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ALKYLATION OF ACYL AND SULFONYL DERIVATIVES OF 3,5-DIAMINO-1-PHENYL-1,2,4-TRIAZOLE

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Alkylation of 3-acylamino-, 5-amino-1-phenyl-3-tosylamino-1,2,4-triazoles and 3,5-diacetylamino-1-phenyl-1,2,4-triazole in the presence of an equimolar amount of sodium methylate in DMSO occurs regioselectively at the amide (sulfamide) group nitrogen atom. The benzylation of 3-acetylamino-5-amino-1-phenyl-1,2,4-triazole with excess base and benzyl chloride also alkylates the amino group at position 5. Alkylamino-1-R-1,2,4-triazoles can be conveniently prepared by alkylation of the corresponding acetylamino-1,2,4-triazoles in the presence of base and subsequent acid hydrolysis of the N-acetyl-N-alkyl derivatives.

Keywords: 5-amino-3-(N-acyl-N-alkyl)amino-1-phenyl-1,2,4-triazoles, 5-amino-3-(N-alkyl-N-tosyl)-amino-1-phenyl-1,2,4-triazoles, acylamino-1,2,4-triazoles, 3,5-di(N-acetyl-N-methylamino)-1-phenyl-1,2,4-triazole, sulfonylamino-1,2,4-triazoles, alkylation, regioselectivity, X-ray structural analysis, structure.

Alkylation of C-amino-1,2,4-triazoles by alkyl halides and alkyl sulfates usually occurs at the nitrogen atom of the heterocycle to give the aminotriazoles or iminotriazolines substituted in the ring [1-6]. Such an alkylation route is typical of the majority of amino azoles and azines in which the amino group is conjugated with the pyridine type nitrogen atom of the heterocycle [7]. Thus alkylamino-1,2,4-triazoles are usually prepared by cyclization of alkyl substituted acyclic precursors [3, 8-10], hydrogenation of arylideneamino- or acylamino-1,2,4-triazoles [11-13], or ammonolysis of halo-substituted 1,2,4-triazoles [4].

We have proposed that the alkylation reaction route for the amino-1,2,4-triazoles can be altered by initial acylation or sulfonation of the amino group. In the presence of base an electron acceptor acyl (sulfonyl) group can facilitate deprotonation and give a conjugated N-anion, alkylation of which can give the N-acyl(sulfonyl)-N-alkylamino-1,2,4-triazoles.

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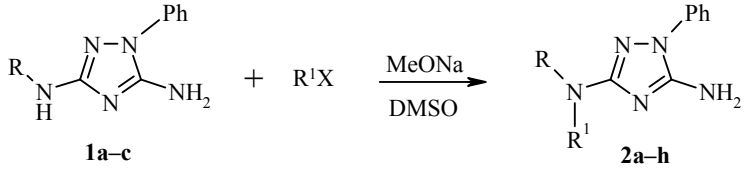
A similar route is used, for example, in the alkylation of 2-acetylamino-5-(benzimidazol-2-yl)thiazole where the reaction course depends strongly on the solvent used [14].

With respect to establishing the reaction route and developing a novel method for preparing alkylamino-1,2,4-triazoles we have studied the alkylation of acyl and sulfonyl derivatives of 3,5-diamino-1-phenyl-1,2,4-triazole in the presence of the strong base sodium methylate. Selection of 3,5-diamino-1,2,4-triazoles for this study was dictated by their use in medicine (see [10, 13] and references cited there).

We have shown that the reaction of the 3-acylamino-5-amino-1-phenyl-1,2,4-triazoles **1a,b** and 5-amino-1-phenyl-3-tosylamino-1,2,4-triazole (**1c**) with alkyl halides in the presence of an equimolar amount or slight excess of MeONa occurs regioselectively to give the 5-amino-3-(N-acyl-N-alkyl)amino-1-phenyl-1,2,4-triazoles **2a-f** and 5-amino-3-(N-alkyl-N-tosyl)amino-1-phenyl-1,2,4-triazoles **2g,h**. Products of alkylation at an endocyclic nitrogen atom are not found.



1a, 2a–**d** R = Ac; **1b**, **2 e**, **f** R = PhCO; **1c**, **2 g**, **h** R = Ts; **2 a**, **e**, **g** R^1 = Me, **b** R^1 = Et, **c** R^1 = All, **d**, **f**, **h** R^1 = Bn, R^1X = MeI, EtI, AllBr, BnCl

Compound **1a** reacts similarly with dimethylsulfate in aqueous KOH solution.

As in the starting compounds **1a-c**, the ^{1}H NMR spectra of compounds **2a-h** retain the two-proton singlet for the 5-NH_2 at 6.5-6.7 ppm but the singlet for the amide NH proton has disappeared. The values of the chemical shifts of the triazole ring carbon atoms in the ^{13}C NMR spectra of compounds **2b,c,f-h** (C-3 155-158 and C-5 154 ppm) are close to those of other 1-R-3,5-diamino-1,2,4-triazoles [8, 15]. In the proton-coupled ^{13}C NMR spectra the signal for the C-3 atom is split due to spin-spin coupling interaction through three bonds with the alkyl group protons to a triplet in compounds **2b,c,f,h** (J = 3.5-4.1) and to a quartet in the methyl derivative **2g** (J = 2.9 Hz) while the signal for the C-5 atom is a singlet (spin-spin interaction of the carbon nucleus with amino group protons not being observed due to rapid exchange of these protons with the solvent [15, 16]). Hence one can exclude a 4-alkyl-substituted alternative structure since a splitting of the C-5 signal due to

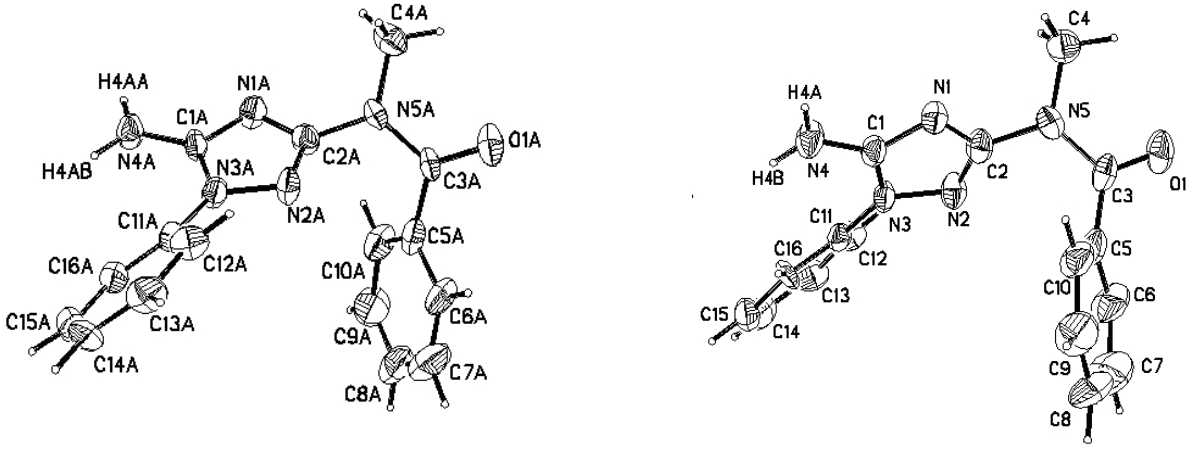


Fig. 1. Structure of compound **2e** (two independent molecules shown).

interaction with alkyl group protons would be observed [8, 16]. In addition, compounds **2d,h** are identical to those synthesized in the study [12]. Unambiguous proof of the structure of the alkyl derivatives was obtained by an X-ray structural investigation of compound **2e** (Fig. 1).

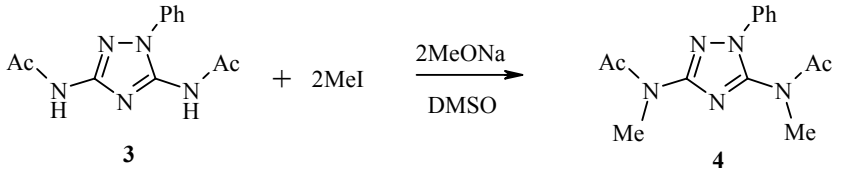
TABLE 1. Some Bond Lengths (*d*) in Compound **2e**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
$N_{(1)}$–$C_{(1)}$	1.337(4)	$N_{(5)}$–$C_{(3)}$	1.396(4)	$N_{(3A)}$–$C_{(1A)}$	1.366(4)
$N_{(1)}$–$C_{(2)}$	1.359(4)	$N_{(5)}$–$C_{(4)}$	1.459(4)	$N_{(3A)}$–$C_{(11A)}$	1.404(4)
$N_{(2)}$–$C_{(2)}$	1.318(4)	$C_{(3)}$–$C_{(5)}$	1.460(5)	$N_{(4A)}$–$C_{(1A)}$	1.334(4)
$N_{(2)}$–$N_{(3)}$	1.408(4)	$O_{(1)}$–$C_{(3)}$	1.244(4)	$N_{(5A)}$–$C_{(2A)}$	1.412(4)
$N_{(3)}$–$C_{(1)}$	1.365(4)	$N_{(1A)}$–$C_{(1A)}$	1.328(4)	$N_{(5A)}$–$C_{(3A)}$	1.393(4)
$N_{(3)}$–$C_{(11)}$	1.408(4)	$N_{(1A)}$–$C_{(2A)}$	1.362(4)	$N_{(5A)}$–$C_{(4A)}$	1.426(4)
$N_{(4)}$–$C_{(1)}$	1.337(4)	$N_{(2A)}$–$C_{(2A)}$	1.303(4)	$C_{(3A)}$–$C_{(5A)}$	1.489(5)
$N_{(5)}$–$C_{(2)}$	1.397(5)	$N_{(2A)}$–$N_{(3A)}$	1.395(4)	$O_{(1A)}$–$C_{(3A)}$	1.244(4)

TABLE 2. Some Valence Angles (ω) in Compound **2e**

Angle	ω, deg	Angle	ω, deg
$C_{(1)}$–$N_{(1)}$–$C_{(2)}$	101.8(3)	$C_{(1A)}$–$N_{(1A)}$–$C_{(2A)}$	102.7(3)
$N_{(1)}$–$C_{(1)}$–$N_{(3)}$	110.9(3)	$N_{(1A)}$–$C_{(1A)}$–$N_{(3A)}$	109.9(3)
$C_{(2)}$–$N_{(2)}$–$N_{(3)}$	101.0(3)	$C_{(2A)}$–$N_{(2A)}$–$N_{(3A)}$	101.8(3)
$C_{(1)}$–$N_{(3)}$–$N_{(2)}$	108.4(3)	$C_{(1A)}$–$N_{(3A)}$–$N_{(2A)}$	108.7(3)
$N_{(2)}$–$C_{(2)}$–$N_{(1)}$	117.6(4)	$N_{(2A)}$–$C_{(2A)}$–$N_{(1A)}$	116.7(4)
$C_{(1)}$–$N_{(3)}$–$C_{(11)}$	132.5(3)	$C_{(1A)}$–$N_{(3A)}$–$C_{(11A)}$	131.0(3)
$N_{(2)}$–$N_{(3)}$–$C_{(11)}$	118.6(3)	$N_{(2A)}$–$N_{(3A)}$–$C_{(11A)}$	119.6(3)
$N_{(1)}$–$C_{(1)}$–$N_{(4)}$	124.5(4)	$N_{(1A)}$–$C_{(1A)}$–$N_{(4A)}$	124.6(4)
$N_{(4)}$–$C_{(1)}$–$N_{(3)}$	124.6(4)	$N_{(4A)}$–$C_{(1A)}$–$N_{(3A)}$	125.4(4)
$N_{(2)}$–$C_{(2)}$–$N_{(5)}$	121.4(4)	$N_{(2A)}$–$C_{(2A)}$–$N_{(5A)}$	122.2(4)
$N_{(1)}$–$C_{(2)}$–$N_{(5)}$	120.8(4)	$N_{(1A)}$–$C_{(2A)}$–$N_{(5A)}$	120.9(4)
$O_{(1)}$–$C_{(3)}$–$N_{(5)}$	118.0(5)	$O_{(1A)}$–$C_{(3A)}$–$N_{(5A)}$	119.4(4)
$O_{(1)}$–$C_{(3)}$–$C_{(5)}$	123.9(4)	$O_{(1A)}$–$C_{(3A)}$–$C_{(5A)}$	122.0(4)
$N_{(5)}$–$C_{(3)}$–$C_{(5)}$	117.9(4)	$N_{(5A)}$–$C_{(3A)}$–$C_{(5A)}$	118.2(4)
$C_{(3)}$–$N_{(5)}$–$C_{(2)}$	120.3(4)	$C_{(3A)}$–$N_{(5A)}$–$C_{(2A)}$	119.2(4)
$C_{(3)}$–$N_{(5)}$–$C_{(4)}$	120.5(4)	$C_{(3A)}$–$N_{(5A)}$–$C_{(4A)}$	120.4(4)
$C_{(2)}$–$N_{(5)}$–$C_{(4)}$	118.0(4)	$C_{(2A)}$–$N_{(5A)}$–$C_{(4A)}$	118.9(3)

In the crystal, compound **2e** consists of two independent molecules (Fig. 1, Tables 1 and 2). The bond lengths and valence angles in the triazole ring agree with the corresponding values in previously reported 1-R-3,5-diamino-1,2,4-triazoles [15, 17-18]. In both molecules the amino group has a planar configuration and is conjugated with the triazole ring (the bond lengths $N_{(4)}$–$C_{(1)}$ and $N_{(4A)}$–$C_{(1A)}$ being 1.337(4) and 1.334(4) Å respectively and the deviation of atoms $N_{(4)}$ and $N_{(4A)}$ from the triazole ring plane being -0.125 and 0.076 Å). Atoms $N_{(5)}$ and $N_{(5A)}$ have almost planar coordination (sum of valence angles 358.7 and 358.6º). The $N_{(5)}$–$C_{(2)}$ and $N_{(5A)}$–$C_{(2A)}$ are lengthened to 1.397(5) and 1.412(4) Å when compared with the corresponding length in the 3-alkylamino-1,2,4-triazoles [17, 19] without the acyl group (1.37 Å) but are close to the corresponding bond length in 3-acylamino-1,2,4-triazoles [15, 20]. The torsional angles $C_{(3)}$–$N_{(5)}$–$C_{(2)}$–$N_{(2)}$ and $C_{(3A)}$–$N_{(5A)}$–$C_{(2A)}$–$N_{(2A)}$ are -49.8(6) and 48.7(5)º respectively.



3 **4**

Methylation of 3,5-diacetylamino-1-phenyl-1,2,4-triazole (**3**) alkylates both amide groups to give the corresponding compound **4** whose structure was proved by spectroscopic data and X-ray analysis (Fig. 2, Tables 3 and 4).

Atoms $N_{(4)}$ and $N_{(5)}$ in the compound **4** molecule (Fig. 2) have a planar coordination, their deviation from the triazole ring plane being 0.039 and 0.078 Å respectively. The $C_{(2)}$–$N_{(5)}$ bond is lengthened to 1.401(3) Å when compared with the similar bond (1.33-1.37 Å) in compound **2e** and other 3,5-diamino-1,2,4-triazoles [15, 17-18]. The $C_{(3)}N_{(4)}C_{(4)}O_{(1)}C_{(5)}$ fragment is planar to within ± 0.01 Å and the torsional angle $C_{(4)}$–$N_{(4)}$–$C_{(1)}$–$N_{(2)}$ is 7.9(4)º.

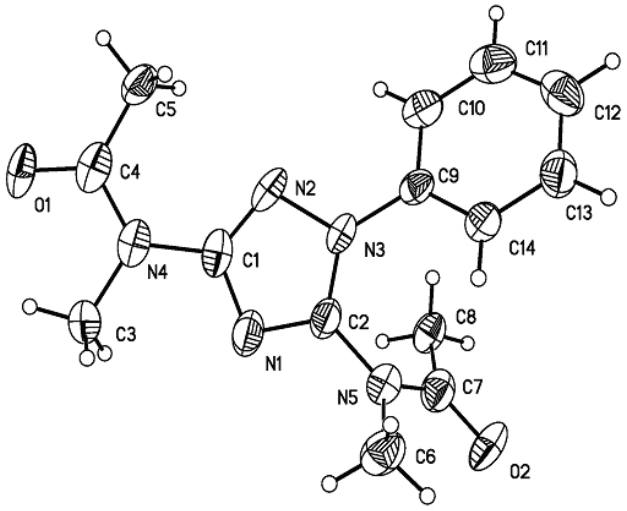


Fig. 2. Structure of the compound **4** molecule.

TABLE 3. Some Bond Lengths (*d*) in Compound **4**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
$N_{(1)}$–$C_{(1)}$	1.346(4)	$N_{(4)}$–$C_{(1)}$	1.406(3)	$N_{(5)}$–$C_{(6)}$	1.464(4)
$N_{(1)}$–$C_{(2)}$	1.324(3)	$N_{(4)}$–$C_{(3)}$	1.481(4)	$N_{(5)}$–$C_{(7)}$	1.358(4)
$N_{(2)}$–$C_{(1)}$	1.319(4)	$N_{(4)}$–$C_{(4)}$	1.365(4)	$O_{(2)}$–$C_{(7)}$	1.223(3)
$N_{(2)}$–$N_{(3)}$	1.376(3)	$O_{(1)}$–$C_{(4)}$	1.230(3)	$C_{(7)}$–$C_{(8)}$	1.506(4)
$N_{(3)}$–$C_{(2)}$	1.341(3)	$C_{(4)}$–$C_{(5)}$	1.501(4)		
$N_{(3)}$–$C_{(9)}$	1.435(3)	$N_{(5)}$–$C_{(2)}$	1.401(3)		

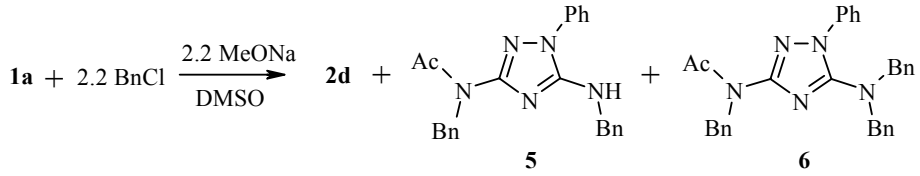
TABLE 4. Some Valence Angles (ω) in Compound **4**

Angle	ω, deg	Angle	ω, deg
$C_{(1)}$–$N_{(1)}$–$C_{(2)}$	101.9(2)	$C_{(3)}$–$N_{(4)}$–$C_{(4)}$	115.9(2)
$N_{(1)}$–$C_{(1)}$–$N_{(2)}$	115.9(2)	$C_{(1)}$–$N_{(4)}$–$C_{(4)}$	126.3(3)
$C_{(1)}$–$N_{(2)}$–$N_{(3)}$	102.4(2)	$N_{(4)}$–$C_{(4)}$–$C_{(5)}$	119.4(3)
$N_{(2)}$–$N_{(3)}$–$C_{(2)}$	108.0(2)	$O_{(1)}$–$C_{(4)}$–$N_{(4)}$	117.8(3)
$N_{(1)}$–$C_{(2)}$–$N_{(3)}$	111.8(2)	$O_{(1)}$–$C_{(4)}$–$C_{(5)}$	122.8(3)
$N_{(1)}$–$C_{(1)}$–$N_{(4)}$	118.5(3)	$C_{(2)}$–$N_{(5)}$–$C_{(6)}$	117.9(2)
$N_{(2)}$–$C_{(1)}$–$N_{(4)}$	125.5(3)	$C_{(2)}$–$N_{(5)}$–$C_{(7)}$	122.7(3)
$N_{(1)}$–$C_{(2)}$–$N_{(5)}$	123.7(3)	$C_{(6)}$–$N_{(5)}$–$C_{(7)}$	119.4(2)
$N_{(3)}$–$C_{(2)}$–$N_{(5)}$	124.4(2)	$O_{(2)}$–$C_{(7)}$–$N_{(5)}$	119.5(3)
$N_{(2)}$–$N_{(3)}$–$C_{(9)}$	120.6(2)	$O_{(2)}$–$C_{(7)}$–$C_{(8)}$	122.7(3)
$C_{(2)}$–$N_{(3)}$–$C_{(9)}$	131.3(2)	$N_{(5)}$–$C_{(7)}$–$C_{(8)}$	117.7(2)
$C_{(1)}$–$N_{(4)}$–$C_{(3)}$	117.7(2)		

The $C_{(6)}N_{(5)}C_{(7)}O_{(2)}C_{(8)}$ fragment is also planar to within ± 0.05 Å but it is twisted relative to the triazole ring plane as a result of a repulsive interaction between the acetyl group and the benzene ring (torsional angle $C_{(7)}$–$N_{(5)}$–$C_{(2)}$–$N_{(3)}$ -68.2(4) Å). A shortened intramolecular contact for $H(C_{(8)})\cdots C_{(9)}$ of 2.60 Å is observed in the molecule.

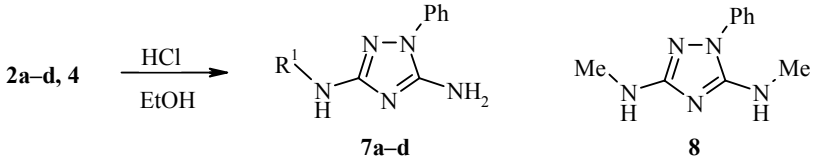
Hence the acyl and sulfonyl fragments in the molecules **1a-c** and **3** take the role of activating groups and this results in a regioselective alkylation of the N-anions formed in basic medium from the amide (sulfamide) group.

Use, however, of an excess of benzyl chloride and sodium methylate relative to the substrate **1a** gave the alkyl derivatives **2d, 5** and **6** in the molar ratio 1.3:1.4:1 from the reaction mixture, the composition and structure of which were confirmed by elemental analysis and spectroscopic data.



The ratio of reaction products indicates that the amide group having greatest acidity is initially alkylated. As a result of deprotonation of the amino group, compound **2d** forms an N-anion which is alkylated to give compound **5**. The latter gives compound **6** similarly. Evidently compounds **2d** and **5** have comparable reactivity towards alkylation in the presence of strong bases.

The acid hydrolysis of compounds **2a-d** and **4** gave the alkylaminotriazoles **7a-d** and **8** in good yields.



7a R^1 = Me, **b** R^1 = Et, **c** R^1 = All, **d** R^1 = Bn

Hence the alkylation of acylamino-1,2,4-triazoles and subsequent hydrolysis of the N-acyl-N-alkyl derivatives is a convenient method for the synthesis of 3- and 5-alkylamino-1,2,4-triazoles.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity-300 (300 and 75 MHz) instrument using DMSO-d_6 and with TMS as internal standard. Mass spectra were obtained on a Finnigan MAT Incos 50 spectrometer with direct introduction of the sample into the ion source and ionization energy 70 eV and on a Finnigan LCQ Deca XP MAX instrument in electrospray mode with positive ionization and direct introduction of the samples in acetonitrile at a concentration of 0.5 mg/ml.

The starting compounds **1a,c** and **3** were synthesized by a known method [12].

5-Amino-3-benzoylamino-1-phenyl-1,2,4-triazole (1b) was prepared similarly. Yield 82%; mp 205-207ºC (a mixture of DMF and EtOH). ^{1}H NMR spectrum, δ, ppm: 6.56 (2H, s, NH_2); 7.35 (1H, m, arom.); 7.49-7.59 (7H, m, arom.); 7.97 (2H, m, arom.); 10.55 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 122.41, 126.67, 127.70, 128.21, 129.29, 134.58, 133.98, 137.15, 153.82 (C-5), 153.94 (C-3), 165.10 (CO). Found, %: C 64.80; H 4.53; N 25.22. $C_{15}H_{13}N_5O$. Calculated, %: C 64.51; H 4.69; N 25.07.

5-Amino-3-(N-acyl-N-alkyl)amino-1-phenyl-1,2,4-triazoles 2a-f and 5-Amino-3-(N-alkyl-N-tosyl)-amino-1-phenyl-1,2,4-triazoles 2g,h (General Method). A. A solution of Na (0.12 g, 5.1 mmol) in MeOH (1.5 ml) was added to a solution of compound **1a-c** (4.6 mmol) in DMSO (10 ml). The product was stirred for 5 min at room temperature, cooled to 0-10ºC, and a solution of the corresponding alkyl halide (5.1 mmol) was added dropwise with vigorous stirring and with cooling. The reaction mixture was stirred for 4 h, the DMSO was distilled off *in vacuo*, and water (10 ml) was added to the residue. The precipitate obtained was filtered off, dissolved in chloroform (30 ml), passed through an alumina column (4×3 cm), the chloroform distilled off, and the residue was crystallized.

B. Compound **1a** (1 g, 4.6 mmol) was dissolved with heating in a solution of KOH (0.52 g, 9.2 mmol) in water (20 ml) and the solution obtained was cooled to 0-5ºC. Me_2SO_4 (0.61 g, 5.52 mmol) was added dropwise with vigorous stirring and cooling. Stirring was continued for 4 h and the precipitate was filtered off, washed with water, and crystallized to give compound **2a** whose physicochemical properties were identical to those obtained using method A.

5-Amino-3-(N-acetyl-N-methyl)amino-1-phenyl-1,2,4-triazole (2a). Yield 82% (method A), 40% (method B); mp 200-202ºC (ethanol). ^{1}H NMR spectrum, δ, ppm: 2.22 (3H, s, CH_3); 3.18 (3H, s, CH_3); 6.51 (2H, s, NH_2); 7.36-7.58 (5H, m, C_6H_5). Mass spectrum (EI), *m/z* (I_{rel}, %): 231 $[M]^+$ (27), 189 (100), 160 (10), 133 (10), 119 (25), 104 (12), 91 (34), 44 (64). Found, %: C 56.90; H 5.81; N 30.18. $C_{11}H_{13}N_5O$. Calculated, %: C 57.13; H 5.67; N 30.28.

TABLE 5. Some Crystal Parameters for Compounds **2e** and **4** and Conditions for Carrying Out the X-ray Structural Investigation

Parameter	Compound	
	2e	**4**
Cell type	triclinic	orthorhombic
Cell parameters		
a, Å	6.608(2)	7.367(2)
b, Å	13.121(4)	14.712(3)
c, Å	19.034(5)	26.912(5)
α, deg.	71.406(5)	
β, deg.	90.000(5)	
γ, deg.	75.415(4)	
Space group	*P*-1	*Pbca*
Cell volume, Å^3	1508.1(7)	2917(1)
Z	4	8
D_{calc}, g/cm^3	1.292	1.309
Absorption coefficient, mm^{-1}	0.086	0.092
Crystal size, mm	0.45×0.30×0.25	0.50×0.35×0.25
Radiation	λMo*K*α	λMo*K*α
$2\theta_{max}$, deg.	58.00	56.00
Number of independent reflections with $I>2\sigma(I)$	7865 (R_{int} = 0.0979)	2750 (R_{int} = 0.0091)
Number of refinement parameters	397	190
Final difference factors,		
R_1	0.0754 (calculated using F_{hkl} for 1749 reflections with $I>2\sigma(I)$)	0.0652 (calculated using F_{hkl} for 1844 reflections with $I>2\sigma(I)$)
wR_2	0.1039 (calculated using F_{hkl} for all 7865 reflections)	0.1243 (calculated using F_{hkl} for all 2750 reflections)
G00F	0.921	0.972

5-Amino-3-(N-acetyl-N-ethyl)amino-1-phenyl-1,2,4-triazole (2b). Yield 60% (method A); mp 172-173ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.0, CH_3); 2.13 (3H, s, CH_3); 3.68 (2H, q, *J* = 7.0, CH_2); 6.66 (2H, s, NH_2); 7.34-7.56 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 13.17 ($NCH_2\underline{C}H_3$); 23.01 ($COCH_3$); 40.78 ($N\underline{C}H_2CH_3$); 122.64, 126.95, 129.28, 136.77, 154.25 (C-5); 157.06 (C-3); 169.12 (CO). Mass spectrum (EI), *m/z* (I_{rel}, %): 245 $[M]^+$ (25), 203 (77), 188 (100), 175 (22), 160 (10), 119 (18), 91 (21), 77 (69). Found, %: C 58.72; H 5.22; N 28.82. $C_{12}H_{15}N_5O$. Calculated, %: C 58.76; H 6.16; N 28.55.

5-Amino-3-(N-acetyl-N-allyl)amino-1-phenyl-1,2,4-triazole (2c). Yield 32% (method A); mp 164-165ºC (benzene). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.19 (3H, s, CH_3); 4.30 (2H, d, *J* = 5.2, CH_2); 5.08 (2H, m, 2CH); 5.77 (1H, m, CH); 6.67 (2H, s, NH_2); 7.34-7.54 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 23.03 ($CO\underline{C}H_3$); 47.94 (NCH_2); 116.17 ($CH=\underline{C}H_2$); 122.61 ($\underline{C}H=CH_2$); 126.98, 129.33, 133.61, 136.77, 154.20 (C-5); 157.07 (C-3); 169.31 (CO). Mass spectrum (EI), *m/z* (I_{rel}, %): 257 $[M]^+$ (47), 215 (69), 188 (30), 160 (35), 123 (10), 119 (51), 91 (27), 77 (100). Found, %: C 60.79; H 5.92; N 27.42. $C_{13}H_{15}N_5O$. Calculated, %: C 60.69; H 5.88; N 27.22.

5-Amino-3-(N-acetyl-N-benzyl)amino-1-phenyl-1,2,4-triazole (2d) Yield 62% (method A); mp 194-196ºC (ethanol, mp 194-196ºC [12]). The ^{1}H NMR spectrum was identical to that obtained in [12]. Mass spectrum (EI), *m/z* (I_{rel}, %): 307 $[M]^+$ (18), 264 (57), 188 (10), 160 (30), 119 (36), 106 (23), 91 (100), 77 (56).

5-Amino-3-(N-benzoyl-N-methyl)amino-1-phenyl-1,2,4-triazole (2e). Yield 62% (method A); mp 209-211ºC (ethanol). ^{1}H NMR spectrum, δ, ppm: 3.31 (3H, s, CH_3); 6.58 (2H, s, NH_2); 7.19-7.43 (10H, m, $2C_6H_5$). Mass spectrum (EI), *m/z* (I_{rel}, %): 293 $[M]^+$ (17), 265 (46), 105 (100), 77 (98). Found, %: C 65.70; H 5.10; N 24.03. $C_{16}H_{15}N_5O$. Calculated, %: C 65.52; H 5.15; N 23.88.

5-Amino-3-(N-benzoyl-N-benzyl)amino-1-phenyl-1,2,4-triazole (2f). Yield 85% (method A); mp 230-231ºC (ethanol). ^{1}H NMR spectrum, δ, ppm: 5.05 (2H, s, CH_2); 6.63 (2H, s, NH_2); 7.16-7.45 (15H, m, $3C_6H_5$). ^{13}C NMR spectrum, δ, ppm: 50.70 (NCH_2), 122.50, 126.89, 126.97, 127.42, 127.51, 127.71, 128.12, 129.18, 130.07, 136.15, 136.53, 137.58, 154.46 (C-5), 157.56 (C-3), 169.30 (CO). Mass spectrum (EI), *m/z* (I_{rel}, %): 369 $[M]^+$ (17), 264 (95), 105 (86), 91 (62), 77 (100). Found, %: C 71.62; H 5.23; N 19.22. $C_{22}H_{19}N_5O$. Calculated, %: C 71.53; H 5.18; N 18.96.

5-Amino-3-(N-methyl-N-tosyl)amino-1-phenyl-1,2,4-triazole (2g). Yield 79% (method A); mp 132.5-134.5ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.17 (3H, s, NCH_3); 6.60 (2H, s, NH_2); 7.32-7.52 (7H, m, Ar); 7.79 (2H, d, *J* = 8.2, Ar). ^{13}C NMR spectrum, δ, ppm: 20.88 (CH_3); 35.83 (NCH_3); 122.37, 126.81, 127.63, 129.27, 129.31, 135.13, 136.79, 143.59, 154.02 (C-5); 155.83 (C-3). Mass spectrum (EI), *m/z* (I_{rel}, %): 343 $[M]^+$ (12), 278 (30), 187 (20), 146 (27), 105 (44), 91 (38), 82 (10), 77 (100). Found, %: C 56.20; H 5.02; N 20.10. $C_{16}H_{17}N_5O_2S$. Calculated, %: C 55.96; H 4.99; N 20.39.

5-Amino-3-(N-benzyl-N-tosyl)amino-1-phenyl-1,2,4-triazole (2h). Yield 81% (method A); mp 170-172ºC (ethanol, mp 170-172ºC [12]). The ^{1}H NMR spectrum was identical to that reported in [12]. ^{13}C NMR spectrum, δ, ppm: 20.88 (CH_3), 51.79 (NCH_2); 122.19, 126.75, 127.11, 127.47, 127.75, 128.05, 129.22, 129.26, 136.23, 136.76, 137.04, 143.56, 153.98 (C-5); 154.93 (C-3). Mass spectrum (EI), *m/z* (I_{rel}, %): 419 $[M]^+$ (2), 264 (28), 160 (10), 105 (12), 91 (100), 77 (54). Found, %: C 63.20; H 5.00; N 16.91. $C_{22}H_{21}N_5O_2S$. Calculated, %: C 62.99; H 5.05; N 16.69.

3,5-Di(N-acetyl-N-methylamino)-1-phenyl-1,2,4-triazole (4). A solution of Na (0.22 g, 9.4 mmol) in MeOH (1 ml) was added with stirring to a solution of the diacetyl derivative **3** (1 g, 3.9 mmol) in DMSO (5 ml). The product was stirred at room temperature for 5 min, cooled to 0-10ºC, and MeI (1.33 g, 9.4 mmol) was added over 10 min with vigorous stirring. The reaction mixture was stirred for 4 h, solvent removed by distillation *in vacuo*, and the residue was dissolved in chloroform (50 ml), washed with a 5% NaOH solution (20 ml) and water (20 ml), passed through an alumina column (4×3 cm), and the chloroform was distilled off to give compound **4** (0.77 g, 70%) with mp 104-106ºC. ^{1}H NMR spectrum, δ, ppm: 1.85 (3H, s, CH_3); 2.27 (3H, s, CH_3); 3.02 (3H, s, NCH_3); 3.26 (3H, s, NCH_3); 7.45-7.60 (5H, m, C_6H_5). Mass spectrum (EI), *m/z* (I_{rel}, %): 287

$[M]^+$ (16), 245 (50), 203 (100), 189 (15), 118 (10), 91 (20), 77 (35). Found, %: C 58.71; H 6.00; N 24.50. $C_{14}H_{17}N_5O_2$. Calculated, %: C 58.52; H 5.96; N 24.37.

5-Amino-3-(N-acetyl-N-benzyl)amino-1-phenyl-1,2,4-triazole (2d), 3-(N-Acetyl-N-benzyl)amino-5-benzylamino-1-phenyl-1,2,4-triazole (5), and 3-(N-Acetyl-N-benzyl)amino-5-dibenzylamino-1-phenyl-1,2,4-triazole (6). A solution of Na (0.24 g, 10.2 mmol) in MeOH (1.5 ml) was added to a solution of compound **1a** (1 g, 4.6 mmol) in DMSO (10 ml). The reaction product was stirred at room temperature for 5 min, cooled to 0-10ºC, and a solution of benzyl chloride (1.29 g, 10.2 mmol) in DMSO was added dropwise with vigorous stirring and cooling. The reaction mixture was then stirred for 4 h, DMSO was distilled off *in vacuo*, and water (10 ml) was added to the residue. The oil produced was extracted with chloroform (30 ml), the extract washed with water and dried over sodium sulphate, and solvent was distilled off. The residue was chromatographed on an alumina column (30×3 cm) using chloroform as eluent.

Compound 2d. R_f 0.19, yield 0.49 g (35%).

Compound 5. R_f 0.46, yield 0.69 g (38%), mp 118-119ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (3H, s, CH_3); 4.43 (2H, d, *J* = 5.4, CH_2); 4.91 (2H, s, CH_2); 7.24-7.51 (16H, m, 3 C_6H_5 + NH). ^{13}C NMR spectrum, δ, ppm: 23.29 (CH_3); 46.72 (CH_2); 48.92 (CH_2); 122.05, 126.62, 126.65, 127.19, 127.35, 127.43, 127.94, 127.98, 129.38, 136.43, 137.88, 139.58, 154.20 (C-5); 157.14 (C-3); 169.66 (CO). Found, %: C 72.28; H 5.72; N 17.77. $C_{24}H_{23}N_5O$. Calculated, %: C 72.52; H 5.83; N 17.62.

Compound 6. R_f 0.57, yield 0.6 g (27%), mp 94-95ºC. ^{1}H NMR spectrum, δ, ppm: 2.08 (3H, s, CH_3); 4.19 (4H, s, $2CH_2$); 4.85 (2H, s, CH_2); 7.08-7.55 (20H, m, $4C_6H_5$). Mass spectrum (ES), *m/z*: 488 $[M+H]^+$. Found, %: C 76.29; H 6.02; N 14.51. $C_{31}H_{29}N_5O$. Calculated, %: C 76.36; H 5.99; N 14.36.

3-Alkylamino-5-amino-1-phenyl-1,2,4-triazoles (7a-d) (General Method). A mixture of the corresponding 5-amino-3-(N-acyl-N-alkyl)amino-1-phenyl-1,2,4-triazole **2a-d** (2 mmol), EtOH (5 ml), and conc. HCl (1 ml) was refluxed for 1 h, the solvent was removed by evaporation, and the residue was neutralized with a 20% aqueous NH_3 solution. The precipitate formed was filtered off and crystallized.

5-Amino-3-methylamino-1-phenyl-1,2,4-triazole (7a). Yield 71%; mp 141-142ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.64 (3H, d, *J* =5.1, CH_3); 5.51 (1H, q, *J* = 5.1, NH); 6.20 (2H, s, NH_2); 7.16-7.52 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 29.11 (CH_3); 121.62, 125.60, 129.08, 137.49, 152.66 (C-5); 160.57 (C-3). Mass spectrum (EI), *m/z* (I_{rel}, %): 189 $[M]^+$ (79), 161 (8), 146 (10), 133 (8), 119 (32), 104 (20), 91 (100), 77 (93). Found, %: C 57.29; H 5.93; N 36.81. $C_9H_{11}N_5$. Calculated, %: C 57.13; H 5.86; N 37.01.

5-Amino-3-ethylamino-1-phenyl-1,2,4-triazole (7b). Yield 91%; mp 110-110.5ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.1, CH_3); 3.06 (2H, m, CH_2); 5.55 (1H, t, *J* = 5.4, NH); 6.21 (2H, s, NH_2); 7.18-7.23 (2H, m, Ar); 7.38-7.50 (3H, m, Ar). Mass spectrum (EI), *m/z* (I_{rel}, %): 203 $[M]^+$ (56), 188 (100), 175 (13), 119 (12), 91 (10), 77 (16). Found, %: C 59.14; H 6.30; N 34.56. $C_{10}H_{13}N_5$. Calculated, %: C 59.10; H 6.45; N 34.46.

3-Allylamino-5-amino-1-phenyl-1,2,4-triazole (7c). Yield 72%; mp 87.5-88.5ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (2H, m, CH_2); 5.02 (1H, dd, *J* = 10.3, *J* = 1.7, CH); 5.17 (1H, dd, *J* = 17.2, *J* = 1.7, CH); 5.79 (1H, t, *J* = 6.2, NH); 5.88 (1H, m, CH); 6.20 (2H, s, NH_2); 7.18-7.50 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 44.87 (CH_2); 114.44, 121.11, 125.02, 128.97, 136.71, 137.93, 153.50 (C-5); 161.33 (C-3). Found, %: C 61.49; H 6.11; N 32.81. $C_{11}H_{13}N_5$. Calculated, %: C 61.38; H 6.09; N 32.53.

5-Amino-3-benzylamino-1-phenyl-1,2,4-triazole (7d). Yield 78%; mp 164-166ºC (mp 165-166ºC [12]). The ^{1}H NMR spectrum was identical to that reported before [12]. Mass spectrum (EI), *m/z* (I_{rel}, %): 265 $[M]^+$ (38), 160 (37), 119 (56), 106 (38), 91 (100), 77 (79).

3,5-Di(N-methylamino)-1-phenyl-1,2,4-triazole (8). A mixture of compound **4** (0.4 g, 1.4 mmol) and conc. HCl (1 ml) was refluxed for 30 min, neutralized with a 20% aqueous solution of NH_3, and the precipitate formed was crystallized from water. Yield 0.2 g (71%); mp 123-123.5ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.65 (3H, d, *J* = 5.0, CH_3); 2.76 (3H, d, *J* = 4.7, CH_3); 5.68 (1H, q, *J* = 5.0, NH); 6.29 (1H, q, *J* = 4.7, NH);

7.19-7.24 (1H, m Ar); 7.39-7.48 (4H, m, Ar). Mass spectrum (EI), *m/z* (I_{rel}, %): 203 $[M]^+$ (71), 175 (10), 146 (24), 133 (19), 118 (39), 104 (50), 96 (35), 91 (100). Found, %: C 59.30; H 6.31; N 34.39. $C_{10}H_{13}N_5$. Calculated, %: C 59.10; H 6.45; N 34.46.

X-Ray structural analysis of compound **2e** was carried out on a Bruker SMART CCD area detector diffractometer at 200K, and of compound **4** on a Syntex $P2_1$ diffractometer at 193K. Single crystals of compounds **2e** were grown from a mixture of DMF and ethanol (1:5) and of compound **4** from a mixture of DMF, ethanol, and water (1:5:0.5). Both structures were solved by a direct method. All non-hydrogen atoms were localized in electron density difference syntheses and refined using F_{hkl}^2 in the anisotropic approximation. All hydrogen atoms were set up in the geometrically calculated positions and refined using the "riding" model with *U(H)* = 1.2 *U(C)* where *U(C)* is the equivalent temperature factor for the carbon atom with which the corresponding atom is bonded. The crystal parameters for compounds **2e** and **4** and the conditions for the X-ray structural experiments are given in Table 5. All calculations were made using the SHELXTL PLUS 5 program package [21].

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