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High yielding synthesis of heterocyclic β-substituted alanine derivatives

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Abstract

Heterocyclic β-substituted alanine derivatives such as β-(pyrazol-1-yl) and β-(1,2,4-triazol-1-yl)-alanine are synthesized in high yields by a Michael addition of heterocyclic nucleophiles to *N,N*-bis(*tert*-butyloxycarbonyl)-dehydroalanine methyl ester, using mild reaction conditions and simple work-up procedures.

1. Introduction

Heterocyclic β-substituted alanines such as β-(pyrazol-1-yl)-alanine and quisqualic acid have been isolated from plant sources such as pressed juice of *Citrullus vulgaris* and from *Quisqualis indica*, respectively [1]; β-(pyrazol-1-yl)-alanine presents hypoglycemic properties [2], whilst quisqualic acid possesses potent neuroexcitatory activities [3,4]. Another heterocyclic β-substituted alanine, *viz.* β-(1,2,4-triazol-1-yl)-alanine, is known as an important metabolite in plants of the fungicide myclobutanil [5].

The synthesis of some of these compounds, i.e. β-(1,2,4-triazol-1-yl)-alanine and β-(pyrazol-1-yl)-alanine, by a Michael addition of nucleophilic heterocycles (NuH) to dehydroalanine derivatives has been recently described [6]. Purification of the products from attempted solution syntheses was found to be very tedious owing to similar solubility between them and the correponding starting materials. Thus, the authors decided to carry out the syntheses by a solid phase strategy in which *N*-acetamidoacrylic acid was anchored to a Wang resin and reacted with nucleophiles in the presence of potassium carbonate under forcing conditions (6 to 15 eq. of nucleophile were used in 2-day reactions at temperatures within the range 50-60 °C). Nevertheless, the yields were still modest, i.e. 78 and 54% for the above mentioned triazole and pyrazole derivatives, respectively.

We have previously reported an efficient synthesis of *N,N*-bis(*tert*-butyloxycarbonyl)-dehydroalanine (ΔAla) methyl ester by reacting serine methyl ester in dry acetonitrile with *tert*-butylpyrocarbonate and DMAP as catalyst [7]. By taking advantage of the extra reactivity imparted by its second acyl group at the nitrogen atom towards the Michael reaction, this compound was used in mostly quantitative, straightforward solution syntheses of several heterocyclic β-substituted alanine derivatives.

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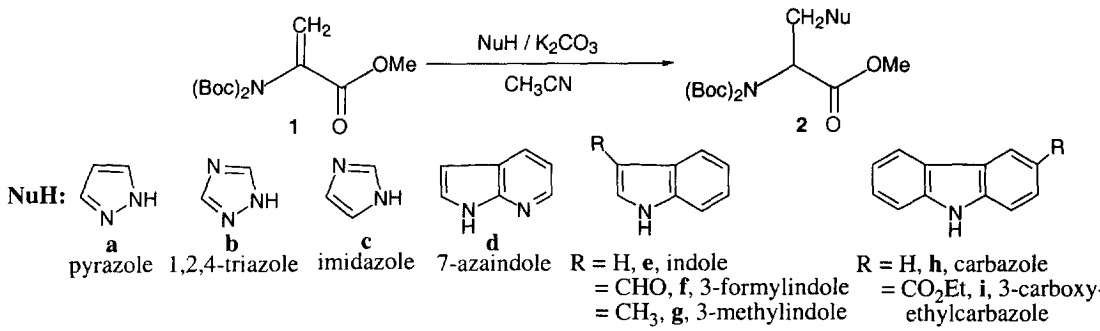
2. Results and discussion

The methyl ester of *N,N*-bis(*tert*-butyloxycarbonyl)-dehydroalanine [Boc-ΔAla(*N*-Boc)-OMe] was reacted at room temperature with one equivalent of each of several nucleophiles in acetonitrile and six equivalents of potassium carbonate (Scheme 1, Table 1).



Scheme 1

Table 1
Results obtained in the synthesis of heterocyclic β-substituted alanine derivatives from Boc-ΔAla(*N*-Boc)-OMe

Entry	NuH	NuH / eq.	Product (compound no.)	Yield / %[a]
1	pyrazole	1	$(Boc)_2$-β-(pyrazol-1-yl)-alanine-OMe (**2a**)	98
2	1,2,4-triazole	1	$(Boc)_2$-β-(1,2,4-triazol-1-yl)-alanine-OMe (**2b**)	99
3	imidazole	1	$(Boc)_2$-β-(imidazol-1-yl)-alanine-OMe (**2c**)	98
4	7-azaindole	1.1	$(Boc)_2$-β-(7-azaindol-1-yl)-alanine-OMe (**2d**)	93
5	indole	3	$(Boc)_2$-β-(indol-1-yl)-alanine-OMe (**2e**)	49[b]
6	3-formylindole	1	$(Boc)_2$-β-(3-formylindol-1-yl)-alanine-OMe (**2f**)	99
7	3-(CO_2Et)-carbazole	1	$(Boc)_2$-β-(3-(CO_2Et)-carbazol-9-yl)-alanine-OMe (**2i**)	93

[a] crude yield of pure material, [b] yield of pure crystallized material

Comparison of entries 1 and 2 in the Table with the corresponding results of reference 6, shows that the presence of two acyl groups at the nitrogen atom greatly increases the reactivity of the β-carbon atom of ΔAla towards nucleophilic attack. This enhanced reactivity allows the reactions to proceed to completion without the need for an excess of nucleophile, thus simplifying greatly the work-up procedures. That this was due to the presence of the two acyl groups was demonstrated when Boc-ΔAla-OMe was used with pyrazole instead of Boc-ΔAla(*N*-Boc)-OMe, as in this case no reaction was detected.

The products of the reactions with imidazole and indole (**2c** and **2e**) are isosteres of the corresponding histidine and tryptophan derivatives, respectively, while that of 7-azaindole (**2d**) is an isostere of 7-azatryptophan, which is used as a fluorescent probe in peptide labelling [6]. The reactivity of this heterocycle towards Boc-ΔAla(*N*-Boc)-OMe was lower than that recorded for nucleophiles **a**, **b** and **c** (Scheme 1); however, a small excess of nucleophile was enough to give **2d** in high yield (entry 4). When indole (1 eq.) was used, after 3 days the

reaction was still incomplete. An NMR spectrum of the reaction mixture showed a 1:1 ratio of addition product to unreacted dehydroamino acid. However, when excess indole was used (entry 5) in a 3-day reaction mixture this ratio was 5:1; work-up of this mixture gave a 49% yield of pure crystallized **2e**. The reaction with 1 eq. of the indole derivative having the electron-withdrawing formyl group in position 3 was quantitative (entry 6). The opposite was observed when the indole derivative with the electron donating methyl group in the same position was used, as in this case no reaction was detected even with excess nucleophile. The NMR spectra of indole and its above mentioned derivatives showed a correlation between the chemical shift of the nitrogen proton and the reactivity of these compounds (δ_H of the NH proton [8]: 3-formylindole, 12.12 ppm; 7-azaindole, 11.68 ppm; indole, 11.12 ppm; and 3-methylindole, 10.75 ppm). Thus, the use of indole derivatives with a high acidity of the NH proton is essential for a quantitative reaction with Boc-ΔAla(*N*-Boc)-OMe. The reaction with carbazole was also incomplete even with an excess of reactant, leading to a 2:1 mixture of addition product and unreacted dehydroamino acid. However, when 3-carboxyethylcarbazole was used [9] (entry 7), the reaction proceeded to completion with only 1 eq. Thus, the presence of an electron-withdrawing group, which in this case was in position *para* with respect to the nitrogen atom, was again essential for a quantitative reaction.

The Boc groups can be easily removed from the *N,N*-bis(*tert*-butyloxycarbonyl) β-substituted alanine derivatives by treatment with TFA, as demonstrated in the cleavage of **2b** and **2d** to give the corresponding N-deprotected compounds as their crystalline trifluoroacetates in yields of 80 and 85%, respectively. Saponification of the methyl esters was obtained by standard procedures and in the case of compounds **2b** and **2d** the respective *N,N*-bis(*tert*-butyloxycarbonyl)-amino acids were obtained in yields of 86 and 94%, respectively. Any of the semi protected compounds thus obtained can be readily used for peptide chain elongation.

Our results show that the use of an *N,N*-diacyl dehydroamino acid derivative as substrate for the nucleophilic attack in a Michael reaction under mild conditions allows the synthesis of a variety of heterocyclic β-substituted alanine derivatives, which were obtained in quantitative yields by extremely simple work-up procedures. Boc-ΔAla(*N*-Boc)-OMe proved to be an excellent substrate for nucleophilic attack, thus becoming a unique reagent for general use in the synthesis of heterocyclic β-substituted alanines.

3. Experimental procedures

Preparation of Boc-ΔAla(N-Boc)-OMe (compound 1): this compound was synthesized according to the general procedure described elsewhere [7], in a yield as indicated in Table 2.

Preparation of compounds 2a, 2b, 2c, 2f and 2i: to a solution of Boc-ΔAla(*N*-Boc)-OMe in acetonitrile (0.1 mol dm^{-3}), K_2CO_3 (6 eq.) was added, followed by pyrazole, 1,2,4-triazole, imidazole, 3-formylindole or 3-carboxyethylcarbazole (1 eq.), respectively, with rapid stirring at room temperature. The reaction was monitored by t.l.c. and when no starting material was

detected, the solution was filtered and evaporated at reduced pressure to give the corresponding heterocyclic β-substituted alanine derivative (Table 2).

*Preparation of compounds **2d** and **2e**:* the same procedure as above was followed, using an excess of nucleophile (1.1 eq. of 7-azaindole and 3 eq. of indole, respectively).

Table 2
Experimental and analytical data of Boc-ΔAla(*N*-Boc)-OMe and heterocyclic β-substituted alanine derivatives

Compound no. (formula)	Yield / % (crude)	M.p. / °C (recr. solv.)	δ_H ($CDCl_3$, 300 MHz; rel. TMS)	Elemental analysis found (calculated)
1 ($C_{14}H_{23}NO_6$)	92	52.0- 52.5.0 (Et_2O-hexane)	1.47 (18H, s, CH_3 Boc), 3.80 (3H, s, CH_3 OMe), 5.65 (1H, s, βCH_2), 6.35 (1H, s, βCH_2).	C, 55.69; H, 7.79; N, 4.73 (C, 55.80; H, 7.69; N, 4.65)
2a ($C_{17}H_{27}N_3O_6$)	98	85.0- 86.0 (Et_2O-hexane)	1.44 (18H, s, CH_3 Boc), 3.77 (3H, s, CH_3 OMe), 4.62 (1H, dd, βCH_2), 4.91 (1H, dd, βCH_2), 5.42 (1H, dd, αCH), 6.22 [1H, t, 4-H pyr.), 7.34 (1H, d, 3-H or 5-H pyr.), 7.51 (1H, d, 3-H or 5-H pyr.).	C, 55.22; H, 7.41; N, 11.45 (C, 55.27; H, 7.37; N, 11.38)
2b ($C_{16}H_{26}N_4O_6$)	99	102.0- 103.0 (Et_2O-hexane)	1.45 (18H, s, CH_3 Boc), 3.78 (3H, s, CH_3 OMe), 4.70 (1H, dd, βCH_2), 4.92 (1H, dd, βCH_2), 5.42 (1H, dd, αCH), 7.93 (1H, s, 3-H or 5-H triaz.), 8.05 (1H, s, 3-H or 5-H triaz.).	C, 51.91; H, 7.23; N, 15.10 (C, 51.88; H, 7.07; N, 15.13)
2c ($C_{17}H_{27}N_3O_6$)	98	102.0- 103.0 (Et_2O-hexane)	1.48 (18H, s, CH_3 Boc), 3.81 (3H, s, CH_3 OMe), 4.53 (1H, dd, βCH_2), 4.69 (1H, dd, βCH_2), 5.28 (1H, dd, αCH), 6.92 (1H, d, 4-H or 5-H imid.), 7.06 (1H, d, 4-H or 5-H imid.), 7.45 (1H, s, 2-H imid.).	C, 55.13; H, 7.46; N, 11.37 (C, 55.27; H, 7.37; N, 11.38)
2d ($C_{21}H_{29}N_3O_6$)	93	73.5- 74.5 (Et_2O-hexane)	1.28 (18H, s, CH_3 Boc), 3.80 (3H, s, CH_3,OMe), 4.74 (1H, dd, βCH_2), 5.13 (1H, dd, βCH_2), 5.48 (1H, m, αCH), 6.44 (1H, d, 3-H aza.), 7.06 (1H, dd, 5-H aza.), 7.11 [1H, d, 2-H aza.), 7.87 (1H, dd, 4-H aza.), 8.31 (1H, 2d, 6-H aza.).	C, 60.15; H, 7.13; N, 10.00 (C, 60.13; H, 6.97; N, 10.02)
2e ($C_{22}H_{30}N_2O_6$)	49[a]	123.0 - 124.0 (Et_2O-hexane)	1.27 (18H, s, CH_3 Boc), 3.79 (3H, s, CH_3 OMe), 4.71 (1H, dd, βCH_2), 4.86 (1H, dd, βCH_2), 5.30 (1H, dd, αCH), 6.47 (1H, d, 3-H ind.), 7.03-7.34 (4H, m, 2-H,5-H,6-H,7-H ind.), 7.57 (1H, d, 4-H ind.)	C, 63.16; H, 7.36; N, 6.84 (C, 63.14; H, 7.23; N, 6.69)
2f ($C_{23}H_{30}N_2O_7$)	99	126.0- 127.0 (Et_2O-hexane)	1.31 (18H, s, CH_3 Boc), 3.81 (3H, s, CH_3 OMe), 4.78 (1H, dd, βCH_2), 4.93 (1H, dd, βCH_2), 5.36 (1H, dd, αCH), 7.30-7.42 (3H, m, 5-H, 6-H, 7-H for.), 7.71 (1H, s, 2-H for.), 8.30 (1H, m, 4-H for.), 10.00 (1H, s, CHO).	C, 61.64; H, 6.99; N, 6.28 (C, 61.87; H, 6.77; N, 6.27)
2i ($C_{29}H_{36}N_2O_8$)	93	124.5- 126.0 (Et_2O-hexane)	1.18 (18H, s, CH_3 Boc), 1.46 (3H, t, CH_3 OEt), 3.84 (3H, s, CH_3 OMe), 4.44 (2H, q, CH_2 OEt), 4.78 (1H, dd, βCH_2), 5.01 (1H, dd, βCH_2), 5.45 (1H, dd, αCH), 7.26-7.51 (4H, m, 1-H, 6-H, 7-H, 8-H carb.), 8.11-8.18 (2H, m, 2-H, 5-H carb.), 8.79 (1H, d, 4-H carb.).	C, 64.80; H, 6.91; N, 5.27 (C, 64.43; H, 6.71; N, 5.18)

[a] yield of crystallized product.

4. References and notes

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