Brief Communications

Synthesis of thiazole-containing amino acids based on asparagine*

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A number of earlier unknown thiazole-containing amino acids were obtained by the Hantzsch reaction through the sequential transformation of asparagine to thio analog with subsequent reaction with α-bromoketones.

Key words: amino acids, thiazoles, thioamides, Hantzsch synthesis, protecting groups.

By now, there is known a comparatively large class of natural compounds possessing biological activity, which contain imidazole, thiazole, or oxazole moieties. Studies of biological activity[1—3] and a total synthesis of cyclic alkaloids[4—8] isolated from marine microorganisms are very important directions. In many cases, they are promising antitumor[9] and antibacterial[10,11] compounds.

Analysis of molecular structures of such alkaloids as micrococcin P1, promothiocin A, amithiacin, *etc.* shows that they have a 2-aminomethyl-1,3-thiazole-4-carboxylic acid moiety as one of the building blocks. Despite that the methods for the synthesis of this compound derivatives are well enough described in the literature[12], we suggest a synthetic approach to the preparation of new thiazole-containing amino acids, the structural analogs of 2-aminomethyl-1,3-thiazole-4-carboxylic acid.

Essentially, this approach consists in the following (Scheme 1). In the first and the second steps, the functional groups of asparagine **1** are protected by the tosylation of α-amino group in aqueous dioxane in the presence of 1 *M* aqueous sodium hydroxide and the benzylation of the carboxy group in DMF in the presence of triethylamine. Then, the amide group of compound **3** is converted to the thioamide one using P_4S_{10} in THF, which gives thioamide **4** in 62% isolated yield after chromatographic purification.

Thioamide obtained was involved in the Hantzsch reaction with various α-bromoketones (bromoacetone (**a**), phenacyl bromide (**b**), *m*-nitrophenacyl bromide (**c**)) upon reflux in ethyl alcohol. As a result, a number of thiazole-containing amino acids **5a—c** were obtained in 49—54% yield, which can be used as building blocks in the synthesis

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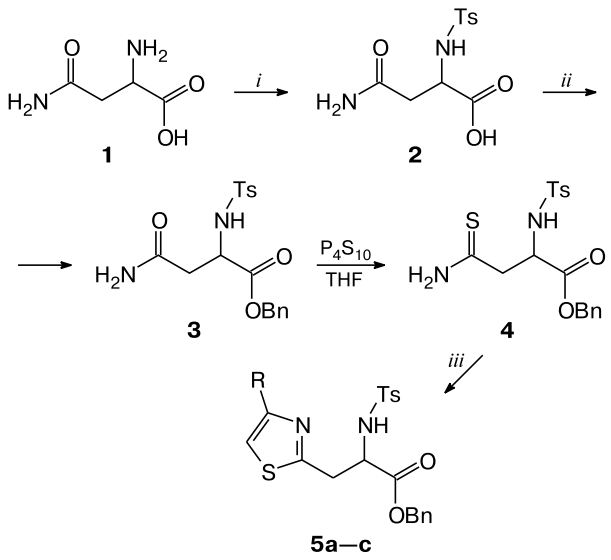
Scheme 1



R = Me (**a**), Ph (**b**), 3-$O_2NC_6H_4$ (**c**)

i. TsCl, NaOH, dioxane—H_2O; *ii*. BnBr, Et_3N, DMF; *iii*. $RC(O)CH_2Br$, EtOH.

of a wide range of peptidomimetics and peptides with new biological properties.

Experimental

Synthesis of compound **2** is described in the work.[13] D- and L-Asparagine, BnBr, TsCl, Et_3N, and P_4S_{10} were purchased from Aldrich. Bromoacetone,[14] phenacyl bromide,[15] and *m*-nitrophenacyl bromide[16] were obtained according to the known procedures. NMR spectra were recorded on a Bruker Avance TM 600 spectrometer (600.22 MHz (^{1}H), 150.93 MHz (^{13}C)) in DMSO-d_6, using $SiMe_4$ as an internal standard. IR spectra were obtained on a FSM-1201 Fourier-transform IR spectrometer in KBr pellets. Elemental analysis was performed on a Vario El Cube analyzer. Melting points were determined on a Boetius heating stage and were not corrected. Chromatographic separation was carried out on silica gel 60 (0.2—0.5 mm, Merck), eluent CCl_4—EtOH (95 : 5).

Benzyl 4-amino-2-{[(4-methylphenyl)sulfonyl]amino}-4-oxobutanoate (3). A solution of compound **2** (10 g, 35 mmol) and triethylamine (3.52 g, 4.86 mL, 35 mmol) in DMF (50 mL) was stirred for 1 h. Then, benzyl bromide (5.97 g, 4.15 mL, 35 mmol) was added dropwise to the solution obtained. The mixture was stirred for 24 h. After the reaction reached completion, the mixture was diluted with 20% aqueous NaCl (50 mL) and extracted with ethyl acetate (3×25 mL). Then, the solution was concentrated, the dry residue was recrystallized from ethyl alcohol to obtain compound **3** (8.43 g, 64%), m.p. 141—142 °C. IR, ν/cm^{-1}: 3477, 3377, 3141, 1741, 1670, 1164. ^{1}H NMR, δ: 2.31—2.40 (m, 4 H, Me, $C(O)CH_2$); 2.54—2.60 (m, 1 H, $C(O)CH_2$); 4.23 (td, 1 H, TsNHC<u>H</u>, *J* = 8.2 Hz, *J* = 6.1 Hz); 4.84—4.96 (m, 2 H, Ph<u>C</u>H_2); 6.94 (s, 1 H, $C(O)NH_2$); 7.24—7.39 (m, 7 H, Ph, Ts); 7.40 (s, 1 H, $C(O)NH_2$); 7.66 (d, 2 H, Ts, *J* = 7.9 Hz); 8.26 (d, 1 H, Ts<u>N</u>H, *J* = 9.2 Hz). Found (%): C, 57.54; H, 5.39; N, 7.47. $C_{18}H_{20}N_2O_5S$. Calculated (%): C, 57.43; H, 5.36; N, 7.44.

Benzyl 4-amino-2-{[(4-methylphenyl)sulfonyl]amino}-4-thioxobutanoate (4). A mixture of compound **3** (7.53 g, 20 mmol) and P_4S_{10} (2.22 g, 5 mmol) in THF (50 mL) was stirred for 12 h. Then, the solvent was evaporated on a rotary evaporator, the dry residue was subjected to chromatographic purification (CCl_4—EtOH (95 : 5), R_f 0.67) to obtain compound **4** (4.87 g, 62%), m.p. 150—151 °C. IR, ν/cm^{-1}: 3382, 3326, 3230, 1735, 1649, 1332, 1157. ^{1}H NMR, δ: 2.34 (s, 3 H, Me); 2.59—2.57 (m, 1 H, $NH_2C(S)CH_2$); 2.94—2.87 (m, 1 H, $NH_2C(S)CH_2$); 4.59 (s, 1 H, TsNHC<u>H</u>); 4.86 (q, 2 H, Ph<u>C</u>H_2, *J* = 12.7 Hz); 7.32—7.25 (m, 7 H, Ph, Ts); 7.63 (d, 2 H, Ts, *J* = 7.9 Hz); 8.28 (s, 1 H, Ts<u>N</u>H); 9.19, 9.44 (both s, 1 H each, $C(S)NH_2$). Found (%): C, 55.13; H, 5.19; N, 7.17. $C_{18}H_{20}N_2O_4S_2$. Calculated (%): C, 55.08; H, 5.14; N, 7.14.

Synthesis of amino acids 5a—c (general procedure). A mixture of thioamide **4** (0.392 g, 1 mmol) and the corresponding α-bromoketone (1 mmol) was refluxed in ethyl alcohol (20 mL) for 7 h. Then, the solution obtained was treated with aqueous saturated $NaHCO_3$ (10 mL). After cooling, a precipitate formed was filtered off and recrystallized from minimum acetonitrile.

Benzyl 2-{[(4-methylphenyl)sulfonyl]amino}-3-(4-methyl-1,3-thiazol-2-yl)propanoate (5a). The yield was 0.232 g (54%), m.p. 148—149 °C. IR, ν/cm^{-1}: 3272, 3093, 1732, 1562, 1338, 1161. ^{1}H NMR, δ: 2.24 (s, 3 H, Me); 2.44 (s, 3 H, Me); 3.02—3.27, 3.47—3.39 (both m, 1 H each, CH_2); 4.47 (t, 1 H, TsNHC<u>H</u>, *J* = 7.0 Hz); 5.01 (s, 2 H, Ph<u>C</u>H_2); 7.31—7.16 (m, 5 H, Ph); 7.35 (d, 2 H, Ts, *J* = 7.5 Hz); 7.84 (d, 2 H, Ts, *J* = 7.5 Hz); 7.88 (s, 1 H, thiazole). ^{13}C NMR, δ: 15.64 (Me); 21.14 (Me); 33.81 (CH_2); 53.62 (TsNH<u>C</u>H); 66.57 (Ph<u>C</u>H_2); 114.89 (C(5), thiazole); 126.42; 128.17; 128.26; 129.39; 137.09; 140.36; 141.51; 153.94; 157.60; 160.52; 173.65 (<u>C</u>O_2Bn). Found (%): C, 58.67; H, 5.21; N, 6.56. $C_{21}H_{22}N_2O_4S_2$. Calculated (%): C, 58.58; H, 5.15; N, 6.51.

Benzyl 2-{[(4-methylphenyl)sulfonyl]amino}-3-(4-phenyl-1,3-thiazol-2-yl)propanoate (5b). The yield was 0.241 g (49%), m.p. 141—142 °C. IR, ν/cm^{-1}: 3266, 3105, 1731, 1598, 1342, 1162. ^{1}H NMR, δ: 2.22 (s, 3 H, Me); 3.30—3.22, 3.44—3.37 (both m, 1 H each, CH_2); 4.37 (t, 1 H, TsNHC<u>H</u>, *J* = 7.0 Hz); 4.94 (s, 2 H, Ph<u>C</u>H_2); 7.47—7.10 (m, 10 H, Ts, Ph, $C_6\underline{H}_5CH_2$); 7.52 (d, 2 H, Ts, *J* = 8.2 Hz); 7.90—7.77 (m, 3 H, thiazole, Ts); 8.45 (s, 1 H, Ts<u>N</u>H). ^{13}C NMR, δ: 21.28 (Me); 35.69 (CH_2); 56.10 (TsNH<u>C</u>H); 66.82 (Ph<u>C</u>H_2); 114.78 (C(5), thiazole); 126.42; 126.67; 128.13; 128.33; 128.47; 128.75; 129.08; 129.76; 134.43; 135.78; 138.31; 143.00; 154.34; 164.71; 170.35 (<u>C</u>O_2Bn). Found (%): C, 63.45; H, 5.01; N, 5.75. $C_{26}H_{24}N_2O_4S_2$. Calculated (%): C, 63.39; H, 4.91; N, 5.69.

Benzyl 2-{[(4-methylphenyl)sulfonyl]amino}-3-(4-(3-nitrophenyl)-1,3-thiazol-2-yl)propanoate (5c). The yield was 0.274 g (51%), m.p. 165—166 °C. IR, ν/cm^{-1}: 3268, 3108, 1729, 1582, 1351, 1164. ^{1}H NMR, δ: 2.16 (s, 3 H, Me); 3.26—3.27, 3.46—3.32 (both m, 1 H each, CH_2); 4.37 (m, 1 H, TsNHC<u>H</u>); 4.97 (s, 2 H, Ph<u>C</u>H_2); 7.12 (d, 2 H, Ph, *J* = 8.1 Hz); 7.38—7.21 (m, 5 H, Ts, Ph); 7.49 (d, 2 H, Ts, *J* = 8.2 Hz); 7.70 (t, 1 H, Ar, *J* = 8.0 Hz); 8.27 (d, 1 H, Ar, *J* = 7.8 Hz); 8.23—8.12 (m, 2 H, thiazole, Ar); 8.64—8.58 (m, 2 H, Ts<u>N</u>H, Ar). ^{13}C NMR, δ: 21.13 (Me); 32.40 (CH_2); 54.05 (TsNH<u>C</u>H); 66.67 (Ph<u>C</u>H_2); 115.51 (C(5), thiazole); 124.30; 126.30; 126.51; 127.69; 128.16; 128.17; 128.32; 129.03; 129.6; 135.53; 139.86; 140.36; 148.37; 155.61; 158.26;

161.05; 173.09 ($\underline{C}O_2Bn$). Found (%): C, 58.17; H, 4.36; N, 7.79. $C_{26}H_{23}N_3O_6S_2$. Calculated (%): C, 58.09; H, 4.31; N, 7.82.

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