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SYNTHESIS OF NEW FUNCTIONALLY SUBSTITUTED 1-R-TETRAZOLES AND THEIR 5-AMINO DERIVATIVES

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It has been shown that amino derivatives of sulfanilamide, and also some functionally substituted primary arylamines and cycloalkylamines, undergo heterocyclization with triethyl orthoformate and sodium azide with the formation of 1-monosubstituted tetrazoles. Primary amines of the azole series, 5-aminotetrazole, 5-amino-1-methyltetrazole, 4-amino-1,2,4-triazole, and also less basic arylamines (4-fluoro-3-nitroaniline, 2,6-dibromo-4-nitroaniline) did not react. An efficient method of introducing an amino group into position $C_{(5)}$ of the tetrazole ring of 1-aryltetrazoles is proposed, based on alkaline decomposition of the tetrazole ring and heterocyclization of the resulting N-arylcyanamides on interaction with ammonium azide generated in situ.

Keywords: 1-R-5-aminotetrazoles, N-arylcyanamides, 1-R-tetrazoles.

C- and N-tetrazolyl groups enter into the composition of a series of biologically active compounds, many of which are used in medicinal practice [1, 2]. This is linked primarily with the unique structure of the tetrazole ring which, depending on the location of substituents, may be a bioisostere of a carboxyl or an amide grouping, possessing several advantages over them [2, 3]. One of the most preferred routes for making a 1-monosubstituted tetrazole ring is the heterocyclization of primary amines with triethyl orthoformate and sodium azide [3]. This process is used for the synthesis of tetrazoles, starting from primary amines of various nature, including aliphatic, aromatic, and heterocyclic [4-9]. It was shown that the reaction proceeds smoothly with the participation of only the simplest alkyl and aryl amines. It was discovered that 2,4-dinitroaniline does not react [7], and in the case of *ortho*-phenylenediamine the process stops at the stage of forming benzimidazole, the condensation product of triethyl orthoformate with the initial amine [6]. Under analogous conditions thiosemicarbazide forms a 2-aminothiadiazole [7]. Conversion products of several other compounds with a primary amino group, including hydrazine, phenylhydrazine, melamine, and aminoguanidine, failed to be identified [7]. The behavior of other functionally substituted primary amines has not been studied up to the present time, in spite of the obvious effect of the nature of the substituent on the course of the heterocyclization reaction.

In the development of these investigations and with the aim of broadening the preparative possibilities of this reaction, the heterocyclization of some alkyl-, aryl-, and hetarylamines has been studied in this work. These include substances of a series of widely known pharmaceutical preparations possessing antibacterial and antiviral action, comprising sulfanilamide, sulfaethidole, sulfadimidine, rimantadine, etc. It was discovered that primary amines **1** react with sodium azide and triethyl orthoformate in acetic acid at a molar ratio of reactants of 1:1.1:3, forming the corresponding 1-monosubstituted tetrazoles **2**.

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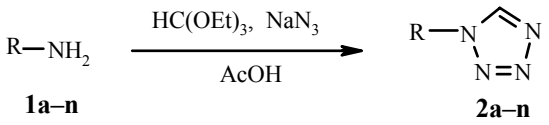
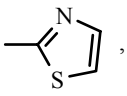
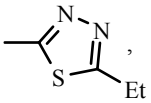
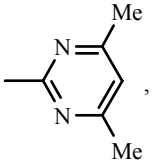
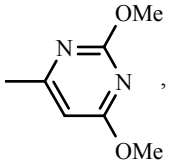
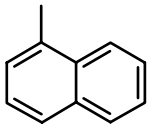


1a–n **2a–n**

1, 2 a–e R = 4-$C_6H_4SO_2NHX$; **a** X = H, **b** X =  , **c** X =  ,

d X =  , **e** X =  , **f** R =  ,

g R = 1-Ad, **h** R = 1-AdCH(Me), **i** R = *cyclo*-C_3H_5, **j** R = $PhCH_2CH_2$, **k** R = 4-F-3-ClC_6H_3,
l R = 4-I-2-MeC_6H_3, **m** R = 4-C_6H_4COOH, **n** R = 4-(4-$O_2NC_6H_4$)C_6H_4

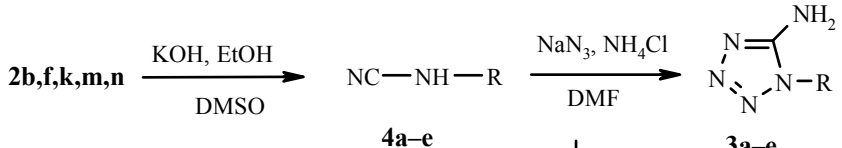
Their functional groups are not affected in this way. High yields of the desired tetrazoles were achieved by heating the reaction mixture at 80-95°C for 4-5 h (Table 1).

It was established that 4-fluoro-3-nitroaniline and 2,6-dibromo-4-nitroaniline do not react under analogous conditions. Probably the low basicity of these amines impedes their interaction with triethyl orthoformate, the initial stage of heterocyclization [11]. It is also possible to explain in an analogous manner the fact that the primary amines of the azole series, *viz*. 5-aminotetrazole, 5-amino-1-methyltetrazole, and 4-amino-1,2,4-triazole also do not react under the studied conditions. In all cases the initial amines or their hydrochlorides were isolated from the reaction medium.

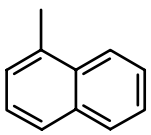
The synthesized 1-R-tetrazoles are of interest not only as subjects for investigation of their biological activity but also as synthons for obtaining other functional derivatives of tetrazole. It is known that certain 5-amino-1-aryltetrazoles possess anti-inflammatory, myorelaxant, antiulcer, analgesic, and other biological activities [12]. However the possibilities of their practical application are substantially limited by a series of synthetic complications, the unavailability of the initial raw material, low yields of products, and dangerously explosive reactants [13-18].

As we have shown, compounds of this series, particularly tetrazoles **3a-e**, may readily be obtained by the recyclization of 1-aryltetrazoles **2**, by alkaline decomposition of the tetrazole and subsequent azidification of the intermediate N-arylcyanamides **4**. We note the high yields of the desired products achieved at each stage of the process (Table 1). In addition, the proposed route of introducing an amino group into position $C_{(5)}$ of 1-aryltetrazoles is significantly simpler experimentally compared with that described previously in [17].

It is extremely important that 5-amino-1-aryltetrazoles **3a-e** are obtained as the sole products on interacting the appropriate cyanamide with an excess of sodium azide, formed *in situ* from sodium azide and ammonium chloride. N-(5-Tetrazolyl)anilines, which may be formed as by-products, were not detected. The results of [13, 17] are thereby confirmed, indicating the regioselectivity of cyclization of guanidinium azides, formed as intermediates in the course of the reaction by addition of azide ion to the nitrile group of the cyanamide.



4a–e **3a–e**

3,4 a R = 4-$C_6H_4SO_2NH$  , **b** R =  ,

c R = 4-F-3-ClC_6H_3, **d** R= 4-C_6H_4COOH, **e** R = 4-(4-$O_2NC_6H_4$)C_6H_4

TABLE 1. Physicochemical Characteristics of 1-Monosubstituted Tetrazoles

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_7H_7N_5O_2S$	37.48 / 37.33	3.59 / 3.13	30.86 / 31.09	205 (dec.)	57
2b	$C_{10}H_8N_6O_2S_2$	38.60 / 38.95	2.49 / 2.62	27.10 / 27.26	235 (dec.)	96
2c	$C_{11}H_{11}N_7O_2S_2$	39.98 / 39.16	3.44 / 3.29	28.68 / 29.06	193-195	66
2d	$C_{13}H_{13}N_7O_2S$	47.28 / 47.12	3.87 / 3.95	29.40 / 29.59	215-217	98
2e	$C_{13}H_{13}N_7O_4S$	43.19 / 42.97	3.90 / 3.61	27.07 / 26.98	195-197	58
2f	$C_{11}H_8N_4$	67.41 / 67.34	4.29 / 4.11	28.68 / 28.55	95-96	73
2g	$C_{11}H_{16}N_4$	64.77 / 64.68	8.01 / 7.89	27.58 / 27.43	135-137*	84
2h	$C_{13}H_{20}N_4$	67.34 / 67.21	8.75 / 8.68	24.39 / 24.12	133-135	85
2i	$C_4H_6N_4$	43.88 / 43.63	5.60 / 5.49	50.90 / 50.88	42-44	74
2j	$C_9H_{10}N_4$	61.85 / 62.05	5.62 / 5.79	32.11 / 32.16	61-63	71
2k	$C_7H_4N_4ClF$	42.22 / 42.34	1.99 / 2.03	28.50 / 28.22	97-98	89
2l	$C_8H_7N_4I$	33.70 / 33.59	2.80 / 2.47	20.40 / 19.58	93-94	73
2m	$C_8H_6N_4O_2$	50.60 / 50.53	3.11 / 3.18	29.62 / 29.46	255-256	91
2n	$C_{13}H_9N_5O_2$	58.30 / 58.43	3.30 / 3.39	26.68 / 26.31	257-259	91
3a	$C_{10}H_9N_7O_2S_2$	37.39 / 37.14	2.90 / 2.81	30.11 / 30.32	225 (dec.)	74
3b	$C_{11}H_9N_2$	62.45 / 62.55	4.41 / 4.29	33.30 / 33.16	230-232	80
3c	$C_7H_5ClFN_5$	39.50 / 39.36	2.50 / 2.36	32.88 / 32.79	188-189	76
3d	$C_8H_7N_5O_2$	46.90 / 46.83	3.56 / 3.44	34.28 / 34.13	290 (dec.)	91
3e	$C_{13}H_{10}N_6O_2$	55.46 / 55.32	3.77 / 3.57	29.50 / 29.77	209-211	85

* Mp 130-132, 140-141°C [10].

The compounds obtained were identified by data of IR, ^{1}H and ^{13}C NMR spectroscopy (Table 2). A characteristic of 1-monosubstituted tetrazoles **2** is the singlet for the proton at $C_{(5)}$ of the tetrazole ring lying in the 9.3-10.2 ppm region of the ^{1}H NMR spectrum [4-9]. A strong absorption band was present in the IR spectra of N-arylcyanamides **4** at 2210-2250 cm^{-1} belonging to the stretching vibration of the C≡N bond, and absorption bands were present at 3100-3500 and 1580-1620 cm^{-1} characteristic of the stretching and deformation vibrations of the N–H bond. In the IR spectra of 5-amino-1-aryltetrazoles **3** there were absorption bands for the stretching (3100-3400 cm^{-1}) and deformation (1580-1600 cm^{-1}) vibrations of the N–H bonds of the primary amino group. The signal for the tetrazole ring carbon atom in the ^{13}C NMR spectrum of tetrazole **3a** is displayed at 158.5 ppm, which corresponds with that for 5-amino-1-R-tetrazoles in [17-19]. The structure of compound **3b** was also confirmed by us by data of X-ray structural analysis [20].

TABLE 2. ^{1}H NMR Spectra of Compounds **2a-n** and **3a-e**

Compound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	
	HC_{cycl}	other signals
2a	10.18	8.08-8.13 (4H, m, C_6H_5); 7.55 (2H, br. s, NH_2)
2b	10.15	8.04-8.10 (4H, m, C_6H_5); 7.28 (1H, d, *J* = 4.6, HC=); 6.87 (1H, d, *J* = 4.6, HC=)
2c	10.11	8.05-8.11 (4H, m, C_6H_5); 2.83 (2H, q, *J* = 8.9, CH_2); 1.22 (3H, t, *J* = 8.9, CH_3)
2d	10.15	8.14-8.19 (4H, m, C_6H_5); 6.72 (1H, s, HC=); 2.26 (6H, s, $2CH_3$)
2e	10.18	8.15-8.20 (4H, m, C_6H_5); 5.98 (1H, s, HC=); 3.80 (3H, s, CH_3); 3.75 (3H, s, CH_3)
2f	9.96	7.44-8.32 (7H, m, C_6H_5)
2g	9.50	2.19 (9H, s, Ad); 1.74 (6H, s, Ad)
2h	9.41	4.46 (1H, q, *J* = 7.0, CH); 1.20-1.98 (15H, m, Ad); 1.46 (3H, d, *J* = 7.0, CH_3)
2i	9.45	3.90-4.11 (1H, m, CH); 1.12-1.21 (4H, m, $2CH_2$)
2j	9.26	7.15-7.27 (5H, m, C_6H_5); 4.73 (2H, t, *J* = 7.2, CH_2); 3.19 (2H, t, *J* = 7.2, CH_2)
2k	10.08	7.64-8.31 (3H, m, C_6H_5)
2l	9.80	7.75-8.00 (2H, m, C_6H_5); 7.28-7.33 (1H, m, C_6H_5); 2.11 (3H, s, CH_3)
2m	10.18	8.00-8.24 (4H, m, C_6H_5)
2n	10.16	7.94-8.40 (4H, m, C_6H_5)
3a*		10.23 (2H, br. s, NH_2); 7.65-7.70 (4H, m, C_6H_5); 7.20 (1H, d, *J* = 4.6, CH); 6.78 (1H, d, *J* = 4.6, CH)
3b		7.38-8.31 (7H, m, C_6H_5); 5.32 (2H, br. s, NH_2)
3c		7.57-7.91 (3H, m, C_6H_5); 6.94 (2H, br. s, NH_2)
3d		7.66-8.18 (4H, m, C_6H_5); 6.99 (2H, br. s, NH_2)
3e		7.50-8.30 (8H, m, $2C_6H_5$); 5.91 (2H, br. s, NH_2)

* ^{13}C NMR spectrum, δ, ppm: 112.3 (C, $C_{(4)}$-thiazole); 127.9 (2C, C_6H_5); 128.4 (C, C_6H_5); 131.1 (2C, C_6H_5); 139.8 (C, C_6H_5); 146.5 (C, $C_{(5)}$-thiazole); 158.5 (C, $C_{(5)}$-tetrazole); 172.7 (C, $C_{(2)}$-thiazole).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Tesla BS 567A spectrometer (100 and 25 MHz respectively) in DMSO-d_6, internal standard was HMDS (δ 0.05 ppm). The IR spectra were taken on a Shimadzu FTIR-8601 spectrometer on thin films of pure substance placed in a diamond cuvette. The homogeneity of compounds was checked by TLC on Merck Kieselgel 60/Kieselgur F_{254} plates.

1-Monosubstituted Tetrazoles 2a-n (General Procedure). Glacial acetic acid (40 ml) was added with stirring to a suspension of primary amine or the corresponding hydrochloride (0.1 mol), and sodium azide (7.2 g, 0.11 mol) in triethyl orthoformate (44 ml, 0.3 mol), and the mixture was heated while being stirred on a boiling water bath for 4-5 h. The reaction mixture was cooled, and conc. hydrochloric acid (0.2 mol) and water (50 ml) were added. The precipitated solid was separated by filtration, washed with water, and dried. The obtained tetrazoles were recrystallized from acetonitrile (**2a-e**), 2-propanol (**2f-m**), or a mixture of ethanol and DMF (**2n**).

N-Arylcyanamides 4a-e (General Procedure). DMSO (10 ml) was added dropwise with constant stirring to a suspension of 1-aryltetrazole **2b,f,k,m,n** (0.01 mol) in 10% aqueous KOH solution (6 ml) [for the synthesis of cyanamides **4a,d** 20% KOH solution (6 ml) was used]. Intense gas evolution was observed, accompanied by self-heating of the reaction mixture. Stirring of the reaction mixture was continued for

15-20 min after the end of visual observation of nitrogen evolution. The mixture was then diluted to 80 ml with water, acidified with hydrochloric acid to pH 3-4 and stored at 5-10°C until precipitation of solid. The obtained product was filtered off, washed with water, and dried in vacuum.

N-(2-Thiazolyl)-4-cyanoaminobenzenesulfonamide (4a). Yield 91%; mp 215-217°C (acetonitrile). IR spectrum, ν, cm^{-1}: 2234 (C≡N), 3190, 1600 (N–H), 1326 (S=O). Found, %: C 43.05; H 2.60; N 20.39. $C_{10}H_8N_4O_2S_2$. Calculated, %: C 42.85; H 2.88; N 19.99.

1-Naphthylcyanamide (4b). Yield 96%; mp 133-134°C (2-propanol) (135°C [21]). IR spectrum, ν, cm^{-1}: 2233 (C≡N), 3182, 1585 (N–H).

3-Chloro-4-fluorophenylcyanamide (4c). Yield 87%; mp 100-101°C (2-propanol). IR spectrum, ν, cm^{-1}: 2241 (C≡N), 3171, 1612 (N–H). Found, %: C 48.85; H 2.39; N 15.65. $C_7H_4ClFN_2$. Calculated, %: C 49.29; H 2.36; N 16.42.

4-(Cyanoamino)benzoic Acid (4d). Yield 74%; mp >350°C (reprecipitated through the sodium salt). IR spectrum, ν, cm^{-1}: 2237 (C≡N), 3344, 1612 (N–H). Found, %: C 59.19; H 3.58; N 17.18. $C_8H_6N_2O_2$. Calculated, %: C 59.26; H 3.73; N 17.28.

4-(4-Nitrophenyl)phenylcyanamide (4e). Yield 95%; mp 252-254°C (ethanol–DMF). IR spectrum, ν, cm^{-1}: 2245 (C≡N), 3197, 1593 (N–H). Found, %: C 65.09; H 3.98; N 17.77. $C_{13}H_9N_3O_2$. Calculated, %: C 65.27; H 3.79; N 17.56.

5-Amino-1-aryltetrazoles 3a-e (General Procedure). A suspension of cyanamide **4a-e** (0.01 mol), sodium azide (0.015 mol), and ammonium chloride (0.02 mol) in DMF (25 ml) was stirred at 70-80°C for 3-4 h, after which water (100 ml) was added to the reaction mixture. The precipitated solid was filtered off, washed with water, and recrystallized from acetonitrile (**3a**), 2-propanol (**3b,c**), reprecipitated from DMF–water (**3e**), or purified through the sodium salt (**3d**).

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