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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 70th Anniversary

Reaction of 1-(*o*-Aminophenyl)-1,2,3-triazole-5-thiols with Cyclizing Reagents

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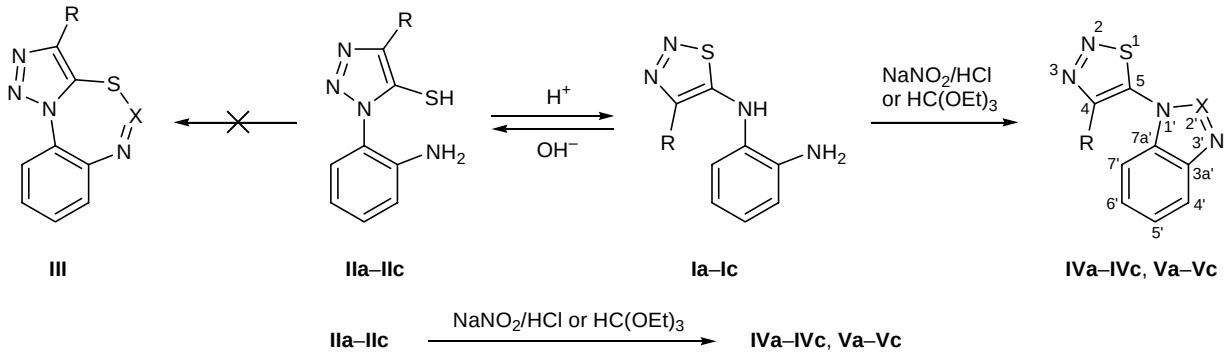
Abstract—Reactions of 1-(*o*-aminophenyl)-1,2,3-triazole-5-thiols with ring-closing reagents destabilize the triazole ring, promoting the Dimroth rearrangement and subsequent cyclization to 5-(1-benzazolyl)-1,2,3-thiadiazoles.

The ability of 1,2,3-thiadiazole and 1,2,3-triazole rings to undergo rearrangements provides a convenient tool in the synthesis of new heterocyclic systems [1]. Such rearrangements have been reported for both single rings and their combinations [2]. Especially interesting are poorly studied Dimroth rearrangements which are initiated by modification of side-chain groups [3]. Dimroth rearrangements in the series of 5-amino-1,2,3-thiadiazoles have been reported [4, 5]; they are induced by heating or variation of the acidity of the medium [4]. Reverse rearrangements of 1,2,3-triazole-5-thiols into the corresponding 5-amino-1,2,3-thiadiazoles have been studied to a considerably lesser extent. It is known that such processes occur in acid medium [4]. However, the available information on the effect of substituent in position *1* of the 1,2,3-triazole ring is clearly insufficient. In particular, no studies on the Dimroth rearrangement in the series of 1-aryl-1,2,3-triazole-5-thiols have been reported.

In the present work we examined the Dimroth rearrangement of 1-(*o*-aminophenyl)-1,2,3-triazole-5-thiols **IIa**–**IIc** by the action of nitrous acid and triethyl orthoformate. Initial triazoles **IIa**–**IIc** were synthesized by heating 5-arylamino-1,2,3-thiadiazoles **Ia**–**Ic** in ethanol in the presence of triethylamine, followed by acidification. Compounds **IIa**–**IIc** were characterized by IR, ^{1}H NMR, and mass spectra. In the ^{1}H NMR spectra of **IIa**–**IIc**, protons of the thiol and amino groups appeared as broadened singlets which can readily be distinguished from the NH signal of initial aminothiadiazoles **Ia**–**Ic** [6]. The IR spectrum of **IIa** lacked N–H absorption bands at 3430 and 3310 cm^{-1}, which were typical of compound **Ia** [6]. The mass spectra of **Ia**–**Ic** and **IIa**–**IIc** were fully identical, for the Dimroth rearrangement can occur in the gas phase while recording the spectra.

Theoretically, the presence of two highly reactive functional groups (SH and NH_2) in molecules **IIa**–**IIc** could give rise to ring closure with formation of a seven-membered ring, e.g., as in structure **III**. However, the reactions of 1-(*o*-aminophenyl)-1,2,3-triazole-5-thiols **IIa**–**IIc** with sodium nitrite in the presence of hydrochloric acid afforded 5-(1,2,3-benzotriazol-1-yl)-1,2,3-thiadiazoles **IVa**–**IVc** (Scheme 1). The structure of products **IVa**–**IVc** was proved by independent synthesis from compounds **Ia**–**Ic**. Diazotization of 5-(*o*-aminophenyl)-1,2,3-thiadiazoles **Ia**–**Ic** gave products which were fully identical to **IVa**–**IVc** in spectral parameters and physical constants. The ^{1}H NMR spectra of **IVa**–**IVc** contained signals from protons in the substituent at C^4 and aromatic protons as several multiplets in the region δ 7.42–8.46 ppm. Compounds **IVb** and **IVc** showed in the mass spectra the molecular ion peaks (no molecular ion peak was observed in the mass spectrum of **IVa**); all compounds **IVa**–**IVc** gave rise to $[M - N_2]^+$ ions typical of 1,2,3-thiadiazoles. In the ^{13}C NMR spectrum of **IVa**, signals from the C^4 and C^5 atoms of the 1,2,3-thiadiazole ring were located at δ_C 145.21 and 153.72 ppm, respectively. Their position is characteristic of 1,2,3-thiadiazoles having an electron-acceptor substituent, e.g., 1,2,3-triazole ring [2], at C^5. In the spectra of

Scheme 1.



I, **II**, **IV**, **V**, R = COOEt (**a**), CONHMe (**b**), $CONH_2$ (**c**); **IV**, X = N; **V**, X = CH.

5-sulfanyl-1,2,3-triazoles, the corresponding carbon signals appear at δ_C 138–145 (C^4) and 128–132 ppm (C^5) [2, 6].

An additional support to the assumed structure of compounds **IVa**–**IVc** was obtained from the ^{15}N NMR spectrum of **IVa**, which was recorded in DMSO-d_6 using ammonia as external reference. The following signals were observed, δ_N, ppm: 411.21 (N^2), 444.46 (N^3), 211.76 ($N^{1'}$), 380.04 ($N^{2'}$), 352.50 ($N^{3'}$). These values are very consistent with the ^{15}N NMR data for 1,2,3-thiadiazole and 1,2,3-triazole derivatives [7].

Triazole **IIa** having an ester group in position *4* turned out to be unstable in acid medium (pH < 1). According to the ^1H NMR data, it underwent partial rearrangement into the corresponding 1,2,3-thiadiazole **Ia**. By contrast, carboxamides **IIb** and **IIc** are stable even in strongly acidic medium: no respective thiadiazole **I** was detected on prolonged storage of compounds **IIb** and **IIc** in 10% hydrochloric acid at room temperature. Therefore, we believe that the Dimroth rearrangement is promoted by diazotization of the amino group rather than by change of pH. An analogous rearrangement was induced by diazotization of 5-amino-1-(*o*-aminophenyl)-1,2,3-triazoles [8].

Similar results were obtained when triethyl orthoformate was used as ring-closing agent. By heating 1,2,3-triazole-5-thiols **IIa**–**IIc** in triethyl orthoformate we obtained compounds **Va**–**Vc** (Scheme 1). The ^1H NMR spectra of **Va**–**Vc** contained signals from the substituent in position *4* of the 1,2,3-thiadiazole ring, signals from protons in the aromatic ring (a two-proton multiplet at δ 7.13–7.43 ppm and two one-proton multiplets at δ 7.42–7.63 and 7.71–7.94 ppm), and signal of the CH proton in the imidazole ring at δ 8.50 ppm. In the mass spectra of **Va**–**Vc** we observed the molecular ion peaks and strong peaks of the $[M - N_2 - CO_2Et]^+$ ions. The ^{13}C NMR spectrum of **Va** is analogous to that obtained for compound **IVa**; the spectral data are consistent with the presence of a 1,2,3-thiadiazole ring with an electron-acceptor substituent at C^5. All compounds **Va**–**Vc** were also synthesized independently, by heating 1,2,3-thiadiazoles **Ia**–**Ic** with triethyl orthoformate.

The cyclization with triethyl orthoformate occurs in neutral medium. Therefore, effect of acid which is necessarily present in the diazotization process (and is capable of initiating the Dimroth rearrangement) may be ruled out. The Dimroth rearrangement in the reaction with triethyl orthoformate could be promoted by heating. However, 1,2,3-thiadiazoles **Ia**–**Ic** were not formed when compounds **IIa**–**IIc** were heated in DMF at 140°C. Therefore, just the reaction at the aromatic amino group induces the Dimroth rearrangement.

EXPERIMENTAL

The NMR spectra were recorded on Bruker WM-250 (250 MHz) and AMX 400 (400.14 MHz) spectrometers from solutions in DMSO-d_6 containing TMS as internal reference. The IR spectra were obtained on a UR-20 spectrometer from samples pelleted with KBr. The mass spectra (electron impact) were run on a Varian MAT-311 instrument. The progress of reactions was monitored, and the purity of products was checked, by TLC on DC-Plastikfolen Kieselgel 60 F 254 plates using chloroform–ethanol (9:1) as eluent. The melting points were not corrected.

Compounds **Ia**–**Ic** were synthesized by the procedure reported in [6].

1-(*o*-Aminophenyl)-1,2,3-triazol-5-thiols IIa–IIc (*general procedure*). A mixture of 5 mmol of 5-*o*-

aminophenyl-1,2,3-thiadiazole **Ia**–**Ic** and 30 ml of triethylamine was heated for 1 h under reflux. The mixture was evaporated, the residue was dissolved in 50 ml of water, and an equivalent amount of 10% hydrochloric acid was added to the solution. The precipitate was filtered off, washed with cold water, and dried. The yields were nearly quantitative.

Ethyl 1-(*o*-aminophenyl)-5-sulfanyl-1,2,3-triazole-4-carboxylate (IIa). Yield 99%, mp 144°C. IR spectrum, ν, cm^{-1}: 2780 (CH), 1700 (C=O), 1450, 1320, 1205. ^{1}H NMR spectrum, δ, ppm: 1.41 t (3H, CH_3), 4.52 q (2H, OCH_2), 7.21–7.45 m (2H, H_{arom}), 7.51–7.62 m (2H, H_{arom}), 9.32 br.s. (2H, NH_2), 9.64 br.s (1H, SH). Found, %: C 50.14; H 4.67; N 21.34; S 12.21. $C_{11}H_{12}N_4O_2S$. Calculated, %: C 49.99; H 4.58; N 21.20; S 12.13.

***N*-Methyl-1-(*o*-aminophenyl)-5-sulfanyl-1,2,3-triazole-4-carboxamide (IIb).** Yield 99%, mp 189–191°C (decomp.). IR spectrum, ν, cm^{-1}: 3330 (NH), 2780 (CH), 1680 (C=O), 1580, 1470, 1310, 1225. ^{1}H NMR spectrum, δ, ppm: 2.82 d (3H, NHC**H**$_3$), 7.22–7.71 m (4H, CH_{arom}), 9.21 q (1H, NH), 10.22 br.s (3H, NH_2, SH). Found, %: C 48.66; H 4.58; N 27.97; S 12.65. $C_{10}H_{11}N_5OS$. Calculated, %: C 48.48; H 4.45; N 28.09; S 12.86.

1-(*o*-Aminophenyl)-5-sulfanyl-1,2,3-triazole-4-carboxamide (IIc). Yield 99%, mp 195–200°C (decomp.). IR spectrum, ν, cm^{-1}: 3320 (NH), 1680 (CO), 1575, 1460, 1310, 1215. ^{1}H NMR spectrum, δ, ppm: 7.13–7.22 m (2H, H_{arom}), 7.43–7.61 m (2H, H_{arom}), 10.00 br.s (3H, NH_2, SH). Found, %: C 46.15; H 3.76; N 28.58; S 13.49. $C_9H_9N_5OS$. Calculated, %: C 45.95; H 3.86; N 28.77; S 13.63.

5-(1,2,3-Benzotriazol-1-yl)-1,2,3-thiadiazoles IVa–IVc (*general procedure*). *a*. 5-Sulfanyl-1,2,3-triazole **IIa**–**IIc**, 3 mmol, was dispersed in 20 ml of 10% hydrochloric acid, and an equivalent amount of sodium nitrite dissolved in a minimal volume of water was added dropwise on cooling. The mixture was stirred for 1 h, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

b. 5-*o*-Aminophenyl-1,2,3-thiadiazole **Ia**–**Ic**, 3 mmol, was dispersed in 20 ml of 10% hydrochloric acid, and an equivalent amount of sodium nitrite dissolved in a minimal volume of water was added dropwise on cooling. The mixture was stirred for 1 h, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

Ethyl 5-(1,2,3-benzotriazol-1-yl)-1,2,3-thiadiazole-4-carboxylate (IVa). Yield 94% (*a*), 87% (*b*); mp 116°C. IR spectrum, ν, cm^{-1}: 2960 (CH), 1700 (C=O), 1520, 1400, 1300, 1280, 1210, 1020. ^{1}H NMR spectrum, δ, ppm: 1.00 t (3H, CH_3), 4.25 q (2H, OCH_2), 7.42–7.55 m (1H, H_{arom}), 7.63–7.72 m (2H, H_{arom}), 8.12–8.21 m (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 13.31 (CH_3), 61.95 (CH_2), 111.82 ($C^{7'}$), 119.85 ($C^{4'}$), 129.56 ($C^{5'}$), 133.48 ($C^{6'}$), 133.48 ($C^{7a'}$), 145.17 ($C^{3a'}$), 145.21 (C^4) 153.72 (C^5), 158.29 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 247(20.5), $[M - N_2]^+$, 147 (100). Found, %: C 47.85; H 3.28; N 25.36; S 11.35. $C_{11}H_9N_5O_2S$. Calculated, %: C 47.99; H 3.30; N 25.44; S 11.65.

***N*-Methyl-5-(1,2,3-benzotriazol-1-yl)-1,2,3-thiadiazole-4-carboxamide (IVb).** Yield 85% (*a*), 80% (*b*); mp 188–189°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 2940 (CH), 1670 (C=O), 1560, 1520, 1510, 1470, 1410. ^{1}H NMR spectrum, δ, ppm: 2.83 d (3H, NHC**H**$_3$), 7.51–7.84 m (3H, H_{arom}), 8.13–8.22 m (1H, H_{arom}), 9.22 q (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 260 (8.2) $[M]^+$, 232 (17.3) $[M - N_2]^+$, 135 (100). Found, %: C 46.07; H 3.06; N 32.19; S 12.24. $C_{10}H_8N_6OS$. Calculated, %: C 46.15; H 3.10; N 32.29; S 12.32.

5-(1,2,3-Benzotriazol-1-yl)-1,2,3-thiadiazole-4-carboxamide (IVc). Yield 74% (*a*), 85% (*b*); mp 185–187°C. IR spectrum, ν, cm^{-1}: 3460 (NH), 3350 (NH), 1670 (C=O), 1570, 1540, 1510, 1430, 1400, 1270, 1210, 1000. ^{1}H NMR spectrum, δ, ppm: 27.51–7.73 m (3H, H_{arom}), 8.00 br.s (1H, NH), 8.21–8.24 m (1H, H_{arom}), 8.46 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 246 (7.7) $[M]^+$, 218 (14.5) $[M - N_2]^+$, 135 (100). Found, %: C 43.97; H 2.55; N 34.24; S 13.19. $C_9H_6N_6OS$. Calculated, %: C 43.90; H 2.46; N 34.13; S 13.02.

5-(1-Benzimidazolyl)-1,2,3-thiadiazoles Va–Vc (*general procedure*). *a*. A mixture of 3 mmol of 5-sulfanyl-1,2,3-triazole **IIa–IIc** and 20 ml of triethyl orthoformate was stirred for 3 h at 140°C. The mixture was cooled, and the precipitate was filtered off, washed with diethyl ether, and recrystallized from ethanol.

b. A mixture of 3 mmol of 5-*o*-aminophenyl-1,2,3-thiadiazole **Ia–Ic** and 20 ml of triethyl orthoformate was stirred for 3 h at 140°C. The mixture was cooled, and the precipitate was filtered off, washed with diethyl ether, and recrystallized from ethanol.

Ethyl 5-(1-benzimidazolyl)-1,2,3-thiadiazole-4-carboxylate (Va). Yield 65% (*a*), 68% (*b*); mp 115–117°C. IR spectrum, ν, cm^{-1}: 2940 (CH), 1700 (C=O), 1570, 1430, 1340, 1290. ^{1}H NMR spectrum, δ, ppm:

1.22 t (3H, CH_3), 4.31 q (2H, OCH_2), 7.21–7.41 m (2H, H_{arom}), 7.45–7.57 m (1H, H_{arom}), 7.82–7.94 m (1H, H_{arom}), 8.50 s (1H, 2'-H). ^{13}C NMR spectrum, δ_C, ppm: 13.55 (CH_3), 61.74 (CH_2), 110.70 ($C^{7'}$), 120.04 ($C^{4'}$), 123.71 ($C^{5'}$), 124.4 ($C^{6'}$), 134.26 ($C^{7a'}$), 143.29 (C^4), 144.61 (C^2), 145.21 (C^4) 145.41 (C^5), 158.64 (CO). Mass spectrum, *m*/*z* (I_{rel}, %): 274 (47.4) $[M]^+$, 174 (100) $[M - N_2 - CO_2Et]^+$, 129 (48.8). Found, %: C 52.58; H 3.69; N 20.38; S 11.38. $C_{12}H_{10}N_4O_2S$. Calculated, %: C 52.55; H 3.67; N 20.43; S 11.69.

***N*-Methyl-5-(1-benzimidazolyl)-1,2,3-thiadiazole-4-carboxamide (Vb).** Yield 66% (*a*), 74% (*b*); mp 186–188°C. IR spectrum, ν, cm^{-1}: 3350 (NH), 2990 (CH), 1640 (C=O), 1520, 1480, 1440. ^1H NMR spectrum, δ, ppm: 2.85 d (3H, NHC**H**$_3$), 7.13–7.31 m (2H, H_{arom}), 7.42–7.53 m (1H, H_{arom}), 7.71–7.88 m (1H, H_{arom}), 8.50 s (1H, 2'-H), 9.00 q (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 259 (81.3) $[M]^+$, 174 (100) $[M - N_2 - CO_2Et]^+$, 130 (37.1). Found, %: C 50.95; H 3.45; N 27.10; S 12.25. $C_{11}H_9N_5OS$. Calculated, %: C 50.96; H 3.50; N 27.01; S 12.37.

5-(1-Benzimidazolyl)-1,2,3-thiadiazole-4-carboxamide (Vc). Yield 74% (*a*), 81% (*b*), mp 229–231°C. IR spectrum, ν, cm^{-1}: 3450 (NH), 3350 (NH), 2990 (CH), 1640 (C=O), 1570, 1520, 1410, 1400. ^1H NMR spectrum, δ, ppm: 7.21–7.43 m (2H, H_{arom}), 7.51–7.63 m (1H, H_{arom}), 7.71–7.85 m (1H, H_{arom}), 7.94 br.s (1H, NH), 8.32 br.s (1H, NH), 8.50 s (1H, 2'-H). Mass spectrum, *m*/*z* (I_{rel}, %): 245 (100) $[M]^+$, 174 (87.1) $[M - N_2 - CO_2Et]^+$, 129 (48.2). Found, %: C 48.89; H 2.89; N 28.36; S 13.18. $C_{10}H_7N_5OS$. Calculated, %: C 48.97; H 2.88; N 28.55; S 13.07.

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