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Synthesis and Transformations of 1-(Azidophenyl)-1*H*-tetrazoles

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Abstract—Diazotization of 1-(aminophenyl)-1*H*-tetrazoles and subsequent treatment of the diazonium salts with sodium azide gave 1-(azidophenyl)-1*H*-tetrazoles which were brought into cyclization with ethyl acetoacetate and cyanoacetanilide to obtain 1,2,3-triazole derivatives. Under these conditions, the tetrazole ring may undergo cleavage with formation of cyanamide group.

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5-Substituted tetrazoles are the most thoroughly studied tetrazole derivatives, for they are readily available via 1,3-dipolar cycloaddition of azides to nitriles. 2- and 1-Substituted tetrazoles have been studied to a lesser extent [1–3]. 1-Substituted tetrazoles became more accessible due to development of a procedure for their preparation by reaction of amines with triethyl orthoformate and sodium azide [4, 5]. This reaction was used to synthesize with high yields tetrazoles having various substituents in position *1* [3–7]. Some 1-substituted tetrazoles were found to exhibit biological activity [8, 9] and complexing ability toward various metals [10–12]. For example, tetrazoles were used as ligands in palladium-catalyzed Suzuki reactions [13].

However, chemical behavior of 1-substituted tetrazoles was studied poorly. Insofar as the tetrazole ring is not very stable, its behavior in various reactions is often unpredictable, and it was not studied. In particular, tetrazole ring is not stable in strongly basic medium. Vorobiov et al. [14] described one-pot synthesis of 5-aminotetrazoles via decomposition of tetrazoles and subsequent cyclization of the cyanamide group thus formed by the action of sodium azide. We recently demonstrated prospects in using 1-substituted tetrazoles as precursors of cyanamides which were generated *in situ* by cleavage of tetrazole ring in the synthesis of 2,3-diaminothieno[2,3-*d*]pyrimidines [6].

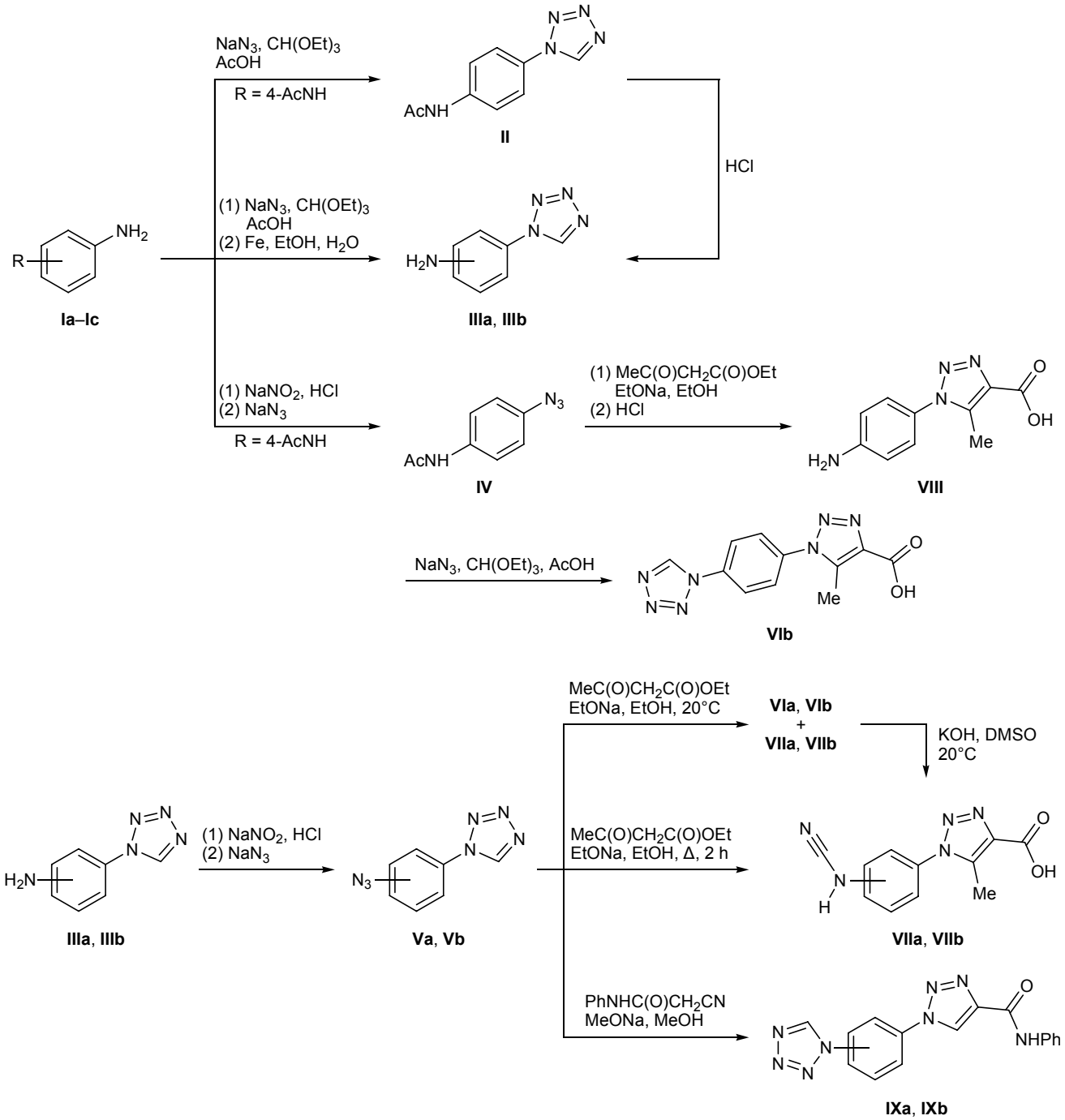
In the present work we tried to find synthetic approaches to (1*H*-tetrazol-1-yl)phenyl-1*H*-1,2,3-triazole derivatives. Phenylenebis(1*H*-tetrazoles) are good complexing agents for copper [11]; therefore, synthesis of structurally related tetrazolylphenyltriazoles attracts interest from the viewpoint of practice.

As starting compounds we used nitroanilines **Ia** and **Ib** which were converted in two steps into tetrazolylanilines **IIIa** and **IIIb**. Compounds **IIIa** and **IIIb** were previously synthesized by reduction of the corresponding nitroaryltetrazoles [11]. The use of tin(II) chloride instead of metallic iron allowed us to raise the yield and reduce the probability for cleavage of the tetrazole ring. 4-(1*H*-Tetrazol-1-yl)aniline (**IIIb**) was also synthesized starting from *p*-phenylenediamine whose acetylation gave *N*-(4-aminophenyl)acetamide (**Ic**). The free amino group in the latter was converted into tetrazole ring, and removal of the acetyl protection from compound **II** afforded compound **IIIb** (Scheme 1).

Anilines **IIIa** and **IIIb** were subjected to diazotization by treatment with sodium nitrite in hydrochloric acid to obtain stable (in solution) diazonium salts [15]. These diazonium salts were found to arylate methyl acrylate, furfurol, and furan-2-carboxylic acid under Meerwein reaction conditions [15]. Treatment of the diazonium salts with sodium azide gave the corresponding azides **Va** and **Vb**. Despite the presence of many nitrogen atoms in their molecules, 1-(azidophenyl)tetrazoles **Va** and **Vb** turned out to be fairly stable. There is an empirical rule according to which organic azides are safe in handling and nonexplosive if the number of nitrogen atoms therein (N_N) does not exceed the number of carbon atoms (N_C) and $(N_C + N_O)/N_N \geq 3$ [16, 17].

Azides **Va** and **Vb** were used to construct triazole ring via cyclization with compounds having an activat-

Scheme 1.



I, R = 3-O_2N (**a**), 4-O_2N (**b**), 4-AcNH (**c**); **III**, **V**–**VII**, **IX**, *meta* substitution (**a**), *para* substitution (**b**).

ed methylene group in the presence of bases. The reactions of azides **Va** and **Vb** with ethylacetoacetate at room temperature gave mixtures of expected cyclization products **VIa** and **VIb** and cyanamides **VIIa** and **VIIb**, the latter being formed as a result of cleavage of the tetrazole ring. To ensure complete hydrolysis of the ester group, the reaction mixtures were heated to the boiling point and treated with water. Under these conditions, complete decomposition of the tetrazole ring occurred with elimination of nitrogen and formation of cyanamide fragment (compounds **VIIa** and **VIIb**). Cyanamides **VIIa** and **VIIb** were also

obtained as individual substances by adding a solution of potassium hydroxide in dimethyl sulfoxide to the above product mixture (**VI**/**VII**). Compound **VIb** was synthesized independently by cyclization of azide **IV** with ethyl acetoacetate and subsequent treatment of acid **VIII** with sodium azide and triethyl orthoformate in acetic acid. We failed to convert compound **IV** into 4-azidoaniline, for the latter decomposed on heating in mineral acid.

Azides **Va** and **Vb** reacted with cyanoacetanilide at room temperature at a very high rate (in 2–3 s) to give compounds **IXa** and **IXb** in high yield. The tetrazole ring remained intact in this reaction. It is difficult to distinguish compounds having a tetrazole ring and cyanamide derivatives by ^{1}H NMR spectroscopy, for signals from the CH proton in the tetrazole ring and from the NH proton in the cyanamide fragment are located in the same region (δ ~10 ppm). However, the signal from the cyanamide proton is slightly broadened due to tautomerism. The 5-H proton in the tetrazole ring resonates at δ 10.15–10.20 ppm. The products were identified by mass spectrometry (chemical ionization).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer (400 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra (chemical ionization) were obtained on an Agilent 1100 LC/MSD system.

1-Substituted 1*H*-tetrazoles II, IIIa, IIIb, and VIb (*general procedure***)** [11]**.** Acetic acid, 40 ml, was added under stirring to a suspension of 0.05 mol of aniline **Ia**–**Ic** or **VIII** and 3.9 g of sodium azide in 25 ml of triethyl orthoformate, and the mixture was heated for 4 h at 95–100°C. The mixture was cooled, treated with 7 ml of concentrated hydrochloric acid, and filtered, the filtrate was evaporated under reduced pressure, and the residue was recrystallized from ethanol.

***N*-[4-(1*H*-Tetrazol-1-yl)phenyl]acetamide (II).** Yield 79%, mp 223–224°C. Mass spectrum: *m*/*z* 204 $[M + H]^+$. Found, %: C 53.16; H 4.24; N 34.12. $C_9H_9N_5O$. Calculated, %: C 53.20; H 4.46; N 34.47. *M* 203.20.

5-Methyl-1-[4-(1*H*-tetrazol-1-yl)phenyl]-1*H*-1,2,3-triazole-4-carboxylic acid (VIb). Yield 81%, mp 243–244°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 7.94 d (2H, *m*-H, J = 8.6 Hz), 8.20 d (2H, *o*-H, J = 8.6Hz), 10.19 s (1H, 5″-H). Mass spectrum: *m*/*z* 272 $[M + H]^+$. Found, %: C 48.77; H 3.34; N 35.90. $C_{11}H_9N_7O_2$. Calculated, %: C 48.65; H 3.56; N 36.04. *M* 271.24.

3(4)-(1*H*-Tetrazol-1-yl)anilines IIIa and IIIb (*general procedure***).** 3- and 4-Nitrophenyltetrazoles were reduced to amino derivatives **IIIa** and **IIIb** as follows. A mixture of 51.8 g of iron powder and 311 ml of water (or 3 : 1 ethanol–water mixture) was heated under stirring, 6.2 ml of concentrated hydrochloric acid was added, and 0.2 mol of 3- or 4-nitrophenyltetrazole was slowly added. The mixture was heated for 8 h and quickly filtered while hot. The filtrate was cooled, and the precipitate was filtered off and purified by recrystallization.

Azides IV, Va, and Vb (*general procedure***).** A solution of 0.05 mol of amine **Ic**, **IIIa**, or **IIIb** in 19 ml of concentrated hydrochloric acid was cooled to 0°C, and a cold solution of 3.45 g of sodium nitrite in a minimal amount of water was added dropwise under stirring. The mixture was stirred at 0–5°C, filtered (if necessary), and cooled to –5°C, and a solution of 3.25 g of sodium azide in 10 ml of water was slowly added dropwise under stirring, maintaining the temperature below 7°C. The mixture was stirred for 2 h at room temperature, and the product was filtered off, washed with ice water until neutral reaction, and dried in a dark cold place.

***N*-(4-Azidophenyl)acetamide (IV).** Yield 88%, mp 116–117°C. ^{1}H NMR spectrum, δ, ppm: 2.03 s (3H, CH_3), 6.96 d (2H, *m*-H, J = 8.8 Hz), 7.60 (2H, *o*-H, ^3J = 8.8 Hz), 9.86 s (1H, NH). Mass spectrum: *m*/*z* 177 $[M + H]^+$. Found, %: C 54.37; H 4.70; N 31.68. $C_8H_8N_4O$. Calculated, %: C 54.54; H 4.58; N 31.80. *M* 176.18.

1-(3-Azidophenyl)-1*H*-tetrazole (Va). Yield 73%, mp 99–100°C. Mass spectrum: *m*/*z* 188 $[M + H]^+$. Found, %: C 44.78; H 2.75; N 52.07. $C_7H_5N_7$. Calculated, %: C 44.92; H 2.69; N 52.39. *M* 187.16.

1-(4-Azidophenyl)-1*H*-tetrazole (Vb). Yield 83%, mp 125–126°C. Mass spectrum: *m*/*z* 188 $[M + H]^+$. Found, %: C 45.10; H 2.53; N 52.03. $C_7H_5N_7$. Calculated, %: C 44.92; H 2.69; N 52.39. *M* 187.16.

1,2,3-Triazole-4-carboxylic acids VIIa, VIIb, and VIII (*general procedure***).** *a*. A solution of 0.3 g of metallic sodium in 5 ml of anhydrous ethanol was cooled, 0.01 mol of ethyl acetoacetate was added, and

0.01 mol of azide **IV**, **Va**, or **Vb** was slowly added on cooling with ice water. The mixture was kept for 30 min in an ice bath, slowly heated to the boiling point, and kept boiling over a period of 1 h. Hot water was added to the precipitate until it dissolved completely (15–20 ml), or a solution of NaOH was added to pH 11–12, and the mixture was heated for 10 min more at the boiling point. The hot solution was poured into 10 ml of concentrated hydrochloric acid and was left to stand for crystallization. The precipitate was filtered off, washed with a small amount of water on a filter, and recrystallized from appropriate solvent.

b. Compounds **VIIa** and **VIIb** were also obtained by treatment of the reaction mixture (after keeping for 30 min without heating) with a solution of 1.8 g (32 mmol) of KOH in 5 ml of DMSO. The mixture was kept for 3 h, diluted with water, and acidified. The products were isolated and purified according to the procedure described above in *a*.

1-[3-(Cyanoamino)phenyl]-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (VIIa). Yield 53%, mp 191–192°C. ^{1}H NMR spectrum, δ, ppm: 2.55 s (3H, CH_3), 7.12 t (1H, 5-H, J = 8.0 Hz), 7.19 d (1H, 4-H, J = 8.0 Hz), 7.79 d (1H, 6-H, J = 8.0 Hz), 8.29 s (1H, 2-H), 9.86 s (1H, NH). Mass spectrum: m/z 244 $[M + H]^+$. Found, %: C 54.20; H 3.59; N 28.63. $C_{11}H_9N_5O_2$. Calculated, %: C 54.32; H 3.73; N 28.79. M 243.22.

1-[4-(Cyanoamino)phenyl]-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (VIIb). Yield 68%, mp 211–212°C. ^{1}H NMR spectrum, δ, ppm: 2.46 s (3H, CH_3), 7.42 d (2H, 3-H, 5-H, J = 8.4 Hz), 7.64 d (2H, 2-H, 6-H, J = 8.4 Hz), 9.18 s (1H, NH). Mass spectrum: m/z 244 $[M + H]^+$. Found, %: C 54.06; H 3.61; N 28.88. $C_{11}H_9N_5O_2$. Calculated, %: C 54.32; H 3.73; N 28.79. M 243.22.

1-(4-Aminophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (VIII). Yield 83%, mp 180–181°C. ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 5.63 br.s (2H, NH_2), 6.72 d (2H, 3-H, 5-H, J = 7.6 Hz), 7.19 d (2H, 2-H, 6-H, J = 7.6 Hz). Mass spectrum: m/z 219 $[M + H]^+$. Found, %: C 54.97; H 4.51; N 25.47. $C_{10}H_{10}N_4O_2$. Calculated, %: C 55.04; H 4.62; N 25.68. M 218.22.

Triazoles IXa and IXb (*general procedure*). Cyanoacetanilide, 1.6 g (0.01 mol), and tetrazolylphenyl azide **Va** or **Vb**, 0.01 mol, were added under vigorous stirring to a solution of 0.3 g of metallic sodium in 20 ml of methanol. The mixture was stirred at room temperature until a solid precipitated, and the product was filtered off.

5-Amino-1-[3-(1*H*-tetrazol-1-yl)phenyl]-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide (IXa). Yield 73%, mp 194–195°C. ^{1}H NMR spectrum, δ, ppm: 6.67 s (2H, NH_2), 7.04 t (1H, *p*-H, J = 7.6 Hz), 7.27 t (2H, *m*-H, J = 7.6 Hz), 7.83 d (2H, *o*-H, J = 7.6 Hz), 7.75 t (1H, 5′-H, J = 8.0 Hz), 7.89 d (1H, 4′-H, J = 8.0 Hz), 8.18 d (1H, 6′-H, J = 8.0 Hz), 8.53 s (1H, 2′-H), 10.02 s (1H, NH), 10.15 s (1H, 5″-H). Mass spectrum: m/z 348 $[M + H]^+$. Found, %: C 55.10; H 3.70; N 36.05. $C_{16}H_{13}N_9O$. Calculated, %: C 55.33; H 3.77; N 36.29. M 347.34.

5-Amino-1-[4-(1*H*-tetrazol-1-yl)phenyl]-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide (IXb). Yield 89%, mp 239–240°C. ^{1}H NMR spectrum, δ, ppm: 6.69 s (2H, NH_2), 7.02 t (1H, *p*-H, J = 7.6 Hz), 7.27 t (2H, *m*-H, J = 7.6 Hz), 7.84 d (2H, *o*-H, J = 7.6 Hz), 7.91 d (2H, 3′-H, 5′-H, J = 8.4 Hz), 8.19 d (2H, 2′-H, 6′-H, J = 8.4 Hz), 10.02 s (1H, NH), 10.17 s (1H, 5″-H). Mass spectrum: m/z 348 $[M + H]^+$. Found, %: C 55.48; H 3.64; N 36.18. $C_{16}H_{13}N_9O$. Calculated, %: C 55.33; H 3.77; N 36.29. M 347.34.

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