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ONE-POT ASSEMBLY OF 3,5-BIS(1*H*-PYRROL-2-YL)-4*H*-1,2,4-TRIAZOL-4-AMINES FROM PYRROLECARBONITRILES AND HYDRAZINE

The reaction of pyrrole-2-carbonitriles with hydrazine hydrate in the presence of hydrazine dihydrochloride (ethylene glycol, 130–132°C, 1–2 h, argon atmosphere) affords hitherto unknown 3,5-bis(1*H*-pyrrol-2-yl)-4*H*-1,2,4-triazol-4-amines in up to 86% yield.

Keywords: 3,5-bis(1*H*-pyrrol-2-yl)-4*H*-1,2,4-triazole-4-amines, hydrazine hydrate, 1*H*-pyrrole-2-carbonitriles.

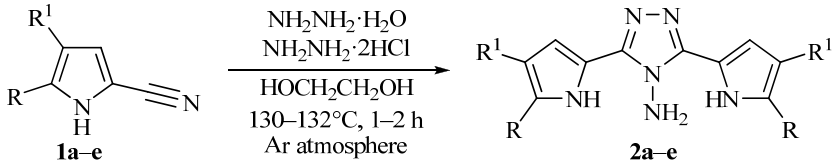
1,2,4-Triazole is known to be a structural unit of diverse pharmaceuticals (Ribavirin, Fluconazole, Triazolam) [1]. Its derivatives exhibit antifungal [2], antimicrobial [3], anti-inflammatory [4], and anticancer [5] activities. Triazoles are widely used in the synthesis of coordination polymers and supramolecules [6, 7] possessing magnetic [8], luminescent [9], and thermochromic [10] properties. 1,2,4-Triazoles substituted at the position 3 or/and 5 by heterocyclic fragments (pyridine, pyrazine, pyrimidine) show the features of multidentate chelating agents [11–13].

The reaction of hydrazine or substituted hydrazines with suitable nitrogen-containing electrophiles is the most common method for the preparation of the triazoles [1]. To synthesize asymmetrically substitutes triazoles, the reactions of hydrazine and its derivatives with acylhydrazides are generally employed [5, 14–17], while 3,5-symmetrically substituted triazoles are obtained *via* the interaction of hydrazine with carbonitriles [18–21].

To the best of our knowledge, the literature lacks the data on the reaction of pyrrolecarbonitriles with hydrazine and 3,5-bispyrrolyl-1,2,4-triazol-4-amines remain also unknown.

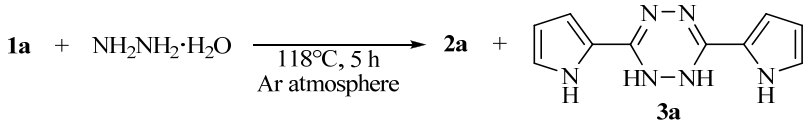
At the same time, the pyrrole structures are frequently met in many biologically and pharmaceutically important compounds [22–24]. Also, they are precursors of optoelectronic materials [25], synthetic metals [26], and sensors [27]. Recently developed convenient method for pyrrole formylation using oxalyl chloride [28] has increases the accessibility of pyrrole-2-carbaldehydes and, hence, pyrrole-2-carbonitriles [29] (prepared therefrom), potential precursors of pyrrole-triazole ensembles.

In the present work, we report on the synthesis of previously unknown 3,5-bis-(1*H*-pyrrol-2-yl)-4*H*-1,2,4-triazole-4-amines **2a**–**e**. The reaction proceeds under heating of equimolar mixture of pyrrole-2-carbonitriles **1a**–**e** and hydrazine dihydrochloride with excess of hydrazine hydrate (4 equivalents per 1 equivalent of nitrile **1a**–**e**) in ethylene glycol (argon atmosphere, 130–132°C, 1–2 h), the yields of aminotriazoles **2a**–**e** are 51–86%. The conditions found allow the reaction to be directed towards selective formation of triazoles **2a**–**e**.



a R = R^1 = H; **b** R = R^1 = Me; **c** R + R^1 = $(CH_2)_4$; **d** R = Ph, R^1 = H; **e** R = 2-thienyl, R^1 = H

Preliminary experiments have shown that the reaction of nitrile **1a** with excess of hydrazine hydrate (6 equivalents per 1 equivalent of carbonitrile **1a**) in ethanol (argon atmosphere, 78°C, 5 h) furnishes a mixture of triazole **2a** and 3,6-bis(pyrrol-2-yl)-1,2-dihydro-1,2,4,5-tetrazine (**3a**) in total yield 64% (the ratio of **2a**:**3a** ≈ 1:2, according to ^{1}H NMR spectral data). Heating nitrile **1a** with hydrazine hydrate (argon atmosphere, 118°C, 5 h) under reflux, the ratio of **2a**:**3a** becomes ≈ 2:1 and total yield reaches 75%.



Structure of compounds **2a** and **3a** have been established using ^{1}H NMR spectral data (DMSO-d_6). Chemical shifts of the NH protons of the pyrrole ring and the amino group for compound **2a** are observed at 11.62 and 6.18 ppm, respectively. The values of chemical shift of the NH protons of the pyrrole ring (11.10 ppm) and the dihydrotetrazine cycle (8.44 ppm) for compound **3a** are in agreement with literature data [30].

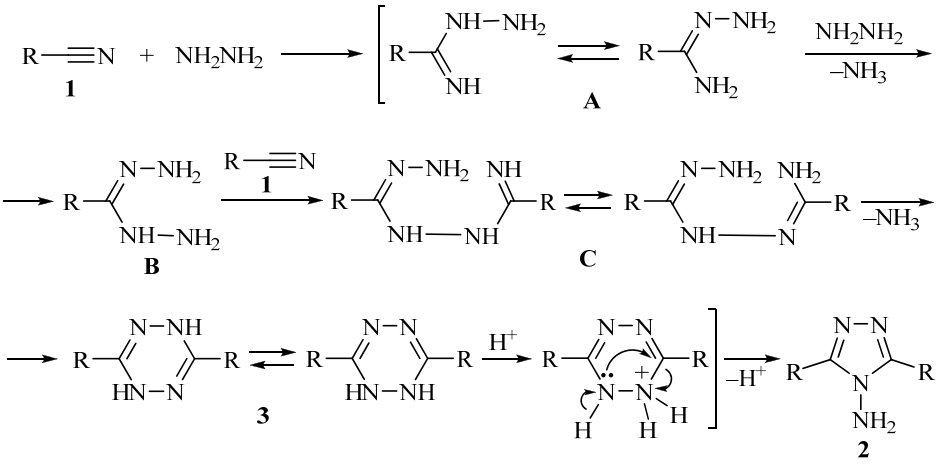
Thus, the increase of the reaction temperature leads to growth of the target products total yield, triazole **2a** being formed predominantly. However, these conditions are not applicable for pyrrolecarbonitriles **1b**–**e** due to the poor solubility of the latter even in boiling hydrazine hydrate. Therefore, for homogenization purpose, ethylene glycol has been introduced in the reaction mixture that has allowed the reaction temperature to be increased up to 130–132°C.

Carbonitriles are known to react with hydrazine to give 1,2-dihydro-1,2,4,5-tetrazines which rearrange at elevated temperatures or on treatment with acid to the corresponding 1,2,4-triazol-4-amines [19–21]. In some case, hydrazine dihydrochloride is used as a proton source promoting this rearrangement [21].

We have employed this protocol, but the content of hydrazine hydrate has been increased up to 4 equivalents (per 1 equivalent of carbonitrile **1a**–**e**). This ensures the augmentation of the target triazoles **2a**–**e** yield by 5–8% as compared to the experiment, where 3 equivalents of hydrazine hydrate have been used (3–5 h), the reaction time being simultaneously reduced to 1–2 h.

The structure of triazoles **2a**–**e** has been unambiguously assigned by ^{1}H, ^{13}C, ^{15}N and 2D NMR spectroscopy. For instance, the 2D NOESY spectrum of compound **2e** shows cross peak between pyrrolic H-4 proton (6.46 ppm) and thienyl H-3 proton (7.59 ppm), as well as between pyrrolic NH proton (12.05 ppm) and NH proton of amino group (6.23 ppm).

A tentative mechanism of triazoles **2** formation is depicted on the next page. Amidrazone **A**, formed on the first stage of the assembly, reacts with second molecule of hydrazine abstracting the ammonium molecule to form carbohydrazonohydrazide **B**. The latter adds to the second molecule of carbonitrile **1** to deliver intermediate **C** which further cyclizes (abstracting the ammonium molecule) to dihydrotetrazine **3**. Acidic-catalytic rearrangement of dihydrotetrazine **3** leads to triazoles **2** [21].



In conclusion, 3,5-bis(1*H*-pyrrol-2-yl)-4*H*-1,2,4-triazole-4-amines, promising ligands, metallocomplex and supramolecule components, monomers of electroconducting polymers, have been synthesized for the first time in good yield by the reaction of pyrrole-2-carbonitriles with hydrazine. The presence of the amino group in 4*H*-1,2,4-triazol-4-amines is a prerequisite of their further modification (preparation of Schiff's bases, diazoderivatives [5, 18, 31]) that even more expands the synthetic potential of the compounds obtained.

EXPERIMENTAL

The IR spectra were recorded on a Bruker IFS25 spectrophotometer from samples prepared as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400 and 100 MHz respectively) in DMSO-d_6 using HMDSO as an external standard. The ^{15}N NMR spectra were recorded at 40 MHz, external standard $MeNO_2$. The assignments of ^{1}H, ^{13}C and ^{15}N NMR spectra were performed by COSY, NOESY, HSQC, and HMBC experiments. Elemental analyses were performed on a Flash EA 1112. Melting points were determined on a Micro-Hot-Stage PolyTherm A.

Hydrazine dihydrochloride is commercially available and was used without any additional purification. Hydrazine monohydrate, ethylene glycol and ethanol were purified by standard procedures prior to use. Pyrrole-2-carbonitriles **1a–e** were obtained according to literature methods [29, 32] and their NMR data corresponds to those given in [33, 34].

Synthesis of triazoles 2a–e (General Method). A mixture of the corresponding pyrrole-2-carbonitrile **1a–e** (2 mmol), hydrazine dihydrochloride (0.210 g, 2 mmol), hydrazine monohydrate (0.400 g, 8 mmol) and ethylene glycol (5 ml) was stirred under argon atmosphere at 130–132°C for 1 h (in the case of compound **2b** – for 2 h). The reaction mixture was cooled, diluted with water (10 ml), the precipitate was filtered off and recrystallized from EtOH–H_2O (1:1).

3,5-Bis(1*H*-pyrrol-2-yl)-4*H*-1,2,4-triazol-4-amine (2a). Yield 0.178 g (83%), colourless crystals, mp 292–294°C (decomp.). IR spectrum, ν, cm^{-1}: 3346, 3214, 3105, 1633, 1595, 1499, 1399, 1265, 1154, 1142, 1125, 1092, 1045, 1030, 916, 883, 829, 737, 605. ^{1}H NMR spectrum, δ, ppm: 6.18 (2H, s, NH_2); 6.20–6.23 (2H, m, H-4 Pyr); 6.95–6.98 (4H, m, H-3,5 Pyr); 11.62 (2H, s, NH Pyr). ^{13}C NMR spectrum, δ, ppm: 108.6 (C-4 Pyr); 109.3 (C-3 Pyr); 118.3 (C-2 Pyr); 120.4 (C-5 Pyr); 148.5 (C-3,5 Tr). ^{15}N NMR spectrum, δ, ppm: –85.0 (sp^2-N); –205.7 (sp^3-N Tr); –218.8 (NH Pyr); –307.0 (NH_2). Found, %: C 56.32; H 4.68; N 39.12. $C_{10}H_{10}N_6$. Calculated, %: C 56.07; H 4.71; N 39.23.

3,5-Bis(4,5-dimethyl-1*H*-pyrrol-2-yl)-4*H*-1,2,4-triazol-4-amine (2b). Yield 0.137 g (51%), colourless crystals, mp 280–282°C (decomp.). IR spectrum, ν, cm^{-1}: 3364, 3269, 3106, 2918, 2858, 1619, 1539, 1492, 1361, 1285, 1159, 956, 957, 803, 711. ^{1}H NMR

spectrum, δ, ppm (*J*, Hz): 1.98 (6H, s, 4',4"-CH_3); 2.15 (6H, s, 5',5"-CH_3); 5.98 (2H, s, NH_2); 6.70 (2H, d, ^4J = 1.9, H-3 Pyr); 11.10 (2H, s, NH Pyr). ^{13}C NMR spectrum, δ, ppm: 10.5 (CH_3); 10.8 (CH_3); 110.7 (C-3 Pyr); 114.1 (C-4 Pyr); 115.5 (C-5 Pyr); 126.5 (C-2 Pyr); 148.2 (C-3,5 Tr). ^{15}N NMR spectrum, δ, ppm: –81.0 (sp^2-N); –216.1 (sp^3-N Tr); –226.5 (NH Pyr); –315.6 (NH_2). Found, %: C 62.43; H 6.71; N 30.88. $C_{14}H_{18}N_6$. Calculated, %: C 62.20; H 6.71; N 31.09.

3,5-Bis(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-4*H*-1,2,4-triazol-4-amine (2c). Yield 0.250 g (78%), beige crystals, mp 254–258°C (decomp.). IR spectrum, ν, cm^{-1}: 3342, 3267, 3105, 2925, 2849, 1618, 1545, 1444, 1357, 1266, 1132, 1058, 957, 801, 711. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70–1.72 (8H, m, 5',5",6',6"-CH_2); 2.45–2.47 (4H, m, 4',4"-CH_2); 2.55–2.57 (4H, m, 7',7"-CH_2); 5.98 (2H, s, NH_2); 6.65 (2H, d, ^4J = 2.2, H-3 Ind); 11.02 (2H, s, NH Ind). ^{13}C NMR spectrum, δ, ppm: 22.4, 22.6, 22.9, 23.4 (CH_2); 108.1 (C-3 Ind); 116.3 (C-2 Ind); 116.7 (C-3a Ind); 129.3 (C-7a Ind); 148.4 (C-3,5 Tr). ^{15}N NMR spectrum, δ, ppm: –87.7 (sp^2-N); –215.5 (sp^3-N Tr); –230.9 (NH Ind); –315.6 (NH_2). Found, %: C 67.26; H 6.68; N 26.11. $C_{18}H_{22}N_6$. Calculated, %: C 67.06; H 6.88; N 26.07.

3,5-Bis(5-phenyl-1*H*-pyrrol-2-yl)-4*H*-1,2,4-triazol-4-amine (2d). Yield 0.304 g (83%), light green crystals, mp 278–280°C (decomp.). IR spectrum, ν, cm^{-1}: 3411, 3323, 3253, 1623, 1604, 1541, 1494, 1301, 1238, 1194, 1061, 964, 753, 709. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.26 (2H, s, NH_2); 6.71 (2H, dd, ^3J = 3.6, ^4J = 2.2, H-4 Pyr); 7.05 (2H, dd, ^3J = 3.6, ^4J = 2.1, H-3 Pyr); 7.22–7.84 (10H, m, H Ph); 11.87 (2H, s, NH Pyr). ^{13}C NMR spectrum, δ, ppm: 107.2 (C-4 Pyr); 111.4 (C-3 Pyr); 119.8 (C-2 Pyr); 124.3, 126.3, 128.6, 132.0 (C Ph); 133.8 (C-5 Pyr); 148.3 (C-3,5 Tr). ^{15}N NMR spectrum, δ, ppm: –80.4 (sp^2-N); –212.4 (sp^3-N Tr); –232.1 (NH Pyr); –314.3 (NH_2). Found, %: C 72.02; H 4.86; N 22.62. $C_{22}H_{18}N_6$. Calculated, %: C 72.11; H 4.95; N 22.93.

3,5-Bis[5-(2-thienyl)-1*H*-pyrrol-2-yl]-4*H*-1,2,4-triazol-4-amine (2e). Yield 0.325 g (86%), light brown crystals, mp 272–274°C (decomp.). IR spectrum, ν, cm^{-1}: 3382, 3315, 3202, 1627, 1592, 1557, 1506, 1438, 1378, 1293, 1180, 1051, 844, 774, 685. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.23 (2H, s, NH_2); 6.46 (2H, dd, ^3J = 3.7, ^4J = 2.4, H-4 Pyr); 7.02 (2H, dd, ^3J = 3.7, ^4J = 2.2, H-3 Pyr); 7.06 (2H, dd, ^3J = 3.4, ^3J = 5.1, H-4 Th); 7.39 (2H, dd, ^3J = 5.1, ^4J = 1.2, H-5 Th); 7.59 (2H, dd, ^3J = 3.4, ^4J = 1.2, H-3 Th); 12.05 (2H, s, NH Pyr). ^{13}C NMR spectrum, δ, ppm: 107.4 (C-4 Pyr); 111.2 (C-3 Pyr); 119.3 (C-2 Pyr); 122.4 (C-3 Th); 123.5 (C-5 Th); 127.9 (C-4 Th); 128.6 (C-5 Pyr); 135.3 (C-2 Th); 148.3 (C-3,5 Tr). ^{15}N NMR spectrum, δ, ppm: –80.4 (sp^2-N); –212.4 (sp^3-N Tr); –230.9 (NH Pyr); –314.9 (NH_2). Found, %: C 57.02; H 3.70; N 21.95; S 16.86. $C_{18}H_{14}N_6S_2$. Calculated, %: C 57.12; H 3.73; N 22.20; S 16.94.

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