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Synthesis of Peptides containing the ß-substituted Aminoethane Sulfinamide or Sulfonamide Transition-state Isostere derived from Amino Acids

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Abstract: α-amino acids can be converted to homochiral ß-substituted aminoethane sulfinamide or sulfonamide transition-state isosteres, which can be incorporated into peptides. These transition-state analogues e.g. the sulfonamide isostere of Phe-Phe will be used for the generation of catalytic antibodies as well as for the development of protease inhibitors.

Transition-state analogues of the amide bond hydrolysis are important both for the design of enzyme inhibitors[1] and the development of catalytic antibodies[2]. Therefore numerous transition-state isosteres of the amide bond hydrolysis have been described[1-3]. Sulfinamides[4] and sulfonamides[4,5] have received relatively little attention, in spite of their good resemblance to the amide bond hydrolysis[6]. In a recent communication[6] we reported the synthesis of peptides incorporating the ß-aminoethane sulfinamide or sulfonamide transition-state analogues (scheme 1, **1** and **2**). These were proposed to mimic the amide bond hydrolysis between glycine and any other amino acid or peptide. In addition, we found that upon α-alkylation of sulfonamides (**2**) analogues of other amino acids than glycine (**3**) became accessible. This enabled us to prepare sulfonamides (figure 1b) mimicking amide bond hydrolysis of the p17/p24 cleavage site Phe-Pro (figure 1a) in the gag-pol precursor protein of HIV[7], thus giving rise to a new type of potential HIV protease inhibitors[8].

In contrast to α-aminosulfinamides or sulfonamides[4,9] the corresponding ß-aminoethane derivatives **1** and **2** are stable. Moreover the presence of the additional ß-carbon atom offers the opportunity to study the influence of functionalization at this position (figure 1c) as compared to functionalization at the α-position. Based on the method of Higashiura and Ienaga[10] we developed a method for the synthesis of homochiral ß-substituted sulfinamide (**4**) and sulfonamide (**5**) transition-state isosteres incorporated in peptides. Since the isosteres can be derived from naturally occuring α-amino acids in principle **all** amino acids can be used as a starting material for the preparation of these potentially interesting compounds (scheme 1). This adds to the scope of this procedure (*vide infra*).

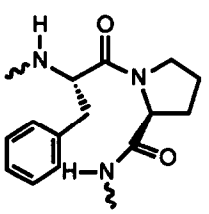


figure 1a

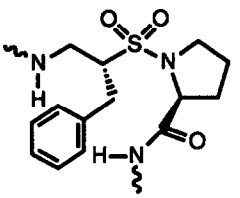


figure 1b

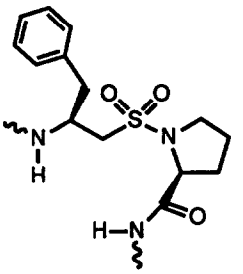
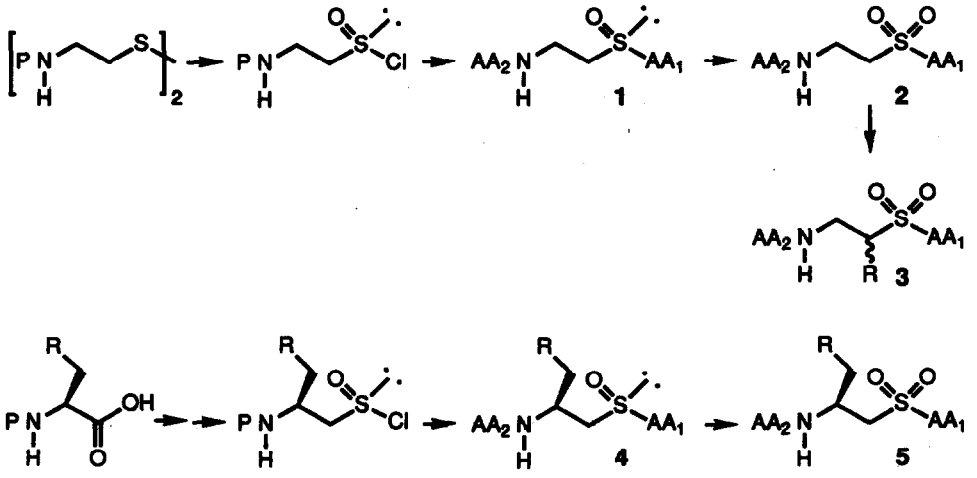
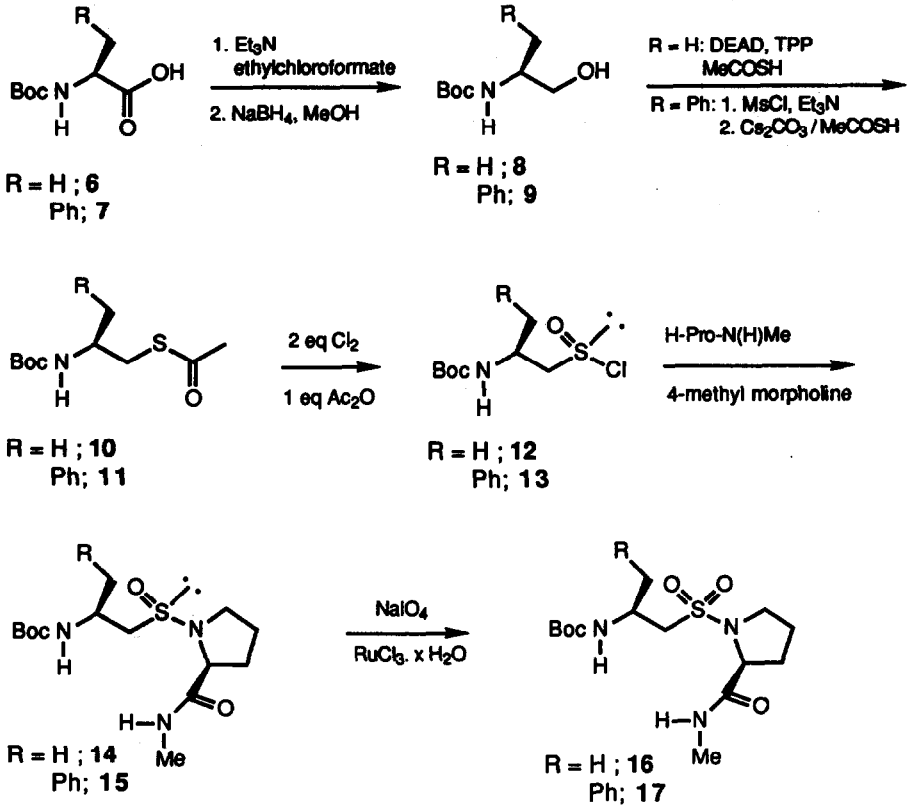


figure 1c

We have illustrated our method with the synthesis of sulfinamide and sulfonamide transition-state isosteres of Ala-Pro and Phe-Pro. Furthermore, as a specific target molecule we chose to synthesize the isostere of Phe-Phe, which will be used as a hapten to generate catalytic antibodies[11].



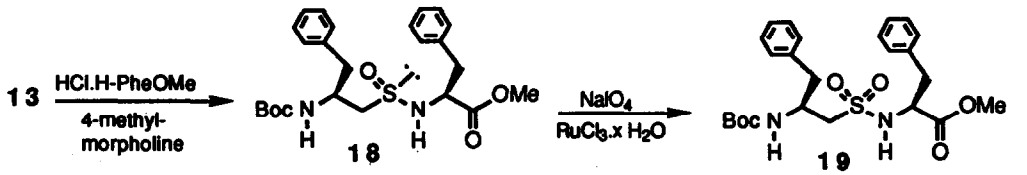
Scheme 1



Scheme 2

The Boc protected aminoacids **6** and **7** were converted to the corresponding amino alcohols **8** and **9** by reduction of the of the *in situ* prepared mixed anhydrides in 68% and 67% yield respectively[12]. The alaninol derivative **8** could be converted to the thioester **10** in 85% yield using Mitsunobu conditions[10,13] . Applying this procedure to phenylalaninol derivative **9** gave the desired product **11** from which, unfortunately, triphenylphosphinoxide could not be separated completely. Therefore **11** was prepared by a two step procedure i.e. formation of the mesylate (96% yield) followed by substitution with cesium thioacetate (97% yield)[10,13,14]. The sulfinylchlorides **12** and **13** were prepared by treatment of the thioesters **10** and **11** with chlorine (approximately 2 eq.) in the presence of acetic anhydride (1 eq.)[15,16]. These were used for coupling without further purification. Sulfinylchlorides **12** and **13** were coupled to H-Pro(N)HMe[17] in the presence of 4-methylmorpholine as base leading to the peptide sulfinamides **14** (72%) and **15** (75%), respectively. The diastereomers of **14** and **15** were isolated in a approximately equal amounts. The corresponding sulfonamides **16** and **17** were obtained by oxidation using $RuCl_3$/ $NaIO_4$[18] in 95% and 96% yield, respectively [19] (scheme 2).

In order to prepare the sulfonamide isostere of Phe-Phe (figure 1c), sulfinylchloride **13** was coupled to H-Phe-OMe in the presence of 4-methylmorpholine as base. The resulting diastereomeric sulfinamides **18** were isolated in 66% yield (diastereomeric ratio 1 to 1.6). Oxidation afforded the sulfonamide isostere **19** in 79% yield[19] (scheme 3).



Scheme 3

In conclusion, we have described a straightforward method for the synthesis of homochiral ß-functionalized aminoethane sulfinamides and sulfonamides. This method enables us to employ in principle every possible α-amino acid in the preparation of sulfinamide or sulfonamide transition-state analogue containing peptides. These peptides might be important both for the development of protease inhibitors and catalytic antibodies.

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14: ^{13}C NMR ($CDCl_3$): 21.1 (Ala^{S}-C^{3}), 25.3 (Pro-C^{4}), 26.1 (N(H)CH_3), 28.2 ($\underline{C}H_3)_3C$), 32.1 (Pro-C^{3}), 42.6 (Ala^{S}-C^{2}), 52.6 (Pro-C^{5}), 56.9 (Pro-C^{2}), 61.2 (CH_2SO), 79.7 ((CH$_3$)$\underline{C}$), 155.1 (C=O Boc), 173.2 (C=O) ^{13}C NMR ($CDCl_3$): 21.0 (Ala^{S}-C^{3}), 24.7 (Pro-C^{4}), 26.2 (N(H)CH_3), 28.3 ($\underline{C}H_3)_3C$), 31.4 (Pro-C^{3}), 40.7 (Pro-C^{5}) 42.5 (Ala^{S}-C^{2}), 61.4 (CH_2SO), 67.1 (Pro-C^{2}), 80.0 ((CH$_3$)$\underline{C}$), 155.2 (C=O Boc), 172.7 (C=O)
16: ^{13}C NMR ($CDCl_3$): 20.4 (Ala^{S}-C^{3}), 24.5 (Pro-C^{4}), 26.0 (N(H)CH_3), 28.0 ($\underline{C}H_3)_3C$), 30.6 (Pro-C^{3}), 42.8 (Ala^{S}-C^{2}) 48.9 (Pro-C^{5}), 54.2 (CH_2SO_2), 61.4 (Pro-C^{2}), 79.3 ((CH$_3$)$\underline{C}$), 154.9 (C=O Boc), 171.9 (C=O)
17: ^{13}C NMR ($CDCl_3$): 24.7 (Pro-C^{4}), 26.2 (N(H)CH_3), 28.2 ($\underline{C}H_3)_3C$), 30.6 (Pro-C^{3}), 39.8 (Phe^{S}-C^{3}), 48.6 (Phe^{S}-C^{2}), 49.1 (Pro-C^{5}), 51.5 (CH_2SO_2), 61.8 (Pro-C^{2}), 79.9 ((CH$_3$)$\underline{C}$), 126.8, 128.6, 129.2, 137.0 (Phe^{S}-$\underline{Ph}$),155.1 (C=O Boc), 171.8 (C=O)
19: ^{13}C NMR ($CDCl_3$): 28.2 ($\underline{C}H_3)_3C$), 39.2, 40.5 (Phe-C^{3},Phe^{S}-C^{3}) 47.7 (Phe^{S}-C^{2}), 52.4 (OMe), 56.4 (CH_2SO_2), 57.1 (Phe-C^{2}), 80.0 ((CH$_3$)$\underline{C}$), 126.8, 127.2, 128.5, 128.6, 129.4, 135.4, 136.5 (Phe-$\underline{Ph}$,Phe^{S}-$\underline{Ph}$),154.1 (C=O Boc), 172.0 (C=O)

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