed by *in situ* reduction.[1]

References and Notes

1. Filira, F.; Biondi, L.; Gobbo, M. and Rocchi, R., *Tetrahedron Letters*, **1991**, *32*, 7463-7464.
2. Wakselman, M.; Mazaleyrat, J.P.; Xie, J.; Boggetto, N.; Montagne, J.J.; Vilain A.C. and Reboud-Ravaux, M., *Peptides 1990*, Giralt, E. and Andreu, D., Eds., ESCOM Science Pub., Leiden, 1991; pp 794-796.
3. Wakselman, M.; Mazaleyrat J.P.; Xie, J.; Montagne, J.J.; Vilain A.C. and Reboud-Ravaux, M., *Eur. J. Med. Chem.*, **1991**, *26*, 699-707.
4. All cyclopeptides **1-4** gave satisfactory analytical data (^{1}H NMR at 300 MHz, C,H,N analysis and/or FAB spectroscopy). Details of synthesis will be published elsewhere. The given yields in **2-4,a-c** correspond to isolated pure compounds.

(Received in France 21 April 1992)