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Synthesis of 1,2,4-Triazolo[1,5-*d*][1,2,4]triazine-2-amines by Thermolysis of 1*H*-Tetrazol-5-amine with 1,2,4-Triazine-5-carbonitriles

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Abstract—A novel method for the synthesis of 1,2,4-triazolo[1,5-*d*][1,2,4]triazine-2-amines by solvent-free thermolysis of the 1*H*-tetrazole-5-amine in presence of the 1,2,4-triazine-5-carbonitriles has been proposed. A mechanism of found interaction has been suggested.

Keywords: 1,2,4-triazine-5-carbonitriles, 1*H*-tetrazole-5-amine, 1,2,4-triazolo[1,5-*d*][1,2,4]triazines, solvent-free reaction, reaction mechanism

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INTRODUCTION

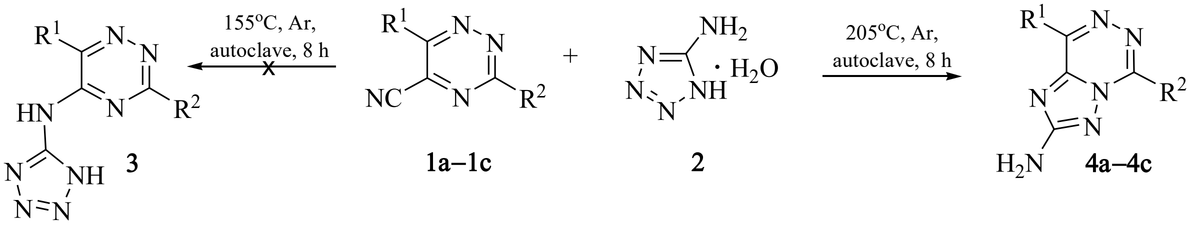
ipso-Substitution of the cyano group at the C^5 position is an effective method for the functionalization of 1,2,4-triazine. In particular, compounds with residues of alcohols [1, 2], amines [3], carboranes [4], etc. can be obtained in this way. These processes can also be carried out in the absence of a solvent, which is important for reducing the reaction *E*-factor. It should be especially noted that the substitution of the cyano group with aromatic amine residues occurs only in this variant [5]. Previously, various anilines [5], as well as derivatives of thiophene [6], pyrazole [7], 1,3,4-thiadiazole [8], 1,2,4-triazole [9], etc., were successfully used in such interactions.

In this work, we studied the possibilities of using 1*H*-tetrazol-5-amine in interaction with 1,2,4-triazine-5-carbonitriles.

RESULTS AND DISCUSSION

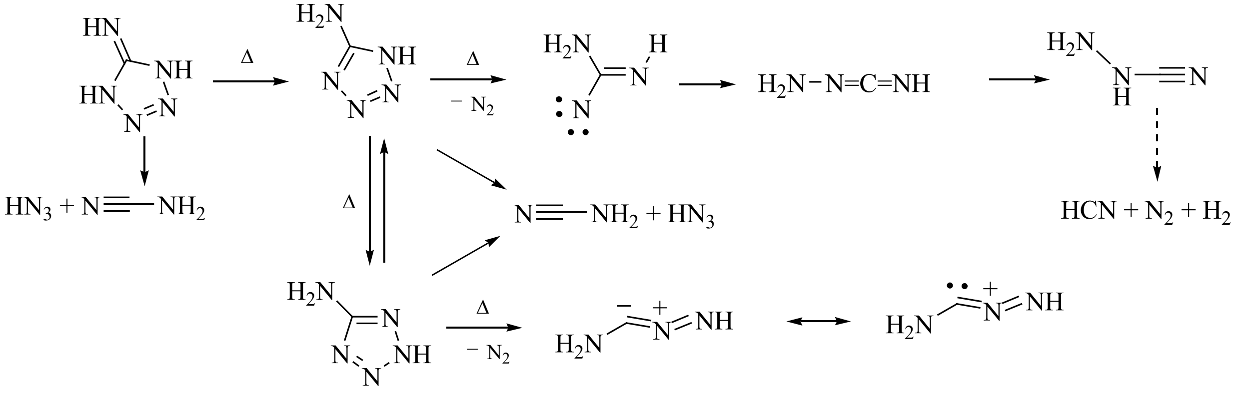
To date, there are a limited number of cases in the literature of introducing tetrazole residues into the 1,2,4-triazine ring. Thus, examples of reactions of nucleophilic substitution of hydrogen or a methylsulfanyl group to a 1*H*-tetrazol-5-amine residue [10], as well as a

Scheme 1.



R^1 = 4-$CH_3C_6H_4$ (**a**), Ph (**b**, **c**); R^2 = 4-$CH_3C_6H_4$ (**a**), Ph (**b**), 2-thienyl (**c**).

Scheme 2.



chlorine atom to an unsubstituted tetrazole, are described [11]. In this work, the interaction of 1,2,4-triazine-5-carbonitriles **1**, described previously [3, 12], with 1*H*-tetrazol-5-amine (Scheme 1) was studied for the first time.

During the experiments, it was found that carrying out the reaction under previously used conditions [5], namely at 150–160°C in an argon atmosphere in the absence of a solvent, incl. in an autoclave, does not lead to the formation of the expected products of *ipso*-substitution of the C^5-cyano group to an aminotetrazole residue, namely compounds **3**, and only the original substrates **1** and **2** were found in the reaction mixture. By increasing the reaction temperature to 205°C, we were able to obtain products that were isolated by column chromatography. However, ^1H, ^{13}C NMR spectra and mass spectrometry data did not confirm their expected structure **3**. Thus, in the ^1H NMR spectrum, in addition to the signals of the protons of two (hetero)aromatic substituents of 1,2,4-triazine, there is a broadened singlet in the region of 4.96–5.04 ppm, which may correspond to the resonance of the protons of the primary amino group. The final determination of their structure was carried out by X-ray diffraction analysis of product **4a**, which turned out to be 5,8-di-*p*-tolyl-1,2,4-triazolo[1,5-*d*][1,2,4]-triazine-2-amine (Fig. 1).

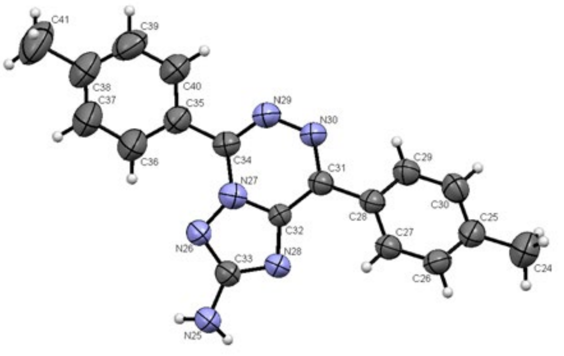


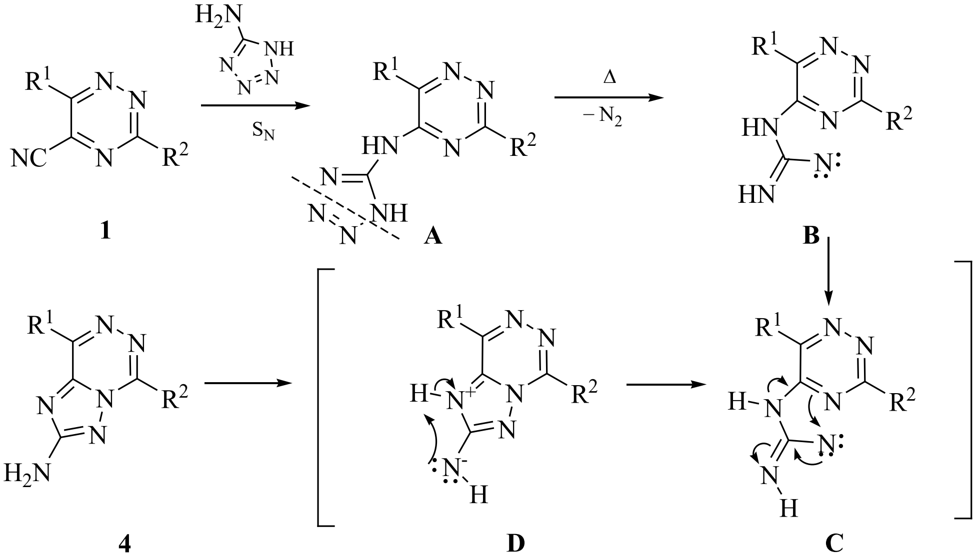
Fig. 1. Structure of compound **4a** according to X-ray diffraction data.

It should be noted that, according to literature data, at room temperature 5-aminotetrazole exists in an imino form [13], which, when heated, transforms into one of two isomeric (1*H*- and 2*H*-) amino forms with an increase in the proportion of 2*H*-amino form with the growth of temperature and pressure. With further heating of 5-aminotetrazole above the melting point (201–205°C), its thermal decomposition occurs [13–15] (Scheme 2).

Based on the presented data, the mechanism of the detected transformation has been proposed (Scheme 3). The mechanism includes at the initial stage the expected nucleophilic substitution of the cyano group in triazine **1** under the action of aminotetrazole with the formation of intermediate **A**, then the thermal decomposition of the tetrazole ring occurs with the loss of a nitrogen molecule and the formation of nitrene-containing intermediate **B** [14], which as a result of an electrocyclic reaction involving π-electrons of the C^5–N^4 bond of triazine (**C**) is transformed into cyclic intermediate **D**, which turns into product **4** after proton migration.

The literature analysis showed that similar transformations are known for various 5-substituted tetrazoles, including 5-aminotetrazoles. Thus, for 1-(2-pyrimidyl)-5-aryl-1*H*-tetrazoles, the possibility of their transformation into 2-aryl-1,2,4-triazolo[1,5-*a*]pyrimidines at a temperature of 180–190°C was shown [16], and also described the preparation of triazolopyrimidines

Scheme 3.



and triazopyrazines by fusing *N*-hetaryl-substituted 1*H*-tetrazol-5-amines [17].

It should also be noted that products **4** are promising representatives of an azoloazines series that exhibit various types of biological activity [18, 19].

CONCLUSIONS

Thus, we have found a new one-step method for the preparation of 1,2,4-triazolo[1,5-*d*][1,2,4]-triazin-2-amine derivatives by thermolysis of readily available 1,2,4-triazine-5-carbonitriles and 1*H*-tetrazol-5-amine. The structure of the resulting product was confirmed by X-ray diffraction data. An estimated reaction mechanism has been proposed.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-400 (400 MHz) and Bruker Avance-500 (500 MHz) spectrometers, internal standard—$SiMe_4$. Mass spectra (ionization type—electrospray) were recorded on a MicrOTOF-Q II Bruker Daltonics device (Germany). Elemental analysis was performed on a CHN analyzer PE 2400 II PerkinElmer (USA).

X-ray diffraction studies were carried out using the equipment of the Shared Use Center "Testing Center of Nanotechnology and Advanced Materials" of the Institute of Metal Physics UB RAS. The experiment was carried out on an automatic X-ray diffractometer with a CCD detector Rigaku XtaLAB Synergy-S (Rigaku Oxford Diffraction, Japan) according to the standard procedure [MoK_α radiation, graphite monochromator, ω-scanning with a step of 1° at $T = 295(2)$ K]. An empirical correction for absorption has been introduced. The solution and refinement of the structures was carried out using the Olex2 software package [20]. The structures were solved using the eigenphase method in the ShelXT program and refined in the ShelXL program using the full-matrix least squares method for non-hydrogen atoms [21]. Hydrogen atoms are placed in geometrically calculated positions and refined in an isotropic approximation in the *riding* model.

The starting 1,2,4-triazine-5-carbonitriles **1** were obtained according to a previously described method [3, 12]. All other reagents are commercially available.

General procedure for the synthesis of compounds 4a–4c. 1,2,4-Triazine-5-carbonitrile **1** (100 mg, 0.35 mmol) and 1*H*-tetrazol-5-amine monohydrate **2** (43.3 mg, 0.42 mmol) were placed in an autoclave flask. The reaction was carried out at 205°C for 8 h in an argon atmosphere. The products were isolated from the resulting mixture by column chromatography (eluent 5% ethyl acetate in chloroform, R_f 0.7)

5,8-Di-4-tolyl-1,2,4-triazolo[1,5-*d*][1,2,4]triazine-2-amine (4a). Yield 45 mg (0.14 mmol, 41%), beige powder, mp ~203°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.45 s (3H, CH_3), 2.47 s (3H, CH_3), 4.96 br. s (2H, NH_2), 7.36–7.42 m (4H, $C_6H_4CH_3$), 8.48–8.53 m (2H, $C_6\underline{H}_4CH_3$), 8.57–8.61 m (2H, $C_6\underline{H}_4CH_3$). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.6, 21.7, 126.5, 128.8, 129.3, 129.5, 129.9, 141.5, 142.7, 144.8, 146.1, 147.9, 165.8. Mass spectrum, m/z (I_{rel}, %): 317.151 $[M + H]^+$. XRD crystallographic data for compound **4a** are registered in the Cambridge Structural Database (CCDC 2304768). Monoclinic crystals, M 316.37, space group $P2_1/c$, unit cell parameters at 293(2) K: a 11.9991(5) Å, b 12.6752(4) Å, c 10.6497(4) Å, β 97.146(4)°, V 1607.14(11) Å^3, Z 4, d_{calc} 1.291 g/cm^3, F(000) 652.0, μ 0.081 mm^{-1}, $3.420 \geq 2\theta \leq 59.144$. Number of measured reflections 21498. Number of independent reflections (R_{int}) 3895 (0.0457). Number of reflections with $I > 2\sigma(I)$ 2007. Number of specified parameters 221. R_1 $[I > 2\sigma(I)]$ 0.0537, wR_2 (all data) 0.1721. GOF on F^2 0.985. Peaks of maximum and minimum residual electron density 0.225/–0.187.

5,8-Diphenyl-1,2,4-triazolo[1,5-*d*][1,2,4]-triazine-2-amine (4b). Yield 39 mg (0.14 mmol, 35%), beige powder, mp ~215°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.01 br. s (2H, NH_2), 7.55–7.65 m (6H, Ph), 8.59–8.63 m (2H, Ph), 8.67–8.71 m (2H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 128.6, 128.8, 128.9, 129.3, 130.1, 131.2, 132.1, 132.7, 144.9, 146.2, 148.2, 166.0. Mass spectrum, m/z (I_{rel}, %): 289.120 (100) $[M + H]^+$.

5-(Thien-2-yl)-8-phenyl-1,2,4-triazolo[1,5-*d*]-[1,2,4]triazine-2-amine (4c). Yield 47 mg (0.16 mmol, 42%), light yellow powder, mp ~195°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.04 br. s (2H, NH_2), 7.27–7.30 m (1H, thiophene), 7.52–7.59 m (3H, Ph), 7.72–7.74 m (1H, thiophene), 8.66–8.70 m (2H, Ph), 8.78–8.80 m (1H, thiophene). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 128.4, 128.7, 128.8, 131.0, 131.6, 132.8, 133.1, 134.1, 142.5, 144.4, 147.0, 166.0. Mass spectrum, m/z (I_{rel}, %): 295.076 (100) $[M + H]^+$.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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