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Synthesis of novel β-substituted α,β-dehydroamino acid derivatives

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Abstract

β-Substituted α,β-dehydroamino acids are synthesised in high yields by a Michael addition of heterocyclic nucleophiles to the methyl esters of *N*-*tert*-butyloxycarbonyl,*N*-(4-toluenesulfonyl)dehydroamino acids, followed by a base-induced elimination of the 4-toluenesulfonyl group with regeneration of the α,β-double bond.

Keywords: α,β-dehydroamino acids; β-substituted alanines; β-substituted α,β-dehydroamino acids.

Non-proteinogenic amino acids constitute an important group of compounds, either as biologically active species or as components of such species. α,β-Dehydroamino acids[1] and β-substituted alanines[2] belong to this group of compounds. We have recently described an efficient method for the synthesis of *N*,*N*-disubstituted α,β-dehydroamino acids.[3] Subsequently, we have demonstrated that these *N*,*N*-disubstituted derivatives are valuable synthons in the synthesis of β-substituted amino acids via a Michael addition of nucleophiles.[4] Since the high reactivity of the *N*,*N*-disubstituted dehydroamino acids was assigned to the double substituted nitrogen, it was expected that the use of a strong electron-withdrawing group at the nitrogen atom, such as 4-toluenesulfonyl, would further enhance the reactivity of the β-carbon towards nucleophilic attack. We now wish to report the synthesis of new β-substituted dehydroamino acids from the methyl esters of *N*-*tert*-butyloxycarbonyl,*N*-(4-toluenesulfonyl)dehydroamino acids.

When the methyl ester of *N*-*tert*-butyloxycarbonyl,*N*-(4-toluenesulfonyl) dehydroalanine[5] [Tos-ΔAla(*N*-Boc)-OMe, **1**] in acetonitrile was reacted overnight with 1,2,4-triazole (**a**) in the presence of an excess of potassium carbonate, the only product obtained was Boc-ΔAla[β-(1,2,4-triazol-1-yl)]-OMe (**3a**). This product differed from the β-substituted alanine derivatives obtained when reacting *N*,*N*-diacyl dehydroalanine with 1,2,4-triazole under identical condi-

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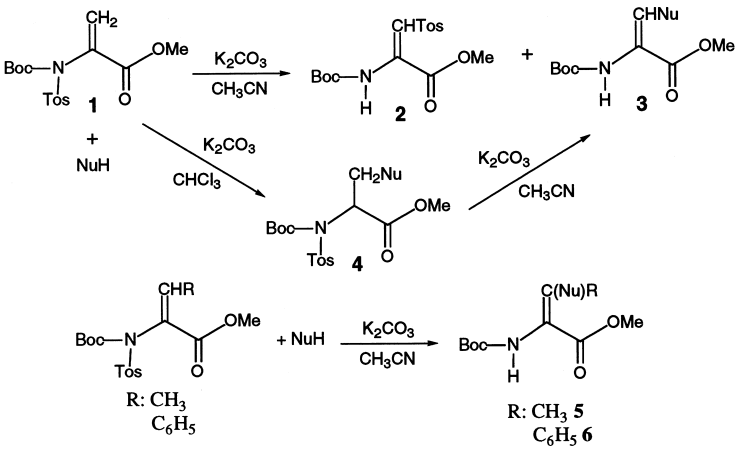
tions.[4] When the reaction was not allowed to proceed for more than 15 minutes it was possible to isolate the addition product Tos-Ala[*N*-Boc,β-(1,2,4-triazol-1-yl)]-OMe (**4a**) in a quantitative yield. However, when further treated with K_2CO_3, this compound was converted both quantitatively and stereoselectively into the *E* isomer of **3a**. Similar results were obtained when 3-formylindole (**b**) was substituted for 1,2,4-triazole: i.e. Boc-ΔAla[β-(3-formylindol-1-yl)]-OMe (**3b**) was obtained in 88% yield.

The reaction was extended to other dehydroamino acid derivatives, namely to the methyl esters of *N*-*tert*-butyloxycarbonyl,*N*-(4-toluenesulfonyl)dehydroaminobutyric acid and dehydrophenylalanine, i.e. Tos-ΔAbu(*N*-Boc)-OMe and Tos-ΔPhe(*N*-Boc)-OMe. In both cases, reaction with 1,2,4-triazole gave the *N*-Boc, β-substituted dehydroamino acid methyl ester in good yields (83 and 86%, respectively). For the ΔAbu derivative a mixture of *E* and *Z* isomers was obtained in the ratio 7:3 as determined by ^{1}H NMR, which could be separated by preparative column chromatography. With the ΔPhe derivative, the *E* to *Z* ratio was 1:1. These results led to the study of the addition of other nucleophiles to compound **1**, namely imidazole (**c**), pyrazole (**d**) and 3-formyl-2-methyl-5-nitroindole (**e**) (Scheme 1).



NuH: 1,2,4-triazole (**a**), 3-formylindole (**b**), imidazole (**c**), pyrazole (**d**), 3-formyl-2-methyl-5-nitroindole (**e**)

Scheme 1.

With imidazole as nucleophile, the yield of Boc-ΔAla(β-imidazol-1-yl)-OMe (**3c**) was 58%. In this case, a by-product was isolated in a 30% yield, which was identified as Boc-ΔAla(β-Tos)-OMe (**2**). For 3-formyl-2-methyl-5-nitroindole, compound **3e** was isolated in a 53% yield together with 36% of compound **2**. Similar results were obtained for pyrazole.

When Tos-ΔAla(*N*-Boc)-OMe was reacted with K_2CO_3 in acetonitrile it was converted quantitatively into **2** within 12 hours (*E* isomer). However, in the absence of base, only traces of Boc-ΔAla(β-Tos)-OMe were detected 60 hours after the compound was dissolved. This suggests that the by-product may result from a base-induced rearrangement. Thus, the use of an alternative base could possibly reduce this side reaction, so triethylamine was substituted for K_2CO_3 in the reaction of Tos-ΔAla(*N*-Boc)-OMe with imidazole and pyrazole. For imidazole, a 46% yield of Tos-Ala(*N*-Boc,β-imidazol-1-yl)-OMe (**4c**) was obtained together with 26% of **2**. Compound **4c** could be subsequently converted quantitatively into **3c** by reacting with K_2CO_3.

For pyrazole, the yield in addition product (**4d**) was 60% with 28% yield in compound **2**. Again, the addition product could further be converted quantitatively into compound **3d**. An alternative approach would be the use of a less polar solvent, which would reduce the solubility of K_2CO_3 and consequently the basicity of the solution. Thus, chloroform was substituted for acetonitrile in the reaction with nucleophiles **c**, **d** and **e**. For nucleophiles **c** and **d**, formation of the addition products occurred in almost quantitative yields (98 and 96%, respectively). When the chloroform was evaporated and the residue redissolved in acetonitrile, the addition products were converted in high yields to the β-substituted ΔAla derivatives **3c** and **3d**, respectively (94 and 92% yields). With nucleophile **e**, due to its low solubility in chloroform, a small quantity of acetonitrile was added ($\approx$10%) so as to promote its solubilisation. In this case, direct conversion to **3e** occurred in a 95% yield.

These results show that reaction of strong nucleophiles such as 1,2,4-triazole with Tos-ΔAla(*N*-Boc)-OMe leads to very fast addition reactions, which prevents competitive formation of compound **2**, thus giving high yields of β-substituted dehydroamino acid derivatives. Furthermore, isolation of the addition product in high yield is also possible if the reaction is not allowed to proceed for more than a few minutes. When weaker nucleophiles such as pyrazole or imidazole are used, the reaction is slower, giving place not only to the addition product, but also to competitive formation of **2**. This can be circumvented by the use of chloroform as solvent instead of acetonitrile, which leads to quantitative formation of the respective addition product, which can be converted in high yields to the corresponding β-substituted dehydroalanine derivative.

In conclusion, this method allows the synthesis of β-substituted dehydroamino acids with highly constrained, hydrophilic side chains. These can be valuable for structure/activity relationship studies and synthesis of peptidomimetics.

Experimental procedures: *Preparation of compounds **3a** and **3b***: To a solution of Tos-ΔAla(*N*-Boc)-OMe in acetonitrile (0.1 mol dm^{-3}), K_2CO_3 (6 equiv.) was added, followed by 1,2,4-triazole or 3-formylindole (1 equiv.), respectively, with fast stirring at room temperature. When no starting material or addition product was detected, the solution was filtered and the solvent evaporated at reduced pressure to give the *E* isomers of **3a** and **3b**, respectively (Table 1).

*Preparation of compounds **3c**, **3d** and **3e***: To a solution of Tos-ΔAla(*N*-Boc)-OMe in chloroform (0.1 mol dm^{-3}), K_2CO_3 (6 equiv.) was added, followed by imidazole, pyrazole or 3-formyl-2-methyl-5-nitroindole (1 equiv.), respectively, with fast stirring at room temperature. For synthesis of **3e**, 10% acetonitrile was added. When all starting material had been consumed the solution was filtered and the solvent evaporated at reduced pressure to give **4c**, **4d** and the *E* isomer of **3e**, respectively. Compounds **4c** and **4d** were redissolved in acetonitrile (0.1 mol dm^{-3}) and K_2CO_3 (6 equiv.) added. When ^{1}H NMR showed complete conversion of the addition product, the solution was filtered and the solvent evaporated at reduced pressure to give the *E* isomers of **3c** and **3d**, respectively (Table 1).

Preparation of (E,Z)*-Boc-ΔAbu(β-1,2,4-triazol-1-yl)-OMe (**5a**) and* (E,Z)*-Boc-ΔPhe(β-1,2,4-triazol-1-yl)-OMe (**6a**)*: The same procedure as above was followed, but substituting Tos-ΔAbu(*N*-Boc)-OMe and Tos-ΔPhe(*N*-Boc)-OMe, respectively, for Tos-ΔAla(*N*-Boc)-OMe to give a 7:3 mixture of the *E* and *Z* isomers of **5a** and a 1:1 mixture of isomers of **6a**, respectively. The diastereomers of **5a** and **6a** were separated by column chromatography (Table 1).

Table 1
Experimental and analytical data of heterocyclic β-substituted dehydroamino acid derivatives

Compound no. (formula)	Yield/% (crude)	Mp/°C (recr. solv.)	δ_H ($CDCl_3$, 300 MHz; rel. TMS)	Elemental analysis found (calculated)
3a ($C_{11}H_{16}N_4O_4$)	87	109.5–110.5 (ethyl acetate–hexane)	1.42 (9H, s, C*H*$_3$ Boc), 3.83 (3H, s, C*H*$_3$ OMe), 7.31 (1H, s, βC*H*), 8.01 (1H, s, 3-H or 5-H triaz.), 8.12 (1H, s, αN*H*), 8.35 (1H, s, 3-H or 5-H triaz)	C, 49.29; H, 6.20; N, 20.42 (C, 49.25; H, 6.01; N, 20.88)
3b ($C_{18}H_{20}N_2O_5$)	88	158.5–160.0 (ethyl acetate–hexane)	1.36 (9H, s, C*H*$_3$ Boc), 3.92 (3H, s, C*H*$_3$ OMe), 4.86 (1H, s, αN*H*), 7.36–7.55 (3H, m, 5-H, 6-H, 7-H ind.), 7.98 (1H, s, 2-H ind), 8.25 (1H, s, βC*H*), 8.30 (1H, m, 4-H ind), 10.05 (1H, s, C*H*O ind)	C, 62.28; H, 5.89; N, 7.91 (C, 62.78; H, 5.85; N, 8.13)
3c ($C_{12}H_{17}N_3O_4$)	92	100.5–101.5 (diethyl ether–hexane)	1.43 (9H, s, C*H*$_3$ Boc), 3.86 (3H, s, C*H*$_3$ OMe), 6.11 (1H, br. s, αN*H*), 7.12 (1H, s, 4–H or 5-H imid), 7.37 (1H, s, βC*H*), 7.72 (1H, s, 4-H or 5-H imid), 7.85 (1H, s, 2-H imid)	C, 53.79; H, 6.45; N, 15.80 (C, 53.92; H, 6.41; N, 15.72)
3d ($C_{12}H_{17}N_3O_4$)	88	147.5–149.0 (ethyl acetate–hexane)	1.47 (9H, s, C*H*$_3$ Boc), 3.86 (3H, s, C*H*$_3$ OMe), 6.40 (1H, m, 4-H pyr), 7.26 (1H, s, βC*H*), 7.64 (1H, d, J=2.1 Hz, 3-H or 5-H pyr), 7.71 (1H, d, J=1.8 Hz, 3-H or 5-H pyr), 8.42 (1H, br. s, αN*H*)	C, 53.68; H, 6.40; N, 15.53 (C, 53.92; H, 6.41; N, 15.72)
3e ($C_{19}H_{21}N_3O_7$)	95	179.5–181.0 (ethyl acetate–diethyl ether)	1.00 (9H, s, C*H*$_3$ Boc), 2.77 (3H, s, C*H*$_3$ ind), 3.98 (3H, s, C*H*$_3$ OMe), 6.86 (1H, s, αN*H*), 7.16 (1H, d, J=8.7 Hz, 7-H ind), 7.43 (1H, s, βC*H*), 8.14 (1H, dd, J=8.7 Hz and J=2.4 Hz, 6-H ind), 9.08 (1H, d, J=2.4 Hz, 4-H ind), 10.15 (1H, s, C*H*O ind)	C, 56.66; H, 5.51; N, 10.14 (C, 56.57; H, 5.25; N, 10.42)
5a ($C_{12}H_{18}N_4O_4$)	83	142.5–144.5 (ethyl acetate–hexane)[a]	1.48 (9H, s, C*H*$_3$ Boc), 2.30 (3H, s, γC*H*$_3$), 3.60 (3H, s, C*H*$_3$ OMe), 6.41 (1H, br. s, αN*H*), 8.02 (1H, s, 3-H or 5-H triaz), 8.19 (1H, s, 3-H or 5-H triaz)[a]	C, 51.24; H, 6.41; N, 19.67 (C, 51.06; H, 6.43; N, 19.85)
		101.0–102.5 (ethyl acetate–hexane)[b]	1.45 (9H, s, C*H*$_3$ Boc), 2.38 (3H, s, γC*H*$_3$), 3.88 (3H, s, C*H*$_3$ OMe), 8.09 (1H, s, 3-H or 5-H triaz.), 8.33 (1H, s, 3-H or 5-H triaz), 9.02 (1H, br s, αN*H*)[b]	
6a ($C_{17}H_{20}N_4O_4$)	86	113.0–114.0 (ethyl acetate–hexane)	1.50 (9H, s, C*H*$_3$ Boc), 3.53 (3H, s, C*H*$_3$ OMe),), 7.38–7.47 (5H, m, Ar*H* ΔPhe), 7.76 (1H, s, 3-H or 5-H triaz), 8.15 (1H, s, 3-H or 5-H triaz), 9.23 (1H, br s, αN*H*)	C, 59.21; H, 5.86; N, 15.86 (C, 59.29; H, 5.85; N, 16.27)
		131.0–132.5 (ethyl acetate–hexane)	1.46 (9H, s, C*H*$_3$ Boc), 3.68 (3H, s, C*H*$_3$ OMe), 6.26 (1H, br. s, αN*H*), 7.30–7.47 (5H, m, Ar*H* ΔPhe), 8.02 (1H, s, 3-H or 5-H triaz), 8.04 (1H, s, 3-H or 5-H triaz)	

[a] *E* isomer.
[b] *Z* isomer.

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