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# Synthesis of non-proteinogenic amino acids from *N*-(4-toluenesulfonyl)dehydroamino acid derivatives

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**Abstract**—By treating *N*-(4-toluenesulfonyl)-*N*-(*tert*-butyloxycarbonyl)-dehydroamino acid derivatives with different reactants under different conditions, a variety of new amino acids are obtained, viz. (i) α-alcoxy-α-amino acids, (ii) α,α-diamino acids and (iii) novel β-substituted dehydroamino acids. 

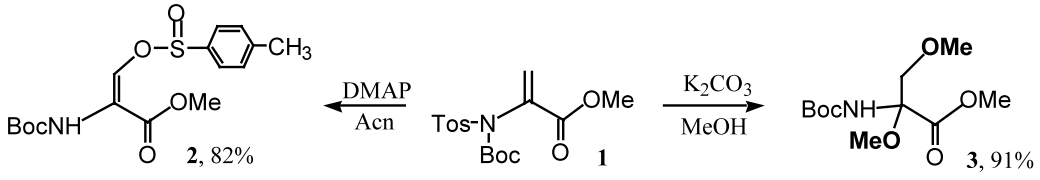
## 1. Introduction

Non-proteinogenic amino acids have several applications either as biologically active substrates or as components for the synthesis of peptidomimetics and for the modification of natural peptides. We have found that *N*,*N*-disubstituted dehydroamino acid derivatives are excellent substrates in Michael addition reactions for the synthesis of a variety of such compounds. We have previously described the synthesis of β-substituted amino acid and β-substituted dehydroamino acid derivatives by reacting the methyl esters of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butyloxycarbonyl)-dehydroamino acids with several types of nucleophiles (nitrogen heterocycles, thiols, carbon nucleophiles and amines).[1,2] Using the corresponding dehydroalanine derivative as substrate [Tos-ΔAla(*N*-Boc)-OMe] with the above nucleophiles in the presence of $K_2CO_3$, in all cases addition to the β-carbon atom occurs to give β-substituted alanine derivatives. When the nucleophile is a nitrogen heterocycle or a thiol the β-substituted alanine obtained undergoes elimination of *p*-toluenesulfinic acid with regeneration of the α,β-double bond, yielding the corresponding dehydroalanine derivative. With certain carbon nucleophiles the addition product suffers cyclization to give 2,3-dihydrofuran derivatives.[2]

## 2. Results and discussion

In view of the results obtained we decided to further investigate the reactivity of *N*-(4-toluenesulfonyl)-*N*-(*tert*-butyloxycarbonyl)-dehydroamino acids. Thus by treating Tos-ΔAla(*N*-Boc)-OMe (**1**) with base in acetonitrile a rearrangement occurs with the formation of the *E*-isomer of a β-sulfinated dehydroalanine derivative (compound **2**, Scheme 1). This derivative had been previously detected as a by-product formed in reactions of Tos-ΔAla(*N*-Boc)-OMe with weak nucleophiles in which longer reaction times were required.[1] By substituting acetonitrile for methanol as solvent and DMAP for $K_2CO_3$ as base it was possible to obtain in 91% yield the methyl ester of *N*-*tert*-butyloxycarbonyl α,β-dimethoxyalanine (compound **3**, Scheme 1).[3]

Due to the electron-withdrawing effect of the β-substituting group in compound **2** it was possible to synthesize several α,α-disubstituted amino acids. In fact,




**Scheme 1.**

*Keywords*: dehydroalanine; α-alcoxy-α-amino acids; α,α-diamino acids; β-substituted dehydroamino acids.

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reaction with primary amines (benzylamine, **a**; propargylamine, **b**) in methanol resulted in addition of the amine function to the α-carbon atom of the dehydroamino acid derivative to give compounds **4a**[4] and **4b**, respectively (Scheme 2).

Using a poor nucleophile such as the sterically hindered *tert*-butylamine, the saturated α-methoxyamino acid **5** was obtained (Scheme 2). This compound can also be obtained from compound **2** using an excess of $K_2CO_3$ (77% yield).

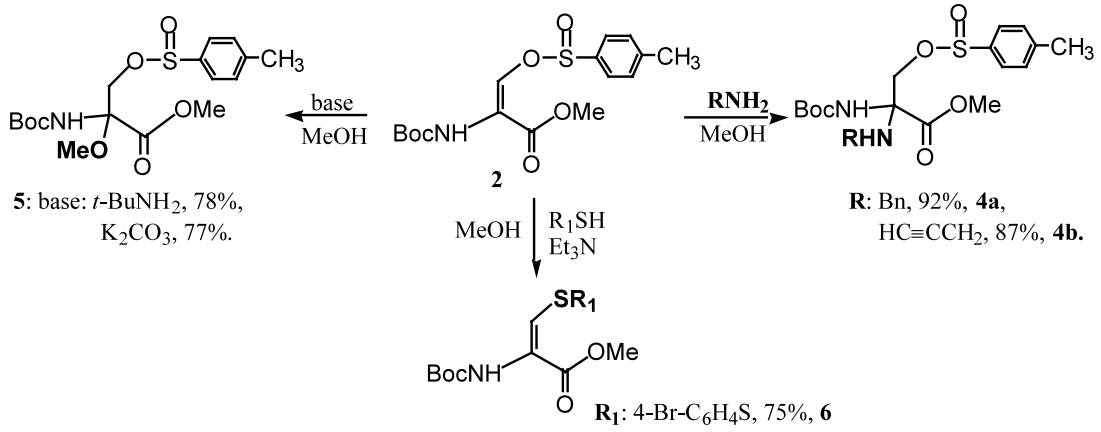
Reaction of **2** with thiols in methanol gave a different result, as in this case the sulfinic group was replaced by the sulfur nucleophile. This allowed the preparation of the previously described Boc-ΔAla(β-methoxycarbonylmethylsulfanyl)-OMe[2] and also of Boc-ΔAla[β-(*p*-bromophenylsulfanyl)]-OMe (compound **6**, Scheme 2).[5] The stereochemistry of the starting material was preserved (*E*-isomer),[6] which indicates addition of the nucleophile followed by spontaneous elimination of the sulfinate group.

Nakazawa et al. reported the synthesis of β-aminodehydroalanines by reaction of the β-toluenesulfonate of dehydroalanine with primary amines.[7] Our results show a different reactivity for the β-sulfinate dehydroalanine derivative from that of the β-sulfonate dehydroalanine since elimination of the sulfinic group only occurs with thiols. With primary amines addition to the α-carbon atom takes place.

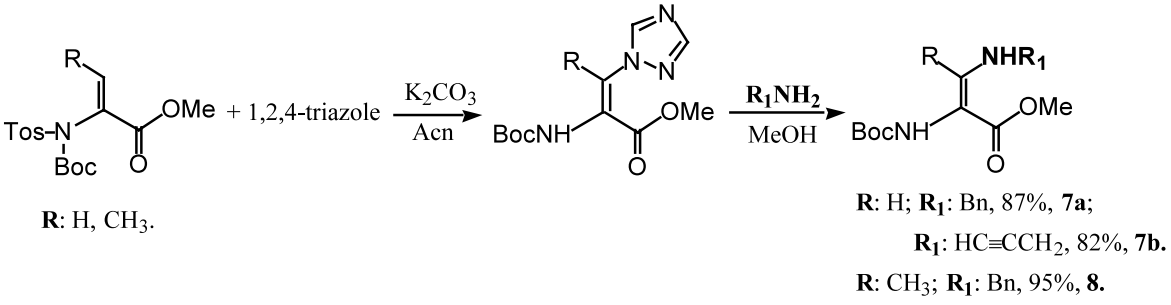
It has been found that addition of amines to compound **1** proceeds without elimination of the Tos group. Thus, only β-substituted alanines could be obtained with this type of nucleophiles. In order to circumvent this limitation, the *E*-isomer of Boc-ΔAla(1,2,4-triazol-1-yl)-OMe[1] obtained from compound **1** was reacted with amines **a** and **b** and replacement of the triazole group for the amine takes place to give the *E*-isomer of the corresponding β-aminodehydroalanine derivative (compounds **7a** and **7b**, Scheme 3).[6]

Derivatives of dehydroaminobutyric acid have shown a lower reactivity towards Michael additions than the corresponding dehydroalanines,[2] since only the more powerful nucleophiles, viz. 1,2,4-triazole, imidazole and 3-formylindole were suitable to react with these substrates. However, with the strategy used above, i.e. by using both *E* or *Z*-isomers of Boc-ΔAbu[β-(1,2,4-triazol-1-yl)]-OMe as intermediate compounds, we were now able to stereoselectively synthesize the *E*-isomer of Boc-ΔAbu(β-benzylamino)-OMe[6,8] (compound **8**, Scheme 3). In view of this result it seems possible to expand the range of β-substituted dehydroaminobutyric acid derivatives that we had been able to obtain.

The present results supply not only an appropriate route to new classes of compounds such as α-alcoxy-α-amino, α,β-dialcoxy-α-amino and α,α-diamino acids, as well as novel β-substituted dehydroamino acids, but also an efficient route to the synthesis of the sterically crowded β-substituted dehydroaminobutyric acid derivatives. This shows that *N*-(4-toluenesulfonyl)-*N*-




**Scheme 2.**




**Scheme 3.**

(*tert*-butyloxycarbonyl)-dehydroamino acid derivatives are versatile starting materials for the synthesis of different types of non-proteinogenic amino acids.

## Acknowledgements

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## References

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2. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3167–3174.
3. To a solution of Tos-ΔAla(*N*-Boc)-OMe (1 mmol) in methanol (0.1 mol $dm^{-3}$), $K_2CO_3$ (6 equiv.) was added with rapid stirring at room temperature. The reaction was monitored by TLC and, when no starting material was detected, 100 $cm^3$ of ethyl acetate were added. The organic phase was then washed with water and brine (2×30 $cm^3$ each), dried over $MgSO_4$ and evaporated at reduced pressure to give **3** (91%), mp 57.5–58.5°C (from diethyl ether/*n*-hexane), (found: C, 50.32; H, 7.79; N, 5.32. Calcd for $C_{11}H_{21}NO_6$: C, 50.18; H, 8.04; N, 5.32%); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 1.47 (9H, s, C*H*$_3$ Boc), 3.30 (3H, s, OC*H*$_3$), 3.40 (3H, s, OC*H*$_3$), 3.71 (1H, d, $J$=9.6 Hz, βC*H*$_2$), 3.85 (3H, s, C*H*$_3$ OMe), 4.07 (1H, d, $J$=9.6 Hz, βC*H*$_2$), 5.96 (1H, s, αN*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 28.11, 51.27, 53.12, 59.60, 73.22, 80.30, 86.77, 153.48, 169.48.
4. The same procedure as described above was followed substituting benzylamine (2.5 equiv.) for $K_2CO_3$ to give **4a** (92%), mp 112.0–112.5°C (from diethyl ether), (found: C, 59.71; H, 6.77; N, 6.06; S, 6.88. Calcd for $C_{23}H_{31}N_2O_6S$: C, 59.59; H, 6.74; N, 6.04; S, 6.92%); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 1.31 (9H, s, C*H*$_3$ Boc), 2.44 (3H, s, 4-C*H*$_3$), 3.00 (1H, s, N*H*), 3.34 (1H, d, $J$=12.0 Hz, βC*H*$_2$), 3.60 (1H, d, $J$=12.0 Hz, βC*H*$_2$), 3.85 (3H, s, C*H*$_3$OMe), 3.95 (1H, d, $J$=14.7 Hz, C*H*$_2$), 4.38 (1H, d, $J$=14.7 Hz, C*H*$_2$), 6.10 (1H, s, αN*H*), 7.20–7.34 (7H, m, Ar*H*), 7.75 (2H, d, $J$=8.4 Hz Ar*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 21.57, 28.02, 46.34, 53.69, 59.69, 71.97, 80.15, 127.28, 128.19, 128.35, 128.38, 129.70, 137.18, 138.32, 144.45, 153.53, 169.52.
5. The same procedure as described above was followed substituting triethylamine (2.5 equiv.) for $K_2CO_3$ and adding 4-bromothiophenol (1 equiv.) to give **6** (75%), mp 114.5–116.0°C (from diethyl ether), (found: C, 46.28; H, 4.77; N, 3.62; S, 8.28. Calcd for $C_{15}H_{18}BrNO_4S$: C, 46.40; H, 4.67; N, 3.61; S, 8.26%); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 1.51 (9H, s, C*H*$_3$Boc), 3.80 (3H, s, C*H*$_3$OMe), 6.35 (1H, s, αN*H*), 7.33 (2H, d, $J$=8.1 Hz, Ar*H*), 7.34 (1H, s, βCH), 7.49 (2H, d, $J$=8.1 Hz, Ar*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 28.13, 52.59, 81.23, 122.27, 122.93, 129.33, 132.39, 133.70, 152.35, 163.46.
6. The stereochemistry was determined using differential NOE enhancements between the β (ΔAla) or γ (ΔAbu) protons and the α-NH.
7. Nakazawa, T.; Suzuki, T.; Ishii, M. *Tetrahedron Lett*. **1997**, *38*, 8951–8954.
8. To a solution of Boc-*E*-ΔAbu[β-(1,2,4-triazol-1-yl)]-OMe (1 mmol) in methanol (0.1 mol $dm^{-3}$), benzylamine (2.5 equiv.) was added. After stirring overnight, TLC still indicated some starting material so, a further 2.5 equiv. of benzylamine were added. When no starting material was detected, 100 $cm^3$ of ethyl acetate were added and the organic layer was washed with $KHSO_4$ 1 M and brine (2×30 $cm^3$ each). After drying over $MgSO_4$ and evaporating the solvent at reduced pressure the *E*-isomer of **8** was obtained (95%), mp 136.5–137.0°C (from diethyl ether), (found: C, 63.80; H, 7.46; N, 8.78. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74%); $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$) 1.47 (9H, s, C*H*$_3$ Boc), 2.02 (3H, s, γC*H*$_3$), 3.67 (3H, s, C*H*$_3$ OMe), 4.44 (2H, d, $J$=6.3 Hz, C*H*$_2$), 5.38 (1H, s, αN*H*), 7.26–7.34 (5H, m, Ar*H*), 9.38 (1H, s, N*H*); $\delta_C$ (75.4 MHz; $CDCl_3$) 14.25, 28.24, 28.36, 47.36, 50.61, 79.38, 126.82, 127.39, 127.56, 128.41, 128.81, 138.41, 161.99, 169.11. The same procedure using Boc-*Z*-ΔAbu[β-(1,2,4-triazol-1-yl)]-OMe gave the *E*-isomer of **8** in 79% yield.