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Efficient synthesis of dehydroamino acid derivatives

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Abstract

By using a DMAP catalysed reaction of β-hydroxyamino acid derivatives with *tert*-butylpyrocarbonate, the corresponding dehydroamino acid derivatives were obtained in high yields.

1. Introduction

Naturally occurring compounds containing α,β-dehydroamino acid residues are frequently encountered in many biologically important peptides, including the class of polycyclic peptide antibiotics known as lantibiotics (*viz.* nisin, epidermin, subtilin) and also several enzymes from plant and bacterial sources. Since they affect both chemical reactivity and conformation, dehydroamino acids have also been introduced into peptides for structure-activity relationship studies [1-4].

Several methods have been developed for the synthesis of dehydroamino acids [1,2,5] but β-elimination has been the main approach to the synthesis of dehydroalanine (ΔAla) and dehydroaminobutyric acid (ΔAbu) [2,3,6,7,8,9]. Although this route has the advantage of starting from readily available serine and threonine derivatives, respectively, most of the β-elimination procedures described in the literature are accompanied by side reactions that may lead to complex mixtures, difficult purifications and poor yields. In the case of dehydroaminobutyric acid, the methyl group at the β-carbon atom gives rise to two geometrical isomers, E and Z, the latter being the only one found in nature; this further complicates isolation and purification of the product required and leaves place for investigation of the possibility of obtaining conditions for stereoselective or even stereospecific dehydration.

2. Results and discussion

In previous work [10], we found that treatment of serine derivatives with benzyl chloroformate, DMAP and triethylamine in DMSO gives the corresponding dehydroalanine derivatives in fairly good yields (51-76%). However, when attempting to use this method with threonine derivatives, a complex reaction mixture was obtained, failing to give any pure product. It was found by Nugent [11] that it was possible to dehydrate β-hydroxyamino acids by treatment with an excess of Ac_2O in the presence of base. However, the yields were only fair (≈60%). In view of these results, we considered increasing the size of the second group at

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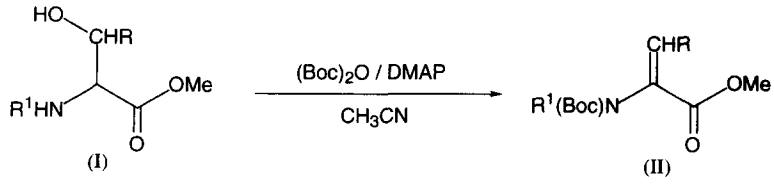
the nitrogen atom of the β-hydroxyamino acid in order to facilitate β-elimination and thus improve the reaction yields. Hence, when reacting N,C-protected serine, threonine or β-hydroxyphenylalanine derivatives in dry acetonitrile with *tert*-butylpyrocarbonate in the presence of DMAP as catalyst, the only product isolated was the corresponding ΔAla, ΔAbu or dehydrophenylalanine (ΔPhe) derivative (II, scheme 1). As shown in Table 1, in all cases but one, the starting material was previously protected with one of the following groups: *tert*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z), *p*-nitrobenzyloxycarbonyl [Z(NO_2)], diphenylphosphinyl (Dpp), *p*-toluenesulfonyl (Tos).



R: H, Me, Ph
R_1: Boc, Z, Z(NO_2), Dpp, Tos

Scheme 1

Table 1
Results obtained in the synthesis of dehydroamino acid derivatives

Reagent	Product	Yield / %[a]
Boc-Ser-OMe	Boc-ΔAla(*N*-Boc)-OMe	92
Z-Ser-OMe	Z-ΔAla(*N*-Boc)-OMe	85
Z(NO_2)-Ser-OMe	Z(NO_2)-ΔAla(*N*-Boc)-OMe	93
Dpp-Ser-OMe	Dpp-ΔAla(*N*-Boc)-OMe	88
Tos-Ser-OMe	Tos-ΔAla(*N*-Boc)-OMe	99
Boc-Ser-OH	Boc-ΔAla(*N*-Boc)-O*t*Bu	73
Z-Ser-OH	Z-ΔAla(*N*-Boc)-O*t*Bu	65
H-Ser-OMe	Boc-ΔAla(*N*-Boc)-OMe	82
Boc-Thr-OMe	Boc-ΔAbu(*N*-Boc)-OMe[b]	87
Z(NO_2)-Thr-OMe	Z(NO_2)ΔAbu(*N*-Boc)-OMe[b]	92
Tos-Thr-OMe	Tos-ΔAbu(*N*-Boc)-OMe[b]	87
Boc-Thr-OH	Boc-ΔAbu(*N*-Boc)-O*t*Bu[b]	73
Z(NO_2)-Phe(β-OH)-OMe	Z(NO_2)-ΔPhe(*N*-Boc)-OMe[b]	93

[a] yield of pure material.
[b] Z-isomer.

An attempt to apply this methodology to an Fmoc derivative of serine failed to give Fmoc-ΔAla(*N*-Boc)-OMe due to base induced cleavage of Fmoc by the catalyst (DMAP); this group was substituted by a further Boc group and, thus, the only product obtained was Boc-ΔAla(*N*-Boc)-OMe. In the case of *N*-trityl serine methyl ester the only product obtained was Trt-Ser(*O*-Boc)-OMe. This suggests that steric hindrance caused by the trityl group in this case does not

allow further reaction at the nitrogen atom, which would be essential to induce elimination at the β-carbon atom. In fact, by sampling the reaction mixture throughout the preparation of Z(NO_2)-ΔAla(*N*-Boc)-OMe, it was found that the reaction proceeds through a three-step pattern, starting with binding of a *tert*-butyloxycarbonyl group at the amine function, followed by carboxylation of the hydroxyl group to give the corresponding *tert*-butylcarbonate, which undergoes *β*-elimination to the final product.

With threonine and β-hydroxyphenylalanine derivatives (threo type) the reaction was stereoselective, giving only the naturally occurring Z-isomer as shown by NMR spectroscopy. This selectivity seems to result from the bulkiness of the groups bound to the nitrogen atom, which would force and thus facilitate a *trans* E_2-elimination. This is in agreement with results obtained by Srinivasan *et al.* [12] who have reported that base induced *β*-elimination of *N*-acyl-DL-Thr(*O*-Tos)-OMe (threo type) proceeds *via* a *trans* E_2-elimination to give the Z-isomer in a 70% yield.

Having in mind to simplify our procedure by saving one of the two required protection steps, the use of derivatives of serine and threonine bearing only one protecting group either at the N- or the C-terminus was investigated. When a derivative with a free carboxyl function was used as starting material, it underwent a DMAP catalysed esterification with dicarbonate as described by Takeda *et al.* [13] to give the *tert*-butyl ester of the N-protected *N*-Boc dehydroamino acid as the only product obtained.

The Boc group can be easily removed selectively from the dehydroamino acid derivatives by treatment with TFA, as demonstrated in the cleavage of Z(NO_2)-ΔAbu(*N*-Boc)-OMe to give Z(NO_2)-ΔAbu-OMe in an 85% yield; the product thus obtained was then saponified, yielding 78% of Z(NO_2)-ΔAbu-OH; finally this N-protected dehydroamino acid was coupled with glycine methyl ester with the aid of DCC in a 74% yield.

The conditions usually required to cleave the Tos and Z(NO_2) groups by standard procedures are possibly too drastic to be applied to dehydroamino acid derivatives. However, these groups were used as we wanted to investigate their cleavage from dehydroamino acids by the use of mild electrolysis, according to procedures previously developed in our laboratory [14,15]. Thus, Tos and Z(NO_2) could be selectively removed by electrolysis at controlled potential from the respective dehydroaminobutyric acid derivatives to give Boc-ΔAbu-OMe in yields of 78% and 93%, respectively.

The applicability of our methodology to the dehydration of peptides containing β-hydroxyamino acids was also investigated. The dipeptides Boc-Ala-Ser-OMe, Boc-Ala-Thr-OMe and Boc-Phe-Phe(β-OH)-OMe were prepared and reacted under the conditions described previously to give Boc-Ala(*N*-Boc)-ΔAla(*N*-Boc)-OMe, Boc-Ala(*N*-Boc)-ΔAbu(*N*-Boc)-OMe and Boc-Phe(*N*-Boc)-ΔPhe(*N*-Boc)-OMe with yields of 91, 84 and 91% respectively. Again, the reaction of the dipeptides containing a β-hydroxyamino acid residue was stereoselective, the product containing only the Z-isomer. Further investigation concerning dehydration of di- and tripeptides is under way.

3. Conclusion

The method reported above allows the high yielding preparation of a variety of dehydroamino acid derivatives, including peptides, by using mild reaction conditions and simple work-up procedures. In the case of β-hydroxyamino acids other than serine, this methodology offers the further advantage of leading only to the Z-isomer, which is the naturally occurring species. Selective cleavage of either Boc or Tos and $Z(NO_2)$ from the fully protected compounds was achieved in good yields to give the corresponding monoprotected esters. Our results make us believe that this is a general and stereoselective method for the preparation of the Z-isomer of derivatives, including peptides, of known or new α,β-dehydroamino acids as obtained from direct dehydration of the corresponding β-hydroxy compounds. Such peptides would be of appreciable importance for pharmacological screening.

4. General experimental procedure (example)

Preparation of Tos-ΔAla(*N*-Boc)-OMe: To a solution of Tos-Ser-OMe (5 mmol) in dry acetonitrile (5 ml), was added DMAP (0.5 mmol) followed by *tert*-butylpyrocarbonate (12.5 mmol) under rapid stirring at room temperature. The reaction was left for 12h, being monitored by t.l.c. (ethyl ether:hexane, 1:1). Evaporation at reduced pressure gave a residue that was partitioned between ethyl ether (200 ml) and $KHSO_4$ 1 M (100 ml). The organic phase was thoroughly washed with $KHSO_4$ 1 M, $NaHCO_3$ 1 M and saturated brine (3 x 50 ml each), and dried over $MgSO_4$. Removal of the solvent afforded the required product. After crystallization (ethyl ether/hexane) a white solid was obtained in a 99% yield: m.p. 129-130°C; ^1H NMR (300 MHz) δ ($CDCl_3$): 1.3 (9H, s, CH_3 Boc); 2.4 (3H, s, CH_3 Tos); 3.7 (3H, s, CH_3 OMe); 6.1 and 6.7 (2H, 2s, $=CH_2$); 7.3 and 7.9 (4H, 2d J=8.6Hz, ArH Tos).; Anal. Calc. for $C_{22}H_{21}NO_6S$ (355.41): C 54.07; H 5.96; N 3.94; S 9.02, Found: C 54.34, H 6.11, N 3.93, S 8.86.

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