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One-pot synthesis of β-amino acid derivatives from α-amino acids

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Abstract—The one-pot transformation of α-amino acid into β-amino acid derivatives is described. The application of this method to the synthesis of modified dipeptides was also illustrated.

The synthesis of β-amino acids[1] and peptides containing them[2] has arisen great interest, due to the promising biological activities shown by many of these compounds. For instance, β-amino acid **1** (methylphenidate or Ritalin®, Fig. 1) is clinically used as a treatment for the attention deficit disorder in children,[3] and dipeptide **2** (bestatine or Ubenimex®) is an immunological response modifier.[4]

In previous articles, we have reported the syntheses of alkaloids and α-amino phosphonates from α-amino acids **3** (Scheme 1) using a tandem radical fragmentation–addition of nucleophiles reaction.[5] When substrates **3** were treated with (diacetoxyiodo)benzene (DIB) and iodine, under irradiation with visible light, an O-radical **4** was generated, which underwent β-scission,[6] generating a C-radical **5**. This intermediate was oxidized in the reaction mixture to an acyliminium ion

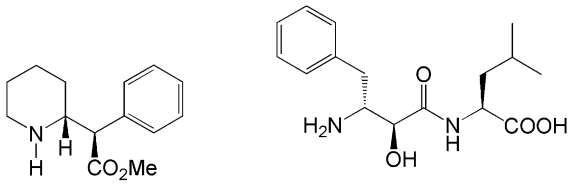

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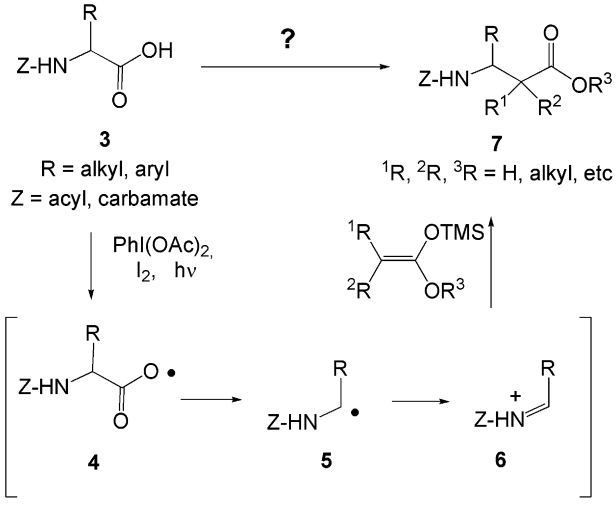
Figure 1. Bioactive β-amino acid derivatives.



Scheme 1. β-Scission in amino acid derivatives.

6,[7,8] which was trapped by oxygen, nitrogen, phosphorous or carbon nucleophiles. We reasoned that the addition of enolsilylethers to the acyliminium ion could generate β-amino acid derivatives **7** or modified peptides (when $Z = [aa]_n$). The feasibility of this strategy is discussed herein.

In order to study the fragmentation–addition reaction, different amino acid derivatives **8**–**12** (Scheme 2) were prepared, in good yields, by the acylation or carbamoylation of commercial precursors. Substrates **8**–**11** were treated with DIB and iodine at room temperature and under irradiation with visible light (Table 1, entries 1–8). The reaction mixture was then cooled to 0 °C and the enolsilylether and $BF_3{\cdot}OEt_2$ were added,

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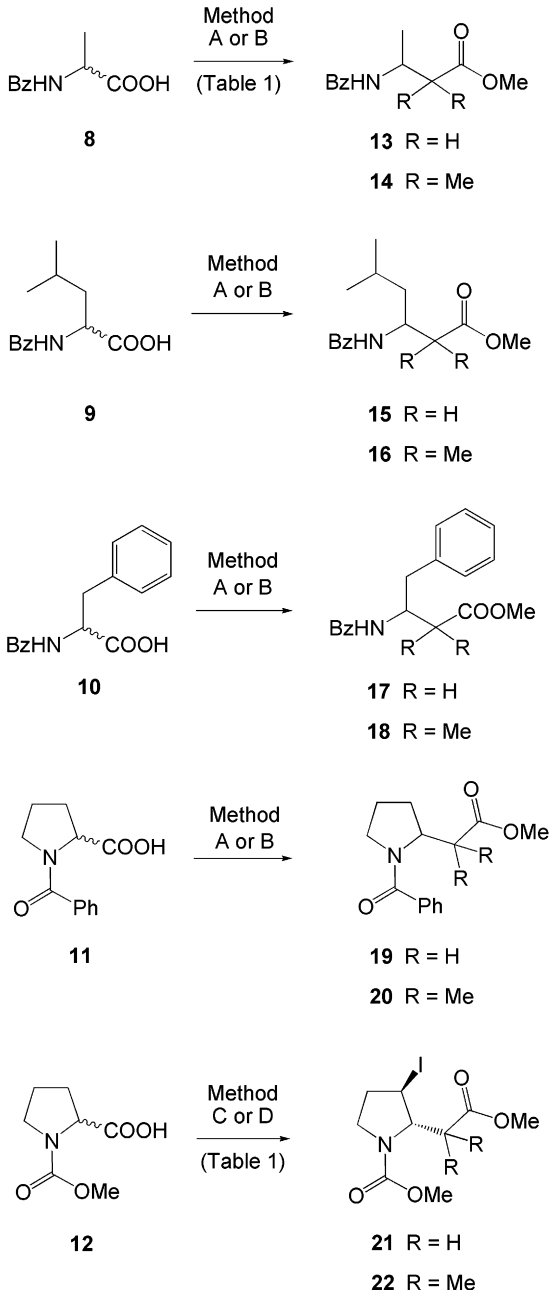

Scheme 2. One-pot transformation of α-amino acid into β-amino acid derivatives.

affording β-amino acid derivatives **13**–**20**. In spite of their different volume, both nucleophiles gave similar product yields. In this way, α-amino acids were transformed in one step into the corresponding β-analogues.

The biological activities of amino acids **13**–**20** are under study. Thus, the derivatives of β-homophenylalanine (related to compounds **17** and **18**) have been reported as a new treatment for type II diabetes.[9] Moreover, their insertion into more complex structures could also be of interest. For example, related β-amino acids are units of aminopeptidase inhibitors such as bestatine **2** or amastatine,[2d] and several β-amino acids with lipophilic side chains (such as compounds **13**, **15** and **17**) have been used as components of glycine reuptake inhibitors in the CNS.[10]

Table 1. One-pot β-fragmentation–alkylation reaction

Entry	Substrate	Conditions[a,b,c,d]	Products[e] (%)
1	**8**	A[a]	**13** (50)
2	**8**	B[b]	**14** (41)
3	**9**	A	**15** (55)
4	**9**	B	**16** (67)
5	**10**	A	**17** (50)
6	**10**	B	**18** (55)
7	**11**	A	**19** (85)
8	**11**	B	**20** (77)
9	**12**	C[c]	**21** (69)
10	**12**	D[d]	**22** (56)

[a] Method A. The substrate (1 mmol) in dry dichloromethane (15 mL) was treated with DIB (2.5 mmol) and iodine (1 mmol) and irradiated with visible light (100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). It was then cooled to 0 °C and $BF_3{\cdot}OEt_2$ (2 equiv) and $CH_2{=}C(OTBS)OMe$ (5 equiv) were added. The reaction mixture was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$–10% $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[b] Method B. As Method A, but using $Me_2C{=}C(OTMS)OMe$ as the nucleophile.

[c] Method C. The substrate (1 mmol) in dry acetonitrile (15 mL) was treated with DIB (2.5 mmol) and iodine (2 mmol) and irradiated with visible light (100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). Dry methanol was then added and the mixture was poured into aqueous 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the crude product was solved in dry acetonitrile, cooled to 0 °C, and treated with $BF_3{\cdot}OEt_2$ (2 equiv) and $CH_2{=}C(OTBS)OMe$ (5 equiv). The reaction mixture was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2.

[d] Method D. As Method C, but using $Me_2C{=}C(OTMS)OMe$ as nucleophile.

[e] Yields are given for products purified by chromatography on silica gel.

The fragmentation–alkylation of methyl carbamate **12** using methods A or B gave a complex mixture of products, so different conditions were tried (methods C or D, entries 9 and 10).[11] In the first step, a tandem fragmentation–β-iodination–addition of methanol reaction took place. The crude product was then treated with the Lewis acid and the nucleophile to give the iodinated β-amino acid derivatives (±)-**21** or (±)-**22** in good yields. The introduction of iodine in a previously non-functionalized position is specially interesting, since these iodinated pyrrolidines could be valuable intermediates in the synthesis of alkaloids and bactericidal iminoglyco acids.[12]

Another interesting application of the scission–alkylation reaction would be the preparation of modified peptides, which is a rapidly growing field in medicinal chemistry.[2] Starting from bioactive peptides, the modification of the C-terminal residue could afford derivatives with different biological activity, potency or selectivity.[13] Since the modified residue would be attached to chiral amino acid units, the reaction was expected to be stereoselective.