Russian Journal of Organic Chemistry, Vol. 38, No. 9, 2002, pp. 1370–1373. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 9, 2002, pp. 1422–1425.

Dedicated to Full Member of the Russian Academy of Sciences V.A. Tartakovskii on the 70th Anniversary of His Birth

Tetrachlorosilane–Sodium Azide System in the Synthesis of Tetrazole-Containing Amino Acid Derivatives

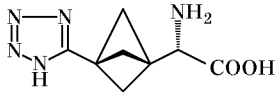
K. A. Esikov, S. E. Morozova, A. A. Malin, and V. A. Ostrovskii

St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 198013 Russia
e-mail: kirill_esikov@mail.ru

Received May 29, 2002

Abstract—Treatment of *N*-acetyl-(*RS*)-phenylalanine and *N*-acetyl-(*RS*)-leucine methyl esters with the system tetrachlorosilane–sodium azide leads to formation of tetrazole-containing amino acid derivatives. The latter can be converted into α-substituted 5-methyl-1-tetrazolylacetic acids and the corresponding bis-tetrazoles.

Structural modification of amino acids and peptides is a conventional method for synthesizing new conjugates as potential biologically active compounds. A promising fragment for such modification is a tetrazole ring which can be regarded as an analog and stable (from the viewpoint of metabolism) substitute for carboxy or carboxamide group. The first amino acid analogs having a 5-tetrazolyl substituent instead of the carboxy group were reported in 1959 by McManus and Herbst [1]. Nevertheless, the problem of molecular design and synthesis of tetrazole-containing amino acids and peptides remains important. For example, Constantino *et al.* [2] recently synthesized a potential mGlu1 receptor antagonist (S-TBPG) whose molecule combines a tetrazole ring and bicyclo[1.1.1]pentane skeleton:



S-TBPG

Biological activity of tetrazole-containing analogs of various biologically active peptides was studied, specifically of Leu-enkephalin [3], bradykinin [4], tyroliberin [5], neuropharmacologically active tripeptide Pro-Leu-Gly-NH_2 [6], and β-casomorphin-7-amide [7]. Also, tetrazol-containing peptidomimetics **II**, which inhibit HIV protease, were prepared [8, 9].

Despite increased interest in such compounds, methods for their preparation have been explored poorly. As a rule, tetrazole fragment is incorporated into peptide chain by the action of PCl_5 on a monosubstituted amide group and subsequent treatment with HN_3 [4]. Taking into account the high toxicity of hydrazoic acid and risk of explosion, as well as the fact that unsubstituted amides cannot be invloved in analogous reactions, the necessity of developing alternative procedures for synthesis of tetrazole-containing peptidomimetics seems to be obvious.

We recently showed that the azidating system tetrachlorosilane–sodium azide is a convenient and relatively safe reagent for the synthesis of tetrazoles from carboxylic acid amides. It is important that this system allows preparation of both 1,5-disubstituted [10] and NH-tetrazoles [10, 11] from monosubstituted or unsubstituted amides, respectively. In the present work we made an attempt to apply the above system to structural modification of amino acids.

By heating *N*-acetyl-(*RS*)-phenylalanine and *N*-acetyl-(*RS*)-leucine methyl esters **IIa** and **IIb** with tetrachlorosilane and sodium azide in boiling acetonitrile we obtained the corresponding α-substituted 5-methyl-1-tetrazolylacetic acid esters **IIIa** and **IIIb**. Their hydrolysis gave carboxylic acids **IVa** and **IVb** (Scheme 1). Esters **IIIa** and **IIIb** reacted with ammonia to give amides **Va** and **Vb**, and treatment of the latter with tetrachlorosilane–sodium azide led to formation of bis-tetrazoles **VIa** and **VIb**.

We previously showed that *N*-monosubstituted and unsubstituted amides exhibit different reactivities toward the system tetrachlorosilane–sodium azide

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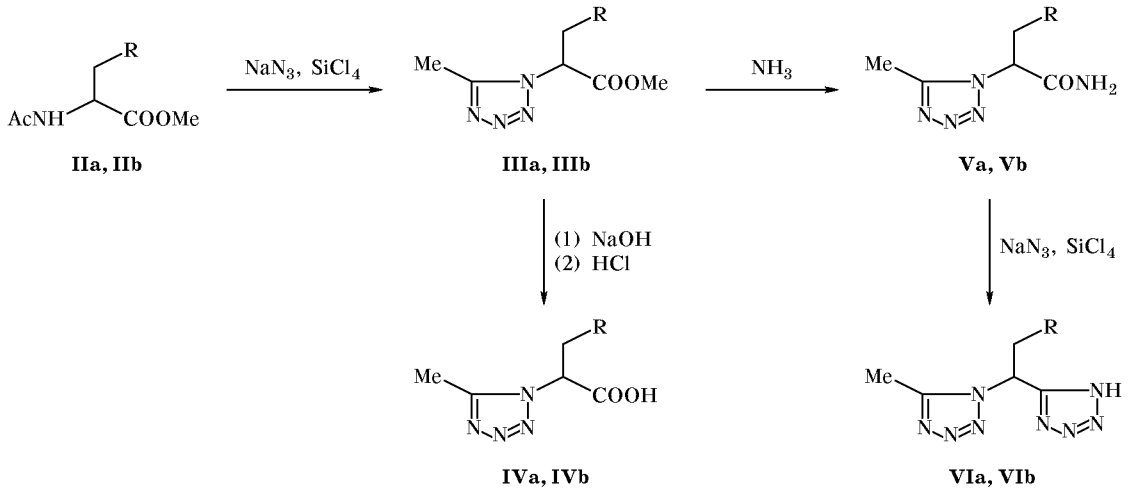
Scheme 1.

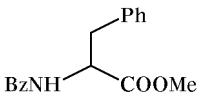


R = Ph (**a**), *i-Pr* (**b**).

[10]. In fact, the rate of formation of NH-tetrazoles is several times higher than the rate of formation of 1,5-disubstituted derivatives. An analogous pattern was observed by us with phenylalanine derivatives. By the action of tetrachlorosilane–sodium azide, unsubstituted amide **Va** was converted into the corresponding tetrazole (**VIa**) in 12 h, i.e., much faster than substituted amide **IIa** (30 h). However, the azidation of both monosubstituted (**Vb**) and unsubstituted leucine derivatives (**IIb**) takes about 10 h.

It should be noted that an additional amount of the azidating reagent (tetrachlorosilane and sodium azide) should be added after a certain time to complete the conversion of amide into tetrazole. Presumably, intermediate silicon azides are unstable, and they decompose on heating [12].

Some limitations intrinsic to the azidating system under study must be noted. Unlike *N*-acetyl derivatives of amino acids, *N*-benzoyl derivatives, e.g., compound **VII**, almost do not react with tetrachlorosilane–sodium azide. A propable reason is steric effect of the benzoyl substituent.



VII

Carboxylic acids **IVa** and **IVb** can be used as terminal amino acids in the synthesis of tetrazole-containing peptidomimetics. In addition, bis-tetrazoles **VIa** and **VIb** may be regarded as substrates suitable for alkylation with various reagent. An analogous approach was applied in [6, 13] to the synthesis of peptidomimetics containing both tetrazole-1,5-diyl and tetrazole-2,5-diyl fragments.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 instrument at 300 and 75 MHz, respectively; the solvent signals ($CDCl_3$ or DMSO-d_6) were used as reference. The mass spectra (70 eV) were run on a Varian MAT-311 mass spectrometer. The progress of reactions was monitored, and the purity of products was checked, by ^{1}H NMR spectroscopy (compounds **IIIb**, **IVb**, **Vb**, and **VIb**) or thin-layer chromatography (**IIIa**, **IVa**, **Va**, and **VIa**) on Kieselgel 60 F_{254} plates (Merck) using $CHCl_3$–MeOH (9 : 1) as eluent; spots were visualized with UV light.

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

Methyl (*RS*)-2-(5-methyl-1-tetrazolyl)-3-phenylpropionate (IIIa). A solution of 7.7 g (0.045 mol) of tetrachlorosilane in 25 ml of acetonitrile was added with stirring to a mixture of 5 g (0.023 mol) of ester **IIa** and 2.95 g (0.045 mol) of sodium azide in 25 ml of acetonitrile. The mixture was refluxed for 6 h with protection from moisture and was analyzed for initial ester **IIa**. If necessary, an additional amount of the azidating reagent was added [0.5 g (0.008 mol) of NaN_3 and 1.7 g (0.01 mol) of $SiCl_4$]. This procedure was repeated every 6 h until the conversion of ester **IIa** was complete. The overall reaction time was 30 h.

The mixture was then poured in small portions under stirring to a solution of Na_2CO_3, maintaining the pH greater than 7. The product was extracted into ethyl acetate (2×50 ml), the solvent was removed under reduced pressure, and the residue was recrystallized from 50–70% ethanol. Yield 4.52 g (81%). Colorless crystalline substance, mp 88–89°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.19 s (3H, 5-CH_3), 3.42 d.d (1H, CH_2, J = 11.0, 14.1 Hz), 3.69 d.d (1H, CH_2, J = 4.4, 14.1 Hz), 3.74 s (3H, OCH_3), 5.92 d.d (1H, CH, J = 4.8, 11.0 Hz), 7.05–7.27 m (5H, Ph). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 7.8 (5-CH_3); 36.3 (CH_2); 53.1 (OCH_3); 60.1 (CH); 127.0, 128.4, 128.8, 135.4 (Ph); 152.8 (C^5); 167.6 (**C**OOMe). Found, %: C 58.99; H 5.98; N 22.81. $C_{12}H_{14}N_4O_2$. Calculated, %: C 58.53; H 5.73; N 22.75.

Methyl (*RS*)-4-methyl-2-(5-methyl-1-tetrazolyl)-pentanoate (IIIb) was synthesized in a similar way. Reaction time 10 h. Yield 90%. Light yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.89 d.d [6H, CH(C**H**$_3$)$_2$, J = 2.2, 6.6 Hz], 1.24–1.43 m [1H, C**H**$(CH_3)_2$], 2.03–2.19 m (1H, CH_2), 2.26–2.42 m (1H, CH_2), 2.53 s (3H, 5-CH_3), 3.72 s (3H, OCH_3), 5.14 d.d (1H, 1-CH, J = 4.9, 11.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 9.4 (5-CH_3), 21.0 and 22.7 [CH(**C**H$_3$)$_2$], 24.6 [**C**H$(CH_3)_2$], 38.9 (CH_2), 53.4 (OCH_3), 58.6 (1-CH), 152.3 (C^5), 168.3 (**C**OOMe). Found, %: C 50.71; H 7.96; N 26.84. $C_9H_{16}N_4O_2$. Calculated, %: C 50.93; H 7.60; N 26.40.

(*RS*)-2-(5-Methyl-1-tetrazolyl)-3-phenylpropionic acid (IVa). Ester **IIIa**, 0.45 g (1.8 mmol), was added in small portions with stirring to a solution of 0.22 g (5.5 mmol) of NaOH in 10 ml of water. When the mixture became homogeneous, it was stirred for 3 h at room temperature, 10 ml of water and charcoal were added, and the mixture was stirred for 0.5 h. It was filtered from charcoal, the filtrate was acidified with hydrochloric acid and cooled, and the precipitate was filtered off. Yield 0.32 g (75%). Colorless crystalline substance, mp 182°C; published data [14]: mp 178°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.18 s (3H, 5-CH_3), 3.38 d.d (1H, CH_2, J = 11.9, 14.1 Hz), 3.64 d.d (1H, CH_2, J = 4.4, 14.1 Hz), 5.81 d.d (1H, CH, J = 4.6, 11.3 Hz), 7.04–7.21 m (5H, Ph), 13.84 br.s (1H, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 7.9 (5-CH_3); 36.2 (CH_2); 60.3 (CH); 126.9, 128.4, 128.8, 135.9 (Ph); 152.8 (C^5); 168.7 (COOH). Found, %: C 56.28; H 4.85; N 24.42. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

(*RS*)-4-Methyl-2-(5-methyl-1-tetrazolyl)pentanoic acid (IVb). Ester **IIIb**, 1 g (4.7 mmol), was added with stirring to a solution of 0.57 g (14 mmol) of NaOH in 20 ml of water. When the mixture became homogeneous, it was stirred for 3 h at room temperature, 20 ml of water and charcoal were added, and the mixture was stirred for 0.5 h and filtered from charcoal. The filtrate was acidified with hydrochloric acid, evaporated by half under reduced pressure, and cooled, and the precipitate was filtered off. Yield 0.51 g (55%). Colorless crystalline substance, mp 131–132°C; published data [14]: mp 127°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.93 d.d [6H, CH(C**H**$_3$)$_2$, J = 4.4, 6.5 Hz], 1.31–1.46 m [1H, C**H**$(CH_3)_2$], 2.12–2.27 m (1H, CH_2), 2.33–2.49 m (1H, CH_2), 2.59 s (3H, 5-CH_3), 5.20 d.d (1H, 1-CH, J = 4.4, 10.9 Hz), 12.92 br.s (COOH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 9.2 (5-CH_3), 21.0 and 22.8 [CH(**C**H$_3$)$_2$], 24.8 [**C**H$(CH_3)_2$], 38.7 (CH_2), 59.1 (1-CH), 152.8 (C^5), 170.2 (COOH). Found, %: C 48.91; H 6.80; N 28.20. $C_8H_{14}N_4O_2$. Calculated, %: C 48.47; H 7.12; N 28.26.

(*RS*)-2-(5-Methyl-1-tetrazolyl)-3-phenylpropionamide (Va). To a solution of 2 g (8.1 mmol) of ester **IIIa** in 10 ml of EtOH we added 15 ml of 25% aqueous ammonia. The mixture was heated for 2 h at the boiling point, the solvent was removed under reduced pressure, and the residue was recrystallized from a minimal amount of ethanol (3–5 ml). Yield 0.9 g (48%). Colorless crystalline substance. mp 130–132°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.21 s (3H, 5-CH_3), 3.34 d.d (1H, CH_2, J = 10.6, 14.1 Hz), 3.61 d.d (1H, CH_2, J = 4.8, 14.1 Hz), 5.47 d.d (1H, CH, J = 4.8, 10.6 Hz), 7.07–7.25 m (5H, Ph), 7.57 br.s and 7.78 br.s (2H, $CONH_2$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 8.4 (5-CH_3); 36.6 (CH_2); 61.4 (CH); 126.9, 128.4, 128.9, 136.3 (Ph); 152.7 (C^5); 167.9 ($CONH_2$). Found, %: C 56.84; H 5.77; N 30.41. $C_{11}H_{13}N_5O$. Calculated, %: C 57.13; H 5.67; N 30.28.

(*RS*)-4-Methyl-2-(5-methyl-1-tetrazolyl)pentanamide (Vb) was synthesized in a similar way from ester **IIIb**. Yield 43%. mp 113°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.92 d [6H, CH(C**H**$_3$)$_2$, J = 6.5 Hz], 1.25–1.44 m [1H, C**H**$(CH_3)_2$], 2.04–2.19 m (1H, CH_2), 2.26–2.41 m (1H, CH_2), 2.60 s (3H, 5-CH_3), 4.98 d.d (1H, 1-CH, J = 5.1, 10.9 Hz), 5.87 br.s and 6.26 br.s (2H, $CONH_2$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 9.3 (5-CH_3), 21.4 and 22.7 [CH(**C**H$_3$)$_2$], 24.8 [**C**H$(CH_3)_2$], 40.9 (CH_2), 60.9 (1-CH), 152.7 (C^5), 169.5 (COOH). Found, %: C 48.25; H 7.20; N 35.01. $C_8H_{15}N_5O$. Calculated, %: C 48.72; H 7.67; N 35.51.

(*RS*)-1-(5-Methyl-1-tetrazolyl)-1-(5-tetrazolyl)-2-phenylethane (VIa). The azidation of amide **Va** (1.03 g, 4.5 mmol) was carried out as described above

in the synthesis of ester **IIIa** (reaction time 12 h). The mixture was then poured in small portions under stirring to a solution of Na_2CO_3, maintaining the pH above 7. The precipitate of silicic acid was filtered off, a solution of sodium nitrite was added to the filtrate, and the mixture was slowly acidified to pH 2 by adding hydrochloric acid. The solution was cooled, and the crystals were filtered off. Yield 0.96 g (84%). Colorless crystalline substance. An analytical sample was obtained by recrystallization from 30–50% EtOH. mp 191–193°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.18 s (3H, 5-CH_3), 3.65 d.d (1H, CH_2, J = 11.0, 13.7 Hz), 3.94 d.d (1H, CH_2, J = 5.3, 13.7 Hz), 6.58 d.d (1H, CH, J = 5.3, 10.6 Hz), 7.07–7.26 m (5H, Ph), 16.74 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 7.9 (5-CH_3); 38.2 (CH_2); 53.4 (CH); 127.3, 128.5, 129.1, 135.1 (Ph); 152.6 (C^5); 155.8 ($C^{5'}$). Found, %: C 51.68; H 4.92; N 44.20. $C_{11}H_{12}N_8$. Calculated, %: C 51.56; H 4.72; N 43.72.

(*RS*)-3-Methyl-1-(5-methyl-1-tetrazolyl)-1-(5-tetrazolyl)butane (VIb). The azidation of amide **Vb** (1.37 g, 6.9 mmol) was carried out as described above in the synthesis of ester **IIIa** (reaction time 10 h). The mixture was poured in small portions under stirring into a solution of Na_2CO_3, maintaining the pH above 7. The precipitate of silicic acid was filtered off, a solution of sodium nitrite was added to the filtrate, the mixture was acidified to pH 2 with hydrochloric acid and extracted with methylene chloride (2×50 ml), and the solvent was removed under reduced pressure. Yield 2.37 g (68%). Light yellow oily substance which crystallizes on storage. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.96 t [6H, $CH(CH_3)_2$, J = 6.5 Hz], 1.33–1.50 m [1H, $CH(CH_3)_2$], 2.37–2.63 m (2H, CH_2), 2.66 s (3H, 5-CH_3), 6.12 d.d (1H, 1-CH, J = 6.5, 9.5 Hz), 13.66 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 9.3 (5-CH_3), 21.6 and 22.4 [$CH(CH_3)_2$], 24.7 [$CH(CH_3)_2$], 41.8 (CH_2), 52.4 (1-CH), 152.6 (C^5), 157.7 ($C^{5'}$). Mass spectrum, m/z: 223 $[MH]^+$. Calculated for $C_8H_{14}N_8$: M 222.

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