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SHORT COMMUNICATIONS

Tetrachlorosilane–Sodium Azide System in the Synthesis of Tetrazole-Containing D,L-Tryptophane Derivatives

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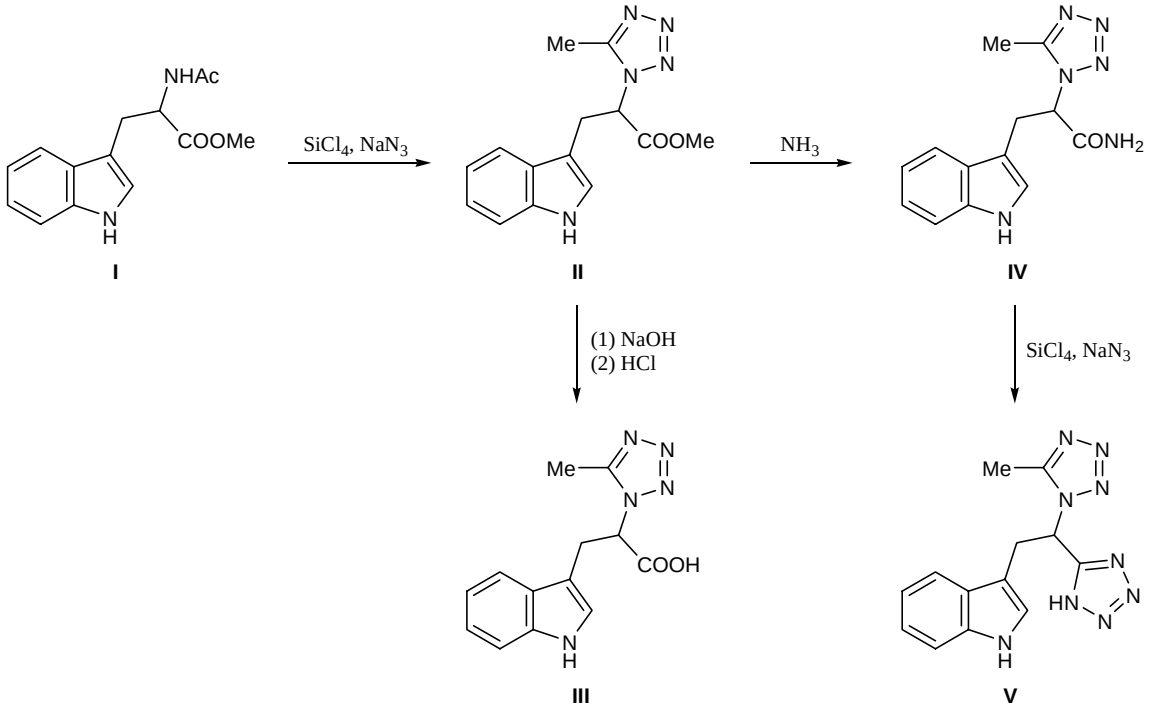
Tetrazole fragment is a metabolically stable substitute for carboxy group and amide bond in molecules of peptidomimetics [1]. The first amino acid derivatives containing a 5-tetrazolyl substituent were described by McManus and Herbst [2]. Zabrocki *et al.* later proposed [3] to use tetrazole-1,5-diyl fragment for the synthesis of peptidomimetics with *cis*-blocked peptide bond. Growing demands for tetrazole-containing components of peptides and peptidomimetics aroused extensive studies aimed at developing effective methods for the preparation of amino acid derivatives having a tetrazole moiety. For example, Demko and Sharpless [4] proposed a scheme for the synthesis of tetrazole-containing amino acid analogs via azidation of the corresponding cyano derivatives with sodium azide in aqueous isopropyl alcohol in the presence of $ZnBr_2$. However, this procedure cannot be regarded as general and universal because of the limited accessibility of the corresponding amino acid nitriles and the necessity of using Lewis acids in water-containing systems. In addition, it should be kept in mind that products obtained in such a way may be contaminated with Zn^{2+}-containing impurities, which is undesirable from the viewpoint of medical chemistry.

We previously showed that treatment of *N*-acetyl-(*R*,*S*)-phenylalanine and *N*-acetyl-(*R*,*S*)-leucine methyl esters with the system tetrachlorosilane–sodium azide

Scheme 1.



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leads to formation of tetrazole-containing derivatives of the corresponding amino acids. At present, a considerable interest is observed in peptidomimetics based on tetrazole-modified D,L-tryptophane structure [5, 6]. Development of the synthesis of such peptidomimetics requires tetrazole-containing D,L-tryptophane derivatives as key intermediates.

We have found that tryptophane derivatives haing a tetrazole fragment can be prepared from accessible *N*-acyl-(*R,S*)-tryptophane esters by the action of tetrachlorosilane–sodium azide. By heating *N*-acetyl-(*R,S*)-tryptophane methyl ester (**I**) with tetrachlorosilane and sodium azide in boiling acetonitrile we obtained α-substituted methyl 5-methyl-1-tetrazolylacetate **II**. Alkaline hydrolysis of ester **II** and subsequent acidification afforded tetrazole-containing carboxylic acid **III** (Scheme 1). This reaction sequence is an example of the synthesis of an amino acid derivative containing only one tetrazole ring. We also succeeded in obtaining bis-tetrazole **V** by treatment with tetrachlorosilane–sodium azide of amide **IV** which was synthesized by ammonolysis of ester **II** (Scheme 1).

It should be noted that the reactivities of secondary amide **I** and primary amide **IV** conform to the general relations found by us previously [7].

CAUTION! *Reactions with the $SiCl_4$–NaN_3 system can be accompanied by evolution of a small amount of hydrazoic acid.*

Methyl (*R,S*)-3-(3-indolyl)-2-(5-methyl-1-tetrazolyl)propionate (II). To a mixture of 10.0 g (0.038 mol) of ester **I**, 5.0 g (0.077 mol) of NaN_3, and 40 ml of acetonitrile we added under stirring 13.05 g (0.077 mol) of $SiCl_4$ in 30 ml of acetonitrile with protection from atmospheric moisture. The mixture was heated for 6 h under reflux, and the reaction completion was checked by TLC. If the initial ester **I** was still present in the reaction mixture, an additional amount of the azidating agent was added. The procedure was repeated every 6 h until complete conversion of ester **I**. The overall reaction time was 45–50 h. The mixture was poured in small portions under stirring into a solution of Na_2CO_3, maintaining pH > 7. The product was extracted into ethyl acetate (3×50 ml), the solvent was removed under reduced pressure, and the residue was recrystallized from 70% ethanol. Yield 7.40 g (68%). Colorless crystals, mp 141–142°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.01 s (3H, CH_3CN_4), 3.53–3.63 m (1H, CH_2), 3.75–3.83 m (4H, CH_2, OCH_3), 5.65 d.d (1H, CH, *J* = 4.4, 10.9 Hz), 6.74 br.s (1H, indole), 6.94–7.08 m (2H, indole), 7.30 d (1H, indole, *J* = 8.0 Hz), 7.48 d (1H, indole, *J* = 7.3 Hz), 10.67 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 7.9 (**C**H_3CN_4); 26.7 (CH_2); 53.0 (OCH_3); 59.7 (CH); 107.6, 111.5, 117.8, 118.6, 121.2, 124.0, 126.5, 136.0 (indole); 152.7 (CN_4); 167.9 (**C**OOMe). Found, %: C 58.63; H 5.59; N 24.44. $C_{14}H_{15}N_5O_2$. Calculated, %: C 58.94; H 5.30; N 4.55.

(*R,S*)-3-(3-Indolyl)-2-(5-methyl-1-tetrazolyl)-propionic acid (III). Ester **II**, 2.0 g (0.007 mol), was added in small portions under stirring to a solution of 0.84 g (0.021 mol) of NaOH in 75 ml of water. When the initial compound dissolved completely, the solution was kept for 1.5 h at room temperature, 25 ml of water and charcoal were added, and the mixture was stirred for 0.5 h and filtered. The filtrate was acidified to pH 2 with hydrochloric acid and cooled, and the precipitate was filtered off. Yield 1.14 g (60%). Colorless crystals, mp 188–190°C (decom.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.11 s (3H, CH_3CN_4), 3.54–3.64 m (1H, CH_2), 3.72–3.78 m (1H, CH_2), 5.76–5.80 m (1H, CH), 6.91–7.10 m (3H, indole), 7.32 d (1H, indole, *J* = 7.3 Hz), 7.52 d (1H, indole, *J* = 7.3 Hz), 10.85 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 8.2 (**C**H_3CN_4); 26.8 (CH_2); 60.3 (CH); 108.4, 111.7, 118.1, 118.8, 121.4, 124.0, 126.7, 136.1 (indole); 152.9 (CN_4); 169.1 (COOH). Found, %: C 57.09; H 4.95; N 25.37. $C_{13}H_{13}N_5O_2$. Calculated, %: C 57.56; H 4.83; N 25.82.

(*R,S*)-3-(3-Indolyl)-2-(5-methyl-1-tetrazolyl)-propionamide (IV). Concentrated aqueous ammonia, 19 ml, was added to a solution of 7.11 g (0.025 mol) of ester **II** in 20 ml of EtOH. The mixture was heated for 0.5 h at the boiling point, and the solvent was removed under reduced pressure. The residue was recrystallized in a minimal amount of ethanol. Yield 4.08 g (61%). Colorless crystals, mp 109–110°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.17 s (3H, CH_3CN_4), 3.50 d.d (1H, CH_2, *J* = 10.2, 14.5 Hz), 3.70 d.d (1H, CH_2, *J* = 5.1, 14.5 Hz), 5.32 d.d (1H, CH, *J* = 5.1, 10.2 Hz), 6.76 br.s (1H, indole), 6.93–7.06 m (2H, indole), 7.28 d (1H, indole, *J* = 8.0 Hz), 7.56 d (1H, indole, *J* = 7.3 Hz), 7.37 br.s and 7.70 br.s (2H, $CONH_2$), 10.63 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 8.5 (**C**H_3CN_4); 27.0 (CH_2); 60.9 (CH); 108.4, 111.5, 118.2, 118.6, 121.2, 123.9, 126.7, 136.0 (indole); 152.6 (CN_4); 168.4 ($CONH_2$). Found, %: C 57.29; H 5.52; N 30.61. $C_{13}H_{14}N_6O$. Calculated, %: C 57.77; H 5.22; N 31.09.

(*R,S*)-2-(3-Indolyl)-1-(5-methyl-1-tetrazolyl)-1-(5-tetrazolyl)ethane (V). The azidation of amide **IV**,

4.27 g (0.016 mol), was performed following the procedure described above for the synthesis of ester **II**. The overall reaction time was 35 h. When the reaction was complete, the mixture was poured in small portions under stirring to a solution of Na_2CO_3, maintaining pH > 7. The precipitate of silica was filtered off with suction, a solution of $NaNO_2$ was added to the filtrate, and the mixture was slowly acidified with hydrochloric acid to pH 2. The solution was cooled, and the crystals were filtered off. Yield 3.19 g (68%). Light yellow crystalline substance. An analytical sample was obtained by recrystallization from 30–50% ethanol. mp 218–220°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.07 s (3H, CH_3CN_4), 3.76–3.85 m (1H, CH_2), 4.02–4.08 m (1H, CH_2), 6.51–6.56 m (1H, CH), 6.95–7.11 m (3H, indole) 7.34 d (1H, indole, J = 7.3 Hz) 7.52 d (1H, indole, J = 7.3 Hz), 10.94 br.s (1H, NH, indole), 16.59 br.s (1H, CN_4H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 8.0 (**C**H_3CN_4); 28.7 (CH_2); 53.1 (CH); 107.4, 111.6, 117.9, 118.8, 121.3, 124.4, 126.6, 136.0 (indole); 152.6 (CH_3**C**N_4); 155.7 (CN_4H). Found, %: C 52.77; H 4.69; N 42.83. $C_{13}H_{13}N_9$. Calculated, %: C 52.87; H 4.44; N 42.69.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300 and 75 MHz, respectively, using the solvent signal as reference (DMSO-d_6). The ^{1}H and ^{13}C signals were assigned with account taken of the data reported in [8, 9]. The progress of reactions and the purity of poducts were monitored by TLC on Kieselgel 60 F_{254} plates (Merck) using $CHCl_3$–MeOH, 9:1 or 95:5, as eluent; spots were visualized by UV irradiation.

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