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Reactivity of *C*-Amino-1,2,4-triazoles toward Electrophiles: A Combined Computational and Experimental Study of Alkylation by Halogen Alkanes

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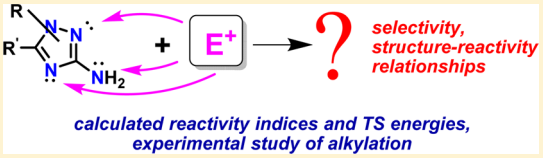
Supporting Information

ABSTRACT: A combination of computational and experimental methods was used to examine the structure−reactivity relationships in the reactions of *C*-amino-1*H*-1,2,4-triazoles with electrophiles. The global nucleophilicity of 3-amino- and 3,5-diamino-1*H*-1,2,4-triazoles was predicted to be higher than that of 5-amino-1*H*-1,2,4-triazoles. Fukui functions and molecular electrostatic potential indicate that reactions involving an amino group should occur more easily for the 3-amino- than for the 5-amino-1*H*-1,2,4-triazoles. Increasing electrophile hardness should increase the probability of attack at the N-4 atom of the triazole ring, whereas increasing softness should enhance the probability of attack at the N-2 atom and 3-NH_2 group. Calculated transition state energies of model S_N2 reactions and experimental studies showed that quaternization of 1-substituted 3-amino- and 3,5-diamino-1*H*-1,2,4-triazoles by many alkyl halides proceeds with low selectivity and can involve the N-2 and N-4 atoms as well as the 3-NH_2 group as reaction centers. A new method for the selective synthesis of 1,4-disubstituted 3-amino- and 3,5-diamino-1,2,4-triazoles based on quaternization of readily available 1-substituted 3-acetylamino-1,2,4-triazoles with subsequent removal of the acetyl protecting group by acid hydrolysis was developed.

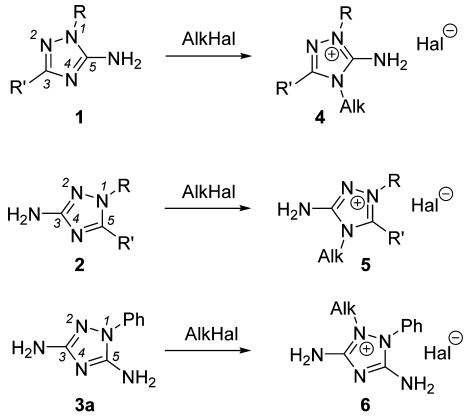


1. INTRODUCTION

C-Amino-1,2,4-triazoles are used as reagents for the synthesis of pesticides,[1] pharmaceuticals,[2] dyes,[3] photographic materials,[4] anticorrosion additives,[5] polymers,[6] magnetic,[7] optical[8] and energetic materials,[9] adsorbents, and catalysts.[10] The wide application of these compounds as reagents is largely based on their high reactivity toward electrophiles.[11] Molecules of *C*-amino-1,2,4-triazoles contain several nucleophilic centers, namely, the NH_2 group and any of the ring nitrogen atoms and, therefore, can be considered as multifunctional nucleophilic reagents. Such multifunctionality, on the one hand, opens up exciting possibilities for the synthesis of various substituted triazoles and condensed heterocycles; however, on the other hand, it causes the problem of low selectivity in the reactions of *C*-amino-1,2,4-triazoles with many electrophilic reagents.[11,12]

Alkylation of *C*-amino-1,2,4-triazoles by alkyl halides is used as a general method for preparing *N*-alkylated aminotriazoles, including quaternary salts.[11,13−15] It is largely reported that, in a neutral medium, the reaction affords products alkylated at the nitrogen atoms of the triazole cycle while the less nucleophilic NH_2 group is not alkylated, even in the case of triazoles **1**, **2**, and **3a**, which are substituted at the N-1 or N-2 atoms (Scheme 1). Thus, products **4** and **5**, which are quaternized at the N-4 of the triazole ring, were obtained by the alkylation of 1-substituted 5-amino- (**1**) and 3-amino-1,2,4-triazoles (**2**).[14,15]

Scheme 1



R = alkyl; R' = H, alkyl, 2-Furyl; Alk = alkyl; Hal = Cl, I

However, quaternization of 3,5-diamino-1-phenyl-1,2,4-triazole (**3a**) in methanol, as reported,[16] afforded N-2 alkylated products **6** (Scheme 1).

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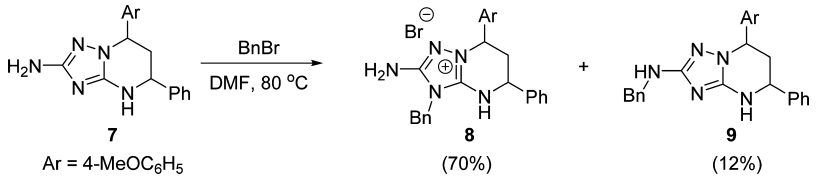
Scheme 2



As far as we know, examples of alkylation of the NH_2-group of 3-amino- and 5-amino-1,2,4-triazoles by alkyl halides in neutral medium have not been described in the literature. However, benzylation of **7** (reactivity of compounds **7**, in many aspects, is analogous to the 1-substituted 3-amino-1,2,4-triazoles **2** and **3**)[17] afforded alkylamino derivative **9** as a byproduct, in addition to the expected quaternary salt **8** (Scheme 2).[18]

Notably, the calculated (MP2/6-31+G*, gas phase) transition state (TS) energies of S_N2 attacks of methyl chloride on N-2 or NH_2 of 3-amino-1,2,4-triazoles (**2**, R = H, Me; R′ = H) are no more than 3 kcal/mol higher than the TS energies of the S_N2 attack on N-4.[15] The published results[15,18] suggest that the formation of alkylamino derivatives is possible in the reactions of aminotriazoles of types **2** or **3** with halogen alkanes, and apparently, the position of the endocyclic R substituent sufficiently affects the selectivity of alkylation of *C*-amino-1,2,4-triazoles. A careful investigation of reactions between aminotriazoles of types **2** and **3** is required for examination of these hypotheses.

In this work, we investigated the influence of the *C*-amino-1,2,4-triazole structure, namely, the position and type of substituent at the hydrazine fragment of triazole molecules, on their reactivity toward electrophiles, particularly halogen alkanes. For these purposes, we applied quantum chemical methods in combination with experimental investigations of alkylation of 1-substituted *C*-amino-1,2,4-triazoles and their acetyl derivatives by halogen alkanes.

2. RESULTS AND DISCUSSION

2.1. Computational Investigation of Reactivity of *C*-Amino-1,2,4-triazoles toward Electrophiles. To assess the influence of the substituent position in the triazole ring on the reactivity of isomeric *C*-amino-1,2,4-triazoles and predict the direction of electrophilic attack, we calculated the so-called static reactivity indices[19−25] as well as the transition state energies of S_N2 alkylation at various potential reaction centers for model molecules of aminotriazoles. It should be noted that the results obtained can be correctly applied to the kinetically controlled reactions in which the initial reaction products cannot isomerize to thermodynamically more stable compounds. Reactions of aminotriazoles with alkyl halides satisfy this limitation in most cases.

2.1.1. Computational Details. Quantum chemical calculations were performed using the Gaussian'09 suite of computational programs.[26] For all investigated species, a charge density analysis was performed by a natural population analysis (NPA)[27] at the DFT B3LYP/6-311++G(2d,2p)[28] or MP2/aug-cc-pVDZ levels of theory.[29] We note that the cationic systems required in the calculations of local reactivity indices were kept at the same geometry of the neutral system. The structures and transition state energies were computed at the B3LYP/6-311++G(2d,2p) level of theory. The character of the stationary points on the potential energy surface (minimum or transition state) was confirmed by calculation of the Hessian matrix at the same level of theory within the harmonic approximation. The optimized ground states had only real frequencies, whereas transition states had one imaginary frequency. The imaginary frequencies of the transition states were subsequently visualized and in all cases clearly indicated connection of reactants to products. Solvent effects were modeled by the integral equation formalism version of the polarizable continuum method (IEF-PCM) of Tomasi.[30] The computed energetic parameters and atomic coordinates of all species are given in the Supporting Information.

2.1.2. Static Reactivity Indices. For static reactivity indices, global and local reactivity descriptors were considered (for a detailed description, see the Supporting Information). The global reactivity descriptors, such as the electronic chemical potential (μ),[19a] chemical hardness (η),[19b] global softness (S),[19c] and nucleophilicity index (Nu),[20a,b] are believed to provide intermolecular reactivity trends.

The global nucleophilicity indices Nu were calculated by three different methods.[20b] According to the first method, $Nu^{(1)}$ was computed as the inverse of the electrophilicity index,[20a] in the second method, $Nu^{(2)}$ was calculated as the inverse of the electrodonating power,[20b] and in the third approach, nucleophilicity $Nu^{(3)}$ is considered as the negative value of the (intrinsic) ionization potential.[22a]

For local reactivity descriptors that reflect the intramolecular reactivity sequence, i.e., site selectivity in an individual molecule, the condensed Fukui functions (f_k^-)[20,21] and molecular electrostatic potential (MESP)[24] were considered. The Fukui functions (f_k^-) reflect reactivity in the frontier-controlled soft−soft reactions at the specific site in a molecule.[23] MESP can be applied as a reasonably good criterion to estimate the probability of hard−hard interactions, i.e., reactivity in charge-controlled reactions.[24] Corresponding descriptors of local reactivity in charge-controlled reactions are the most negative valued points (V_{min}) in electron-rich regions obtained from the MESP topography calculation.[25]

1-Methyl substituted *C*-amino-1,2,4-triazoles **1a** and **2a** and 3,5-diamino-1-methyl-1,2,4-triazole (**3b**) were applied as model molecules for the calculations of the static reactivity indices (Figure 1). The use of diaminotriazole **3b** as an object of theoretical investigation was stipulated by an effective combination of reactive fragments of both isomers **1a** and **2a** in one molecule. Analysis of the electron density of the molecules according to the "atoms-in-molecules" (AIM)[31] theory reveal that topological parameters of **1a** and **2a** are

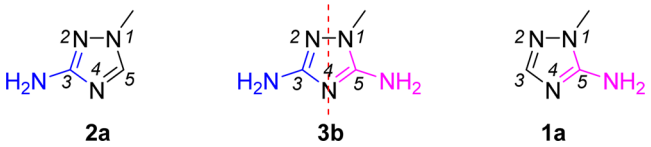


Figure 1. Structures of model compounds **2a**, **3b**, and **1a**.

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Table 1. HOMO and LUMO (ε_{HOMO}, ε_{LUMO}) Energies and Global Reactivity Indices (Electronic Chemical Potential (μ), Chemical Hardness (η), Global Softness (S), and Nucleophilicity Index[a] ($Nu^{(i)}$)) for C-Amino-1,2,4-triazoles 1a, 2a, and 3b Calculated at the DFT B3LYP/6-311++G(2d,2p) and MP2/aug-cc-pVDZ Levels of Theory in Gas and Aqueous Phases

	gas phase						aqueous phase					
	DFT			MP2			DFT			MP2		
reactivity index	2a	3b	1a	2a	3b	1a	2a	3b	1a	2a	3b	1a
ε_{HOMO}, eV	−6.101	−5.683	−6.477	−8.842	−8.558	−9.220	−6.355	−5.927	−6.525	−9.093	−8.783	−9.292
ε_{LUMO}, eV	−0.343	−0.559	−0.642	0.802	0.766	0.723	−0.240	−0.273	−0.244	1.002	1.002	1.009
μ, au	−0.118	−0.115	−0.131	−0.148	−0.143	−0.156	−0.121	−0.114	−0.124	−0.149	−0.143	−0.152
η, au	0.106	0.094	0.107	0.177	0.171	0.183	0.112	0.104	0.115	0.185	0.180	0.189
S, au^{-1}	4.726	5.310	4.664	2.822	2.918	2.737	4.450	4.813	4.332	2.696	2.781	2.642
$Nu^{(1)}$, au^{-1}	15.09	14.31	12.53	16.24	16.71	14.99	15.30	16.01	14.92	16.79	17.59	16.34
$Nu^{(2)}$, au^{-1}	8.42	8.63	7.57	6.71	6.93	6.37	8.24	8.76	8.03	6.65	6.90	6.49
$Nu^{(3)}$, eV	3.39	3.81	3.02	2.98	3.26	2.60	3.14	3.57	2.97	2.73	3.04	2.53

[a]The HOMO energy of the reference system (TCE) has been calculated at the MP2/aug-cc-pVDZ (−11.821 eV) and B3LYP/6-311++G(2d,2p) (−9.496 eV).

similar to the parameters of analogous fragments, especially C−NH_2 bonds, in **3b** (see the Supporting Information, Tables S-02, S-03, and S-04). This topological similarity, in our opinion, allows the application of 1-substituted 3,5-diamino-1,2,4-triazoles as suitable models for comparative analysis of reactivity of isomeric 1-substituted 3-amino- and 5-amino-1,2,4-triazoles.

As seen from the global reactivity indices presented in Table 1, 3-amino-1*H*-1,2,4-triazoles, modeled by **2a**, should be stronger nucleophiles than 5-amino-1*H*-1,2,4-triazoles, modeled by **1a** (indices N, ε_{HOMO}, S, and μ are higher for the molecule **2a**). Changing the method of calculation or the medium polarity did not fundamentally affect the ratio of reactivity indices. Apparently, these findings are also valid for the analogous tautomers of aminotriazoles (hydrogen as a substituent at the N atoms of the triazole cycle). It should be noted that the higher nucleophilicity of the 3-amino tautomer compared to the 5-amino tautomer follows from the values of global reactivity indices obtained by the B3LYP/6-31G** calculations.[32] Nucleophilicity of diaminotriazole **3b** should be higher compared to the aminotriazoles **1a** and **2a**, presumably owing to the presence of two electron-donating amino groups in the molecule.

Local Fukui functions presented in Table 2 show that N-2 and the 3-NH_2 group are the most probable sites for the attack

Table 2. Nucleophilic Fukui Functions (f_k^-) for the Molecule 3b Calculated at the DFT B3LYP/6-311++G(2d,2p) and MP2/aug-cc-pVDZ in Gas and Aqueous Phases

	gas phase		aqueous phase	
atom	DFT	MP2	DFT	MP2
N-2	0.225	0.175	0.246	0.193
N-4	0.061	0.042	0.066	0.050
3-$\underline{N}H_2$	0.196	0.223	0.184	0.193
5-$\underline{N}H_2$	0.109	0.076	0.124	0.105

of soft electrophiles in **3b**. Values of V_{min} and MESP contours (Figure 2) predict that N-4 of the triazole ring is the most probable center for attack of hard electrophiles in all types of aminotriazoles. Chances of attack of hard electrophiles on the N-2 atom or the nitrogen of 3-NH_2 are also sufficiently high. Values of Fukui functions and V_{min} also show that, in reactions with either soft or hard electrophiles, nucleophilicity of the 3-NH_2 group should be substantially higher than that of the 5-NH_2 group because electron density on the latter is substantially decreased. This finding is in agreement with the experimental data for the reactions of 1-substituted 3,5-diamino-1,2,4-triazoles with various carbonyl compounds and derivatives of carboxylic acids and sulfonyl chlorides.[17]

In summary, local reactivity indices indicate that reactions involving amino groups will proceed more readily for 3-amino-1*H*-1,2,4-triazoles than for 5-amino-1*H*-1,2,4-triazoles. Increasing electrophile hardness should enhance the likelihood of attack on N-4 in all of the above types of aminotriazoles. With increasing electrophile softness, the probability of attack on N-2 and 3-NH_2 in 3-amino-1*H*-1,2,4-triazoles and diaminotriazoles should rise.

2.1.3. Transition State Free Energies. Tautomers **1b** and **2b** of 3(5)-amino-1*H*-1,2,4-triazole and 1-substituted 3,5-diamino-1,2,4-triazoles **3a−c** with different R substituents (see Figure 3) were selected as model molecules for the calculation of free energies of activation ($\Delta G^{\ddagger}$). The $\Delta G^{\ddagger}$ (Table 3) of hypothetical transition states (TSs) that form during S_N2 alkylation by chloromethane in aqueous solution were calculated as the difference between the Gibbs free energy of the transition state G^{298}(TS) and the Gibbs free energies of starting compounds.[30b,33] Figure 3 also shows the relative free energies of activation ($\Delta\Delta G^{\ddagger}$) representing the difference between $\Delta G^{\ddagger}$ for a given reaction center and that calculated for the lowest energy. Rate constants (k) were estimated using transition state theory (TST) according to eq 1[33]

$$k = \frac{k_B T}{h} \exp\left(-\frac{\Delta G^{\ddagger}}{RT}\right) = \frac{k_B T}{h} \exp\left(-\frac{\Delta H^{\ddagger}}{RT}\right)\exp\left(\frac{\Delta S^{\ddagger}}{R}\right) \quad (1)$$

where k_B is the Boltzmann constant and h is the Planck constant, $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ are the Gibbs free energy, enthalpy and entropy of activation, correspondingly, and R is the gas constant.

As seen in Figure 3 and Table 3, N-4 (TS $\mathbf{B}^{\ddagger}$) and N-2 (TS $\mathbf{A}^{\ddagger}$) are preferable sites for S_N2 attack of chloromethane in the aminotriazoles **1−3**. Furthermore, formation of the products of alkylation of the 3-NH_2 group can be expected for **2b** and **3a−c** because relative Gibbs free energies of TS $\mathbf{C}^{\ddagger}$ were 0.7−2.2 kcal/mol higher than the energies of the most stable transition states $\mathbf{B}^{\ddagger}$ or $\mathbf{A}^{\ddagger}$. Thus, for **3b**, the estimated rate constant for alkylation at 3-NH_2 is 3 times less than those at N-4. On the

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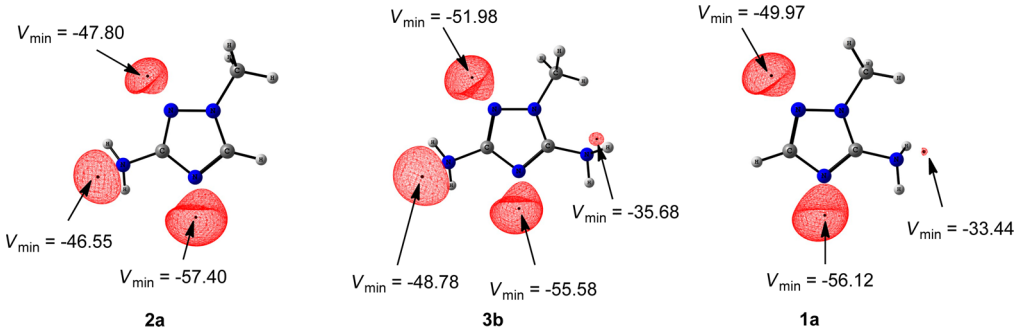

Figure 2. Molecular electrostatic potential isosurface at −33 kcal·mol^{-1} of molecules **2a**, **3b**, and **1a** computed at the MP2/aug-cc-pVDZ level in vacuum. The black dots represent the location of the V_{min} points (in kcal·mol^{-1}).

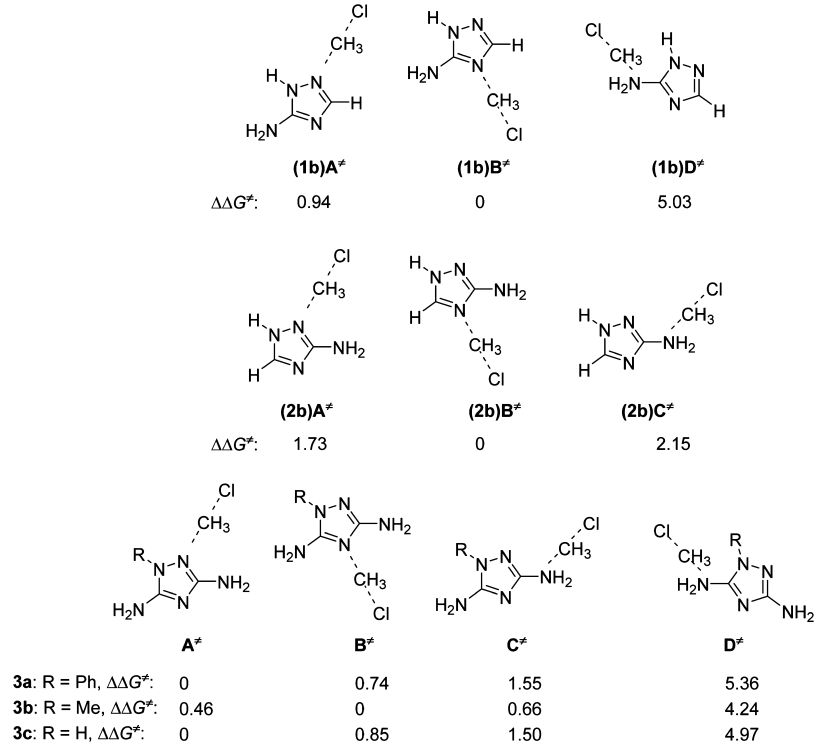

Figure 3. Transition states $A^{\ddagger}$–$D^{\ddagger}$ and their relative Gibbs free energies ($\Delta\Delta G^{\ddagger}$, kcal/mol).

Table 3. Calculated Transition State Gibbs Free Energies ($\Delta G^{\ddagger}$)[a] and Rate Constants (k) for S_N2 Alkylation of Compounds 1b, 2b, 3a–c at Various Reaction Centers at 298 K in Water (DFT B3LYP/6-311++G(2d,2p), IEF-PCM)

	$\Delta G^{\ddagger}$, kcal/mol					k, $M^{-1}\cdot s^{-1}$				
TS	1b	2b	3a	3b	3c	1b	2b	3a	3b	3c
$A^{\ddagger}$	30.0	30.3	28.5	29.2	28.5	6.3×10^{-10}	3.9×10^{-10}	7.7×10^{-9}	2.5×10^{-9}	7.5×10^{-9}
$B^{\ddagger}$	29.1	28.6	29.3	28.7	29.4	3.1×10^{-9}	7.2×10^{-9}	2.2×10^{-9}	5.5×10^{-9}	1.8×10^{-9}
$C^{\ddagger}$		30.7	30.1	29.4	30.0		1.9×10^{-10}	5.6×10^{-10}	1.8×10^{-9}	6.0×10^{-10}
$D^{\ddagger}$	34.1		33.9	33.0	33.5	6.3×10^{-13}		9.0×10^{-13}	4.3×10^{-12}	1.7×10^{-12}

[a] $\Delta G^{\ddagger} = G^{298}(TS) - [G^{298}(CH_3Cl) + G^{298}(aminotriazole)]$, corresponding values of $G^{298}(TS)$, $G^{298}(CH_3Cl)$, and $G^{298}(aminotriazole)$ are presented in the Supporting Information.

examples of substrates **1b** and **3a–c**, it is clear that alkylation of the 5-NH_2 group is scarcely probable because TS $D^{\ddagger}$ is sufficiently higher in energy (~4–5 kcal/mol) than other possible TSs.

It is interesting to consider the effect of the R substituent on the relative energy of the transition states $A^{\ddagger}$ and $B^{\ddagger}$ in **3a–c**. TS $A^{\ddagger}$ is more favorable if R = H (TS (**3c**)$A^{\ddagger}$) or Ph (TS (**3a**) $A^{\ddagger}$), whereas TS $B^{\ddagger}$ is slightly more stable if R = CH_3 (TS (**3b**) $B^{\ddagger}$). Owing to these differences, the ratios $k(A^{\ddagger})/k(B^{\ddagger})$ are 4.2 and 3.5 for **3a** and **3c**, respectively, whereas the same ratio is only 0.46 for **3b** (R = Me). It is likely that the transition state (**3b**)$A^{\ddagger}$ is destabilized by steric repulsions between R = Me (which is more bulky than a small hydrogen or a phenyl group that can be twisted almost perpendicularly relative to the plane of the triazole ring to decrease steric repulsions) and attacking methyl chloride. Nevertheless, in the optimized transition states

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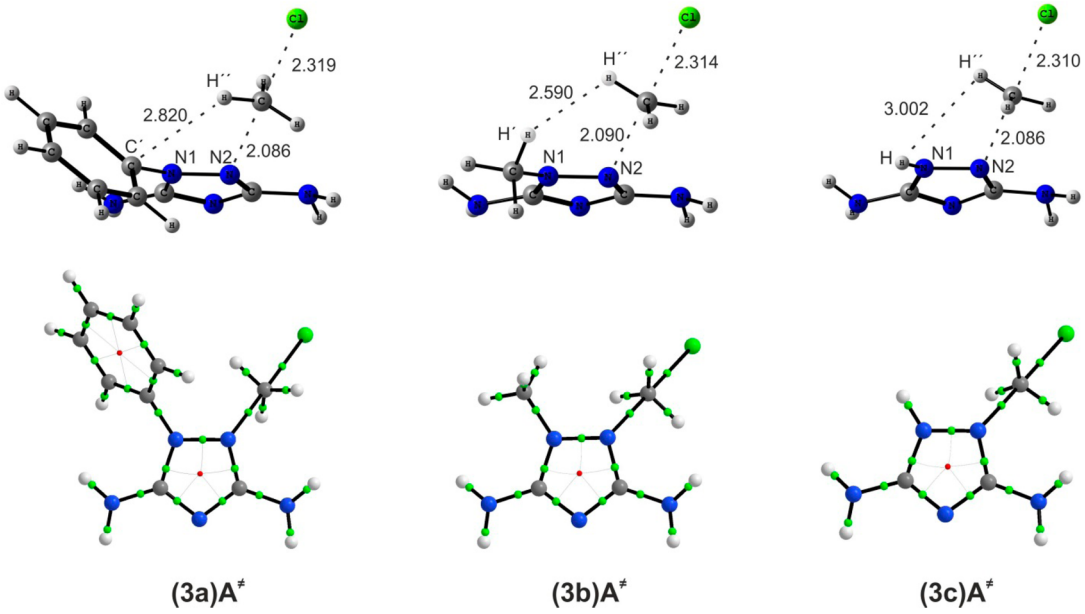

Figure 4. Structures and molecular graphs (AIMALL[34] representation) of the transition states (**3a**)$A^{‡}$, (**3b**)$A^{‡}$, and (**3c**)$A^{‡}$. Numbers at the dotted lines show the distances (Å) between specific atoms.

$A^{‡}$, the distances between the R substituent and the attacking molecule of methyl chloride are greater than or equal to the sum of the van der Waals radii (Figure 4). Furthermore, AIM[31] analyses do not show any bond paths between the atoms of R and methyl chloride (Figure 4). More detailed examination of the activation parameters (Table 4) shows that the change in

Table 4. Entropy [$\exp(\Delta S^{‡}/R)$] and Enthalpy [$\exp(\Delta H^{‡}/RT)$] Components of the Rate Constant for the Transition States $A^{‡}$ and $B^{‡}$

	$\exp(\Delta S^{‡}/R)$ for the transition state		$\exp(\Delta H^{‡}/R)$ for the transition state	
substrate	$A^{‡}$	$B^{‡}$	$A^{‡}$	$B^{‡}$
3a	7.61×10^{-8}	6.80×10^{-8}	1.62×10^{-14}	5.21×10^{-15}
3b	2.54×10^{-8}	8.30×10^{-8}	1.60×10^{-14}	1.06×10^{-14}
3c	4.10×10^{-8}	4.48×10^{-8}	2.96×10^{-14}	6.51×10^{-15}

the positional selectivity in the case of R = Me is caused by two factors. First, the entropy component of the rate constant for TS (**3b**)$A^{‡}$ is slightly decreased in relation to TS (**3a**)$A^{‡}$ and (**3c**)$A^{‡}$, presumably owing to the decreased probability of the bulky methyl group adopting an appropriate conformation in the (**3b**)$A^{‡}$. Second, the enthalpy component of the rate constant for TS (**3b**)$B^{‡}$ is slightly increased relative to TS (**3a**)$B^{‡}$ and (**3c**)$B^{‡}$, likely due to the higher electron-donating character of the methyl substituent.

Calculated TS energies indicate that aminotriazoles quaternized at the N-4 or N-2 atoms are the expected major products in S_N2 reactions of *C*-amino-1*H*-1,2,4-triazoles with halogen alkanes in the absence of strong bases. Formation of 3-alkylaminotriazoles as byproducts is expected in the alkylation of 3-amino- and 3,5-diamino-1*H*-1,2,4-triazoles; however, quaternization of 5-amino- or 3,5-diamino-1*H*-1,2,4-triazoles at the 5-NH_2 group is unlikely because of its poor nucleophilicity. These findings are consistent with the conclusions based on the static reactivity indices (section 2.1.2).

2.2. Experimental Investigation of Alkylation of 1-Substituted *C*-Amino-1,2,4-triazoles by Halogen Alkanes. Alkylation of 1-substituted *C*-amino-1,2,4-triazoles was investigated experimentally with **2c**, **3a**, and **3d** (Scheme 3). Three nucleophilic centers, N-2, N-4, and the 3-NH_2 group, were determined to take part in the reaction. Quaternization products of N2 and N4 are dominant, and the selectivity for such products is determined by the nature of the alkyl halide and aminotriazole. Interaction of **3a** (R = Ph) with a majority of alkyl halides resulted in the formation of the N2-alkylated compounds **6b–e** as major products. In the reaction with iodomethane, a mixture of N-2- and N-4-alkylated products, **6a** and **10a**, was obtained, whereas, with iodoacetamide, the only product isolated was compound **10b**. It is likely that, in the case of iodomethane and particularly iodoacetamide, the role of charge control of the reaction selectivity increases, thus leading to an enhanced yield of N-4-alkylated products, as predicted by the static reactivity indices (section 2.1.2). In agreement with the TS energy calculation predictions (section 2.1.3), the benzylation of 1-alkylsubstituted triazoles **2c** and **3d** affected the N-4 atom of the triazole ring, resulting in formation of **10c** and **5a**, while N-2-alkylated products were not obtained.

In most cases, 3-alkylamino derivatives were detected chromatographically as byproducts in the reaction mixtures (see the Supporting Information for GC–MS data); moreover, the 3-benzylamino triazoles **11a–c** and *N,N*-dibenzylamino-triazoles **12a** and **12b** were isolated from the reaction mixtures (Scheme 3). Formation of **12a** and **12b** indicates that alkylamino derivatives are formed by the direct alkylation of the 3-NH_2 group rather than by the possible Dimroth rearrangement[35] of N-4- or N-2-alkylated products. Notably, the proposed Dimroth rearrangements of **6** and **10** were not obtained under the reaction conditions. Thus, **6e** and **10d** did not undergo transformation upon heating in acetonitrile or ethanol at 80–90 °C for 48 h, despite the addition of an equimolar amount of 40% aqueous HBr as a catalyst. In aqueous NaOH solution, **6e** decomposes to form a complex

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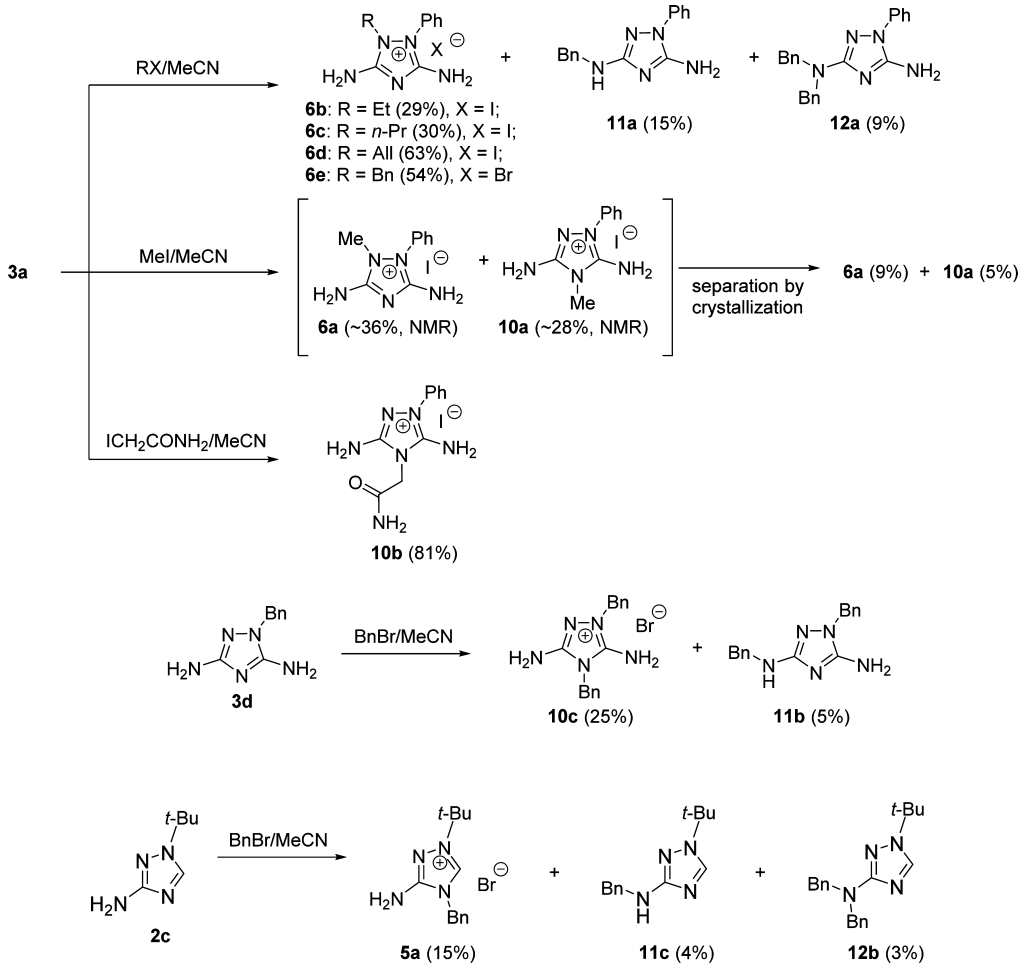
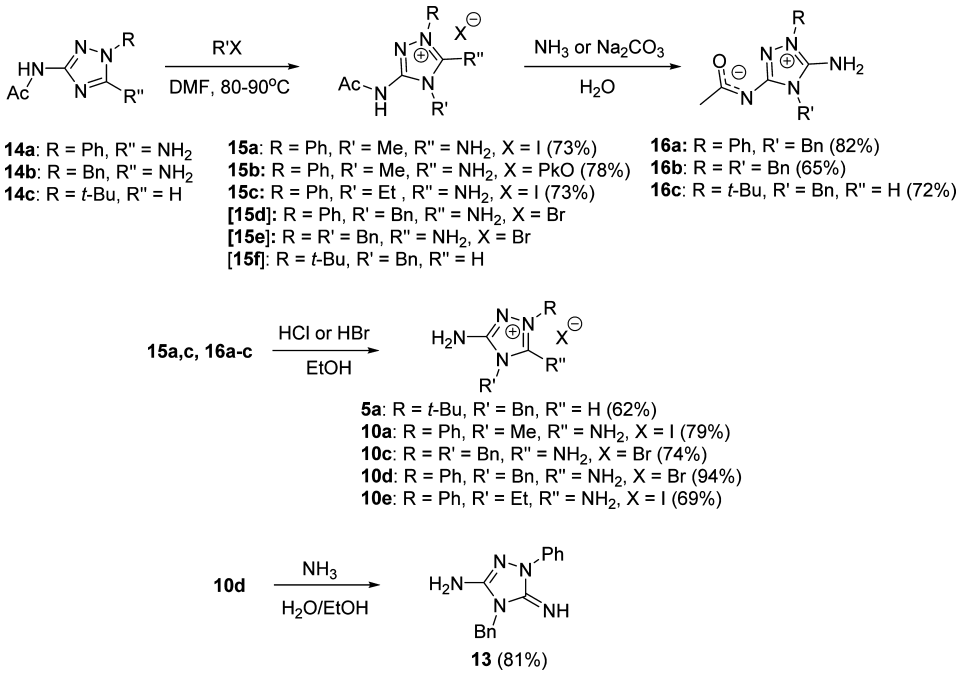
Scheme 3



Scheme 4



mixture of products, while **10d** gives the free base **13** (Scheme 4).

Therefore, the experimentally obtained results are in accordance with the theoretical predictions discussed in section

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2.1: alkylation of 1-substituted 3-amino- and 3,5-diamino-1,2,4-triazoles generally proceeded with low selectivity and involved N-4, N-2, and the 3-NH_2 group, while the 5-NH_2 group was unaffected by alkyl halides.

As previously mentioned, quaternization of 1-substituted 5-amino-1,2,4-triazoles, in many cases, proceeds selectively at N-4 of the triazole cycle and serves as an important method for the preparation of 1,4-disubstituted 5-amino-1,2,4-triazoles.[14,15] However, our theoretical and experimental results indicate that the analogous approach is inefficient for the preparation of 1,4-disubstituted 3-amino- and 3,5-diamino-1,2,4-triazoles due to low reaction selectivity of these substrates with the majority of alkyl halides. We proposed that the selectivity of alkylation can be enhanced if the 3-NH_2 group is protected and its electron-donating influence on N-2 of the triazole cycle is decreased by acylation. An analogous approach (acetylation of 3-NH_2 before *N*-alkylation of the triazole ring) was applied in the synthesis of alkylated 2-amino-4,5,6,7-tetrahydro[1,2,4]-triazolo[1,5-*a*]pyrimidines to prevent the formation of alkylamino byproducts.[18] While the quaternization of 3-acylamino-1*H*-1,2,4-triazoles was not studied previously, we expected that acylation of the 3-NH_2 group would enhance the selectivity of the subsequent N-4 alkylation of the triazole ring. This proposition was partly based on the observation of regioselective cyclization of 3-chloropropanoyl derivatives of partially hydrogenated 2-amino[1,2,4]triazolo[1,5-*a*]-pyrimidines; the key step of the cyclization is the selective intramolecular alkylation at N-4 of the 1,2,4-triazole ring.[36] Therefore, we investigated the alkylation of 3-acetylamino-1,2,4-triazoles **14a**,[17a] **14b**,[17a] and **14c**, which are readily available from the acetylation of the corresponding amino-triazoles **2c**, **3a**, and **3d**.

It was established that the quaternization of 3-acetylamino-1,2,4-triazoles **14a–c** by alkyl halides in DMF resulted in selective formation of N-4-alkylated compounds **15a** and **15c–f** (Scheme 4). The methylation product of **14a** was isolated also in the form of the picrate **15b**. Some alkyl derivatives were separated as the free bases **16a–c** (Scheme 4). Target compounds **5a**, **10a**, and **10c–e** were obtained by acid hydrolysis of the acetyl derivatives **15** and **16** (Scheme 4). Therefore, alkylation of 1-substituted 3-acetylamino-1,2,4-triazoles by alkyl halides with subsequent elimination of the acetyl group by hydrolysis is a new method for the selective synthesis of 1,4-disubstituted 3-amino- and 3,5-diamino-1,2,4-triazoles.

The structures of the synthesized compounds were established by elemental analysis, mass spectrometry, and NMR spectroscopic data, including $^{1}H-^{13}C$ heteronuclear correlation HSQC and HMBC spectra for the majority of compounds, NOESY spectra for **6e** and **10b**, and X-ray diffraction studies of **6e**, **10a** (for details, see the Supporting Information), and **16a**.[37]

Some NMR spectral peculiarities and schemes of key correlations in the HMBC and NOESY spectra used for the assignment of structures of **6** and **10** are presented in Figure 5. It is notable that, in the ^{13}C NMR spectra of compounds **6**, the signals of both carbon atoms of the triazole cycle are observed in the region of 160–162 ppm, whereas, in the spectra of isomers **10**, these signals are shifted upfield to 146–151 ppm, which is analogous to other salts of 1,4-disubstituted *C*-amino-1,2,4-triazoles.[38]

The ^{1}H NMR spectra of the mesoionic compounds **16a** and **16b** displayed significantly broadened NH_2 proton signals that

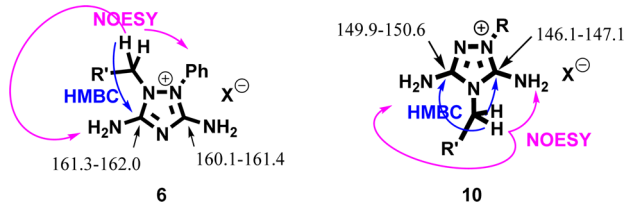

Figure 5. NMR spectral characteristics (chemical shifts, δ, ppm) of compounds **6** and **10** in DMSO-d_6 and key correlations in the NOESY and HMBC spectra.

merged into the background, apparently due to rapid exchange with the solvent. Similar broadening was observed for the NH signals of the structurally analogous mesoionic compounds.[18,36b] Moreover, the mesoionic structure of **16a** was supported by pK_a measurements[36b] and X-ray analysis.[37]

3. CONCLUSION

The position of the endocyclic R substituent has a significant influence on the reactivity of *C*-amino-1-R-1,2,4-triazoles. The global nucleophilicity of the 1-substituted 3-amino- and 3,5-diamino-1,2,4-triazoles is higher than that of the 1-substituted 5-amino-1,2,4-triazoles. Therewith, the amino group in the 3-position of the triazole ring is substantially more nucleophilic than in the 5-position. N-2 and N-4 of the triazole ring as well as the 3-NH_2 group in the 1-substituted *C*-amino-1,2,4-triazoles are the most favorable sites for the attack of electrophiles, including the majority of alkyl halides. The selectivity of alkylation of 1-substituted 3,5-diamino-1,2,4-triazoles by alkyl halides can be sufficiently enhanced if the 3-NH_2 group is initially acetylated. The acetyl group not only protects the highly nucleophilic 3-amino group but also affects the selectivity of endocyclic alkylation in favor of the quaternization at N-4 in the substrates where alkylation at N-2 is sterically possible. An increase in the selectivity of the endocyclic alkylation is likely achieved by the reduction of the electron-donating resonance effect of the acylated 3-amino group on N-2 in the transition state.

4. EXPERIMENTAL SECTION

4.1. General Information. Melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. IR spectra were recorded using a single reflection diamond ATR system as a sampling accessory. ^{1}H NMR spectra were acquired at 300, 500, or 600 MHz, and ^{13}C $\{^{1}H\}$ NMR spectra were acquired at 125 or 150 MHz in DMSO-d_6 using TMS as an internal standard. Mass spectra were recorded in the form of *m*/*z* (intensity relative to base 100) using electron impact ionization (70 eV). GC–MS measurements were acquired with a GC system equipped with a mass-selective detector (electron impact, 70 eV) and an HP-5-MS column (30 m × 0.25 mm × 0.25 μm film) using He as carrier gas at a flow of 1.0 mL/min. The following temperature program was used in all GC–MS measurements: initial temperature 65 °C, hold for 7 min, then 25 °C/min to 190 °C for 1 min, then 10 °C/min to 260 °C for 20 min, and then 10 °C/min to 280 °C for 18 min. High-resolution mass spectra (HRMS) were obtained on a TOF MS instrument using electrospray ionization (ESI) in positive ion mode (interface capillary voltage −4500 V).

Starting compounds **3a**,[16] **3d**,[39] **2c**,[12a] and **14a**,**b**[17a] were prepared by known methods. All other chemicals are commercially available.

4.2. General Procedure for the Synthesis of Compounds 6b–d and 10b. A magnetically stirred mixture of **3a** (0.5 g, 2.86 mmol), the corresponding alkyl halide (3.43 mmol), and acetonitrile (1.5 mL) was heated in a sealed ampule at 80–90 °C for 12 h and then cooled to room temperature. The solid obtained was isolated by filtration and recrystallized from an appropriate solvent.

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*3,5-Diamino-1-ethyl-2-phenyl-1H-1,2,4-triazol-2-ium Iodide (**6b**).* Yield 0.274 g (29%) of yellowish crystals, mp 260−261 °C (from *i*-PrOH). IR (cm^{-1}): 3319, 3279, 3104, 2950, 1680, 1630, 1585, 1549, 1518, 1488, 1458, 1107, 773. ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.96 (t, J = 7.0 Hz, 3H, Me), 3.59 (q, J = 7.0 Hz, 2H, CH_2), 7.51−7.63 (m, 5H, Ph), 8.14 (br s, 4H, $2NH_2$). ^{13}C NMR (150 MHz, DMSO-d_6): δ 10.9 (CH_3), 41.2 (CH_2), 127.4, 130.4, 130.6, 132.7 (carbons of Ph), 161.3 (C-3), 161.8 (C-5). MS (EI, 70 eV), m/z (%): 203 (15) [M − HI]$^+$, 188 (18) [M − HI − CH_3]$^+$, 175 (100), 128 (94) [HI]$^+$. Anal. Calcd for $C_{10}H_{14}N_5I$: C, 36.27; H, 4.26; N, 21.15. Found: C, 35.98; H, 4.39; N, 21.29.

*3,5-Diamino-2-phenyl-1-propyl-1H-1,2,4-triazol-2-ium Iodide (**6c**).* Yield 0.297 g (30%) of yellowish crystals, mp 223−224 °C (from water). IR (cm^{-1}): 3319, 3238, 3121, 2968, 1689, 1629, 1588, 1546, 1514, 1490, 1458, 1102, 774. ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.73 (t, J = 7.4 Hz, 3H, CH_3), 1.40 (m, 2H, CH_2), 3.56 (t, J = 7.2 Hz, 2H, CH_2), 7.50−7.63 (m, 5H, Ph), 7.91 (br s, 2H, NH_2), 8.23 (br s, 2H, NH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 10.2 (CH_3), 19.6 (CH_2), 46.9 (CH_2), 127.6, 130.3, 130.6, 132.7 (carbons of Ph), 161.1 (C-3), 161.3 (C-5). MS (EI, 70 eV), m/z (%): 217 (9) [M − HI]$^+$, 175 (100), 128 (12) [HI]$^+$. Anal. Calcd for $C_{11}H_{16}N_5I$: C, 38.28; H, 4.67; N, 20.29. Found: C, 37.95; H, 4.84; N, 20.01.

*3,5-Diamino-2-phenyl-1-(prop-2-en-1-yl)-1H-1,2,4-triazol-2-ium Bromide (**6d**).* Yield 0.618 g (63%) of white crystals, mp 212−213 °C (from *i*-PrOH). IR (cm^{-1}): 3492, 3370, 3283, 3094, 2936, 1688, 1629, 1589, 1542, 1515, 1488, 1456, 1419, 1108, 928, 775. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.27 (d, J = 5.6 Hz, 2H, CH_2), 5.07 (m, 1H, CH), 5.20 (m, 1H, CH), 5.67 (m, 1H, CH), 7.46−7.47 (m, 2H, Ph), 7.59−7.60 (m, 3H, Ph), 8.03 (br s, 2H, NH_2), 8.45 (br s, 2H, NH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 48.0 (CH_2), 119.8 (C-1′), 127.9 (C-2′), 129.6, 130.3, 130.7, 132.6 (carbons of Ph), 161.1 (C-3), 161.3 (C-5). MS (EI, 70 eV), m/z (%): 215 (54) [M − HBr]$^+$, 175 (56), 77 (100). Anal. Calcd for $C_{11}H_{14}N_5Br$: C, 44.61; H, 4.76; N, 23.65. Found: C, 44.86; H, 4.52; N, 23.39.

*3,5-Diamino-4-(2-amino-2-oxoethyl)-1-phenyl-4H-1,2,4-triazol-1-ium Iodide (**10b**).* Yield 0.834 g (81%) of cream-colored crystals, mp 217−219 °C (from EtOH). IR (cm^{-1}): 3391, 3340, 3261, 3174, 3111, 2974, 1677, 1648, 1607, 1523, 1497, 1457, 1396, 1303, 1089, 809, 764. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.58 (s, 2H, CH_2), 6.75 (br s, 2H, 3-NH_2), 7.45 (br s, 1H, $CONH_2$), 7.47−7.51 (m, 3H, Ph), 7.58−7.59 (m, 2H, Ph), 7.72 (br s, 1H, $CONH_2$), 8.32 (br s, 2H, 5-NH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 44.4 (CH_2), 124.1, 128.8, 129.8, 134.8 (carbons of Ph), 147.1 (C-5), 150.6 (C-3), 165.9 (CO). MS (EI, 70 eV), m/z (%): 232 (100) [M − HI]$^+$, 175 (22). Anal. Calcd for $C_{10}H_{13}N_6IO$: C, 33.35; H, 3.64; N, 23.33. Found: C, 33.59; H, 3.51; N, 23.18.

4.3. 3,5-Diamino-1-methyl-2-phenyl-1*H*-1,2,4-triazol-2-ium Iodide (6a) and 3,5-Diamino-4-methyl-1-phenyl-4*H*-1,2,4-triazol-1-ium Iodide (10a). A magnetically stirred mixture of **3a** (0.5 g, 2.86 mmol), iodomethane (0.49 g, 3.43 mmol), and acetonitrile (2 mL) was heated in a sealed ampule at 80−90 °C for 12 h and then cooled to room temperature. The solid obtained was isolated by filtration and dried at room temperature to give a mixture that contained ∼56% **6a** (yield 36%) and ∼44% **10a** (yield 28%) according to ^{1}H NMR. The mixture was crystallized four times from *i*-PrOH and twice from water to give pure **6a**. Yield 0.078 g (9%) of yellowish crystals, mp 246−247 °C. IR (cm^{-1}): 3342, 3282, 3117, 2940, 1680, 1633, 1587, 1547, 1516, 1486, 1457, 772. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.14 (s, 3H, CH_3), 7.48−7.51 (m, 2H, Ph), 7.61−7.63 (m, 3H, Ph), 7.92 (br s, 2H, NH_2), 8.16 (br s, 2H, NH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 33.4 (CH_3), 127.9, 130.3, 130.7, 132.3 (carbons of Ph), 160.1 (C-3), 161.6 (C-5). MS (EI, 70 eV), m/z (%): 189 (5) [M − HI]$^+$, 175 (75), 127 (100). Anal. Calcd for $C_9H_{12}N_5I$: C, 34.09; H, 3.81; N, 22.08. Found: C, 33.75; H, 4.01; N, 21.81.

Mother liquors, after removal of **6a**, were combined and evaporated to dryness. A residue obtained was crystallized three times from water (last crystallization was performed by slow evaporation of the solution to a small volume at room temperature for 3 days) to give pure **10a**. Yield 0.045 g (5%) of yellowish crystals, mp 238−239 °C. IR (cm^{-1}): 3260, 3200, 3125, 2928, 1679, 1643, 1592, 1541, 1497, 1457, 1158, 1118, 1013, 758. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.37 (s, 3H, CH_3), 6.78 (br s, 2H, 3-NH_2), 7.44−7.61 (m, 5H, Ph), 8.24 (br s, 2H, 5-NH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 29.5 (CH_3), 124.2, 128.8, 129.7, 134.9 (carbons of Ph), 146.8 (C-5), 150.5 (C-3). MS (EI, 70 eV), m/z (%): 189 (100) [M − HI]$^+$, 91 (98). Anal. Calcd for $C_9H_{12}N_5I$: C, 34.09; H, 3.81; N, 22.08. Found: C, 34.18; H, 3.69; N, 21.87.

4.4. 3,5-Diamino-1-benzyl-2-phenyl-1*H*-1,2,4-triazol-2-ium Bromide (6e), N^3-Benzyl-1-phenyl-1*H*-1,2,4-triazole-3,5-diamine (11a), and N^3,N^3-Dibenzyl-1-phenyl-1*H*-1,2,4-triazole-3,5-diamine (12a). A magnetically stirred mixture of **3a** (0.5 g, 2.86 mmol), benzyl bromide (0.58 g, 3.43 mmol), and acetonitrile (2 mL) was heated in a sealed ampule at 80−90 °C for 12 h, and acetonitrile was evaporated off at reduced pressure. The residue obtained was dissolved in a hot (80−90 °C) water solution (6 mL) of sodium acetate trihydrate (10%). The precipitate formed after cooling to 20 °C was filtered off and recrystallized from EtOH to give **12a**. Yield 0.091 g (9%) of colorless crystals, mp 142−143 °C (from EtOH). IR (cm^{-1}): 3448, 3298, 3087, 2922, 1685, 1644, 1590, 1546, 1485, 1454, 1388, 1369, 1296, 1123, 940, 751. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.48 (s, 4H, $2CH_2$), 6.36 (br s, 2H, NH_2), 7.22−7.32 (m, 11H, Ar), 7.42−7.44 (m, 2H, Ar), 7.52−7.53 (m, 2H, Ar). ^{13}C NMR (150 MHz, DMSO-d_6): δ 49.9 ($2CH_2$), 121.2, 125.2, 126.7, 127.6, 128.2, 129.1, 137.9, 138.8 (carbons of benzene rings), 154.0 (C-5), 162.3 (C-3). MS (EI, 70 eV), m/z (%): 355 (18) [M]$^+$, 91 (100). Anal. Calcd for $C_{22}H_{21}N_5$: C, 74.34; H, 5.96; N, 19.70. Found: C, 74.05; H, 6.12; N, 19.83.

The mother liquor after separation of **12a** was extracted by chloroform (3 × 3 mL). The extract was dried by anhydrous Na_2SO_4 and evaporated to dryness. The residue obtained was recrystallized from acetonitrile to give **11a**: yield 0.113 g (15%), colorless crystals with mp 165−166 °C (lit. mp 165−166 °C).[17a] The product obtained was identical in both its physical and spectral characteristics with an authentic sample of **11a**.[17a]

The water solution, after extraction of **11a**, was evaporated to a volume of ∼2 mL and cooled to 5−10 °C. The solid obtained was isolated by filtration and recrystallized from water, then from *i*-PrOH to give **6e**. Yield 0.532 g (54%) of colorless crystals, mp 225−226 °C (from *i*-PrOH). IR (cm^{-1}): 3348, 3246, 3060, 2750, 1685, 1629, 1591, 1547, 1517, 1494, 1456, 1115, 768. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.91 (s, 2H, CH_2), 7.03−7.04 (m, 2H, Ar), 7.31−7.35 (m, 5H, Ar), 7.55 (m, 3H, Ar), 8.03 (br s, 2H, NH_2), 8.65 (br s, 2H, $2NH_2$). ^{13}C NMR (150 MHz, DMSO-d_6): δ 49.0 (CH_2), 127.48, 127.53, 128.3, 128.7, 130.2, 130.4, 132.7, 133.5 (carbons of benzene rings), 161.4 (C-3), 162.0 (C-5). MS (EI, 70 eV), m/z (%): 265 (5) [M − HBr]$^+$, 91 (100). Anal. Calcd for $C_{15}H_{16}N_5Br$: C, 52.04; H, 4.66; N, 20.23. Found: C, 51.78; H, 4.68; N, 19.92.

4.5. 3,5-Diamino-1,4-dibenzyl-4*H*-1,2,4-triazol-1-ium Bromide (10c) and N^3,1-Dibenzyl-1*H*-1,2,4-triazole-3,5-diamine (11b). A magnetically stirred mixture of **3d** (0.541 g, 2.86 mmol), benzyl bromide (0.58 g, 3.43 mmol), and acetonitrile (2 mL) was heated in a sealed ampule at 80−90 °C for 12 h. After cooling to room temperature, the precipitate formed was collected by filtration and recrystallized from acetonitrile to give 0.258 g (25%) of **10c** as colorless crystals (mp 215−217 °C). IR (cm^{-1}): 3433, 3329, 3267, 3094, 1681, 1648, 1588, 1529, 1456, 1362, 1143, 737. ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.08 (s, 2H, 1-C$\underline{H}_2$Ph), 5.14 (s, 2H, 4-C$\underline{H}_2$Ph), 6.77 (s, 2H, 3-NH_2), 7.23−7.42 (m, 10H, 2Ph), 8.44 (s, 2H, 5-NH_2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 44.5 (1-$\underline{C}H_2$Ph), 49.9 (4-$\underline{C}H_2$Ph), 126.8, 127.8, 127.98, 128.00, 128.6, 128.7, 134.0, 134.8 (carbons of benzene rings), 147.1 (C-5), 150.1 (C-3). MS (EI, 70 eV), m/z (%): 280 (2) [M − Br]$^+$, 279 (10) [M − HBr]$^+$, 91 (100). Anal. Calcd for $C_{16}H_{18}N_5Br$: C, 53.34; H, 5.04; N, 19.44. Found: C, 53.01; H, 5.19; N, 19.27.

The reaction mixture, after separation of **10c**, was evaporated to a small volume in vacuum, and the residue obtained was dissolved in a hot (80−90 °C) 5% water solution of sodium acetate trihydrate (50 mL). The resulting solution was extracted by $CHCl_3$ (4 × 5 mL). The extract was dried by Na_2SO_4, evaporated to a small volume (∼5 mL), and chromatographed on a neutral Al_2O_3 (activity III) column (2.5 cm

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× 30 cm) with elution by $CHCl_3$ to give **11b**, R_f = 0.22. Yield 0.04 g (5%), mp 173−175 °C (from EtOH), (lit. mp 173−175 °C).[17c] The product obtained was identical in both its physical and spectral characteristics with an authentic sample of compound **11b**.[17c]

4.6. 3-Amino-4-benzyl-1-*tert*-butyl-4*H*-1,2,4-triazol-1-ium Bromide (5a), *N*-Benzyl-1-*tert*-butyl-1*H*-1,2,4-triazol-3-amine (11c), and *N*,*N*-Dibenzyl-1-*tert*-butyl-1*H*-1,2,4-triazol-3-amine (12b). A magnetically stirred mixture of **2c** (0.8 g, 5.72 mmol), benzyl bromide (1.16 g, 6.86 mmol), and acetonitrile (4 mL) was heated in a sealed ampule at 80−90 °C for 12 h and then cooled to room temperature. The precipitate formed was collected by filtration and recrystallized from EtOH to give **5a**. Yield 0.267 g (15%) of colorless crystals, mp 223−224 °C (from EtOH). IR (cm^{-1}): 3281, 3242, 3137, 3023, 2973, 1645, 1598, 1552, 1465, 1371, 1197, 1092, 988, 871, 739. ^1H NMR (300 MHz, DMSO-d_6): δ 1.53 (s, 9H, $3CH_3$), 5.27 (s, 2H, CH_2), 7.36−7.42 (m, 7H, Ph + NH_2), 9.83 (s, 1H, H-5). ^{13}C NMR (150 MHz, DMSO-d_6): δ 27.7 ($3CH_3$), 47.2 (CH_2), 61.4 ($\underline{C}(CH_3)_3$), 128.0, 128.4, 128.7, 133.7 (carbons of benzene ring), 137.2 (C-5), 154.0 (C-3). HRMS (ESI-TOF), m/z $[C_{13}H_{19}N_4]^+$ calcd for $C_{13}H_{19}N_4Br$ 231.1604, found 231.1606.

The reaction mixture, after removal of **5a**, was evaporated to a small volume in vacuum, and the residue obtained was dissolved in a hot (80−90 °C) water solution (50 mL) of sodium acetate trihydrate (5%). The solution obtained was extracted by $CHCl_3$ (4 × 5 mL). The extract was dried by Na_2SO_4, evaporated to a small volume (∼5 mL), and chromatographed on a neutral Al_2O_3 (activity III) column (2.5 cm × 30 cm). The column was initially eluted with hexane, and the first fraction (predominantly BnBr) was rejected. Then, the column was eluted by hexane/$CHCl_3$ (9:1) to afford **12b**, yield 0.056 g (3%), viscous oil, IR (cm^{-1}): 3028, 2975, 2858, 1562, 1494, 1453, 1228, 1029, 749. ^1H NMR (600 MHz, DMSO-d_6): δ 1.47 (s, 9H, *t*-Bu), 4.49 (s, 4H, $2CH_2$), 7.21−7.29 (m, 10H, 2Ph), 8.10 (s, 1H, H-5). ^{13}C NMR (150 MHz, DMSO-d_6): δ 28.7 ($3CH_3$), 50.5 ($2CH_2$), 56.8 ($\underline{C}(CH_3)_3$), 126.7, 127.8, 128.1, 138.7 (carbons of benzene rings), 139.7 (C-5), 156.0 (C-3). MS (EI, 70 eV), m/z (%): 320 (30) $[M]^+$, 173 (100). Anal. Calcd for $C_{20}H_{24}N_4$: C, 74.97; H, 7.55; N, 17.48. Found: C, 75.24; H, 7.49; N, 17.27.

Further, the column was eluted by hexane/$CHCl_3$ (1:1) to afford the compound **11c** (0.053 g, yield 4%) as colorless crystals, mp 95−97 °C (from CCl_4). IR (cm^{-1}): 3236, 3071, 2975, 2858, 1567, 1452, 1368, 1228, 1115, 992, 850, 746. ^1H NMR (600 MHz, DMSO-d_6): δ 1.44 (s, 9H, $3CH_3$), 4.30 (d, J = 6.5 Hz, 2H, CH_2), 6.28 (t, J = 6.5 Hz, 1H, NH), 7.18−7.33 (m, 5H), 7.98 (s, 1H, H-5). ^{13}C NMR (150 MHz, DMSO-d_6): δ 28.8 ($3CH_3$), 46.6 (CH_2), 56.6 ($\underline{C}(CH_3)_3$), 126.3, 127.4, 127.9, (carbons of Ph), 139.3 (C-5), 141.1 (C-ipso of phenyl), 164.3 (C-3). MS (EI, 70 eV), m/z (%): 230 (58) $[M]^+$, 173 (100). Anal. Calcd for $C_{13}H_{18}N_4$: C, 67.80; H, 7.88; N, 24.33. Found: C, 68.05; H, 7.76; N, 24.19.

4.7. General Procedure for the Synthesis of Compounds 15a−c and 16a−c. A magnetically stirred mixture of **14a−c** (2.30 mmol), the corresponding alkyl halide (2.99 mmol), and dry DMF (1 mL) was heated in a sealed ampule at 80−90 °C for 8 h. To isolate **15a** and **15c**, the reaction mixture was evaporated to almost dryness at reduced pressure and the residue obtained was dissolved in hot acetonitrile (3 mL). The crystals that separated after cooling to 0−5 °C were collected by filtration, recrystallized from an appropriate solvent, and dried at 100 °C to give **15a** and **15c**. To isolate picrate **15b**, the reaction mixture was evaporated to almost dryness at reduced pressure and the residue obtained was dissolved in water (1 mL). Then, the solution was mixed with a solution of picric acid (0.69 g, 2.3 mmol) and $LiOH·2H_2O$ (0.18 g, 3.0 mmol) in water (3 mL). The precipitate formed was collected by filtration and recrystallized to give **15b**. To isolate **16a** and **16b**, the reaction mixture was cooled to room temperature and diluted with 10% NH_3 solution in water (6 mL). The solid obtained was collected by filtration, recrystallized from an appropriate solvent, and dried at 100 °C to give **16a** and **16b**. To isolate **16c**, the reaction mixture was evaporated to dryness at reduced pressure and the residue obtained was dissolved in hot water (30 mL). The solution obtained was evaporated to ∼3 mL at atmospheric pressure to remove traces of DMF and BnBr. The resulting solution was diluted with water (5 mL), alkalized to pH 8−9 by addition of Na_2CO_3, and extracted by $CHCl_3$ (4 × 4 mL). The extract was dried by Na_2SO_4 and evaporated to dryness. The residue obtained was recrystallized from acetonitrile to give pure **16c**.

3-(Acetylamino)-5-amino-4-methyl-1-phenyl-4H-1,2,4-triazol-1-ium Iodide (15a). Yield 0.603 g (73%) of yellowish crystals, mp 194−195 °C (from *i*-PrOH). IR (cm^{-1}): 3220, 3043, 2904, 2725, 1694, 1662, 1608, 1529, 1484, 1455, 1398, 1369, 1325, 1247, 1006, 867, 760. ^1H NMR (600 MHz, DMSO-d_6): δ 2.15 (s, 3H, $C\underline{H}_3CO$), 3.37 (s, 3H, CH_3), 7.57−7.66 (m, 5H, Ph), 8.65 (br s, 2H, NH_2), 11.02 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 22.7 ($\underline{C}H_3CO$), 30.7 (CH_3), 125.0, 129.8, 129.9, 134.2 (carbons of Ph), 143.5 (C-3), 148.8 (C-5), 170.4 (CO). MS (EI, 70 eV), m/z (%): 232 (2) $[M - I^-]^+$, 231 (16) $[M - HI]^+$, 43 (100). Anal. Calcd for $C_{11}H_{14}N_5IO$: C, 36.78; H, 3.93; N, 19.50. Found: C, 37.05; H, 4.05; N 19.21.

3-(Acetylamino)-5-amino-4-methyl-1-phenyl-4H-1,2,4-triazol-1-ium Picrate (15b). Yield 0.825 g (78%) of yellow crystals, mp 193−194 °C (from EtOH). ^1H NMR (600 MHz, DMSO-d_6): δ 2.15 (s, 3H, $C\underline{H}_3CO$), 3.38 (s, 3H, CH_3), 7.59−7.63 (m, 5H, Ph), 8.59 (s, 2H, PkO^-), 8.66 (br s, 2H, NH_2), 11.03 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 22.6 ($\underline{C}H_3CO$), 30.6 (CH_3), 124.2 (C-4′, PkO^-), 125.0 (Ph), 125.1 (C-3′, PkO^-), 129.86, 129.91, 134.2 (carbons of Ph), 141.8 (C-2′, PkO^-), 143.6 (C-3), 148.9 (C-5), 160.8 (C-1′, PkO^-), 170.4 (CO). Anal. Calcd for $C_{17}H_{16}N_8O_8$: C, 44.35; H, 3.50; N, 24.34. Found: C, 44.01; H, 3.68; N 24.61.

3-(Acetylamino)-5-amino-4-ethyl-1-phenyl-4H-1,2,4-triazol-1-ium Iodide (15c). Yield 0.626 g (73%) of yellowish crystals, mp 235−236 °C (from EtOH). IR (cm^{-1}): 3232, 3044, 2924, 2730, 1693, 1660, 1595, 1521, 1485, 1455, 1417, 1248, 1019, 771. ^1H NMR (600 MHz, DMSO-d_6): δ 1.27 (t, 3H, J = 6.9 Hz, $C\underline{H}_3CH_2$), 2.16 (s, 3H, $C\underline{H}_3CO$), 3.92 (q, 2H, J = 6.9 Hz, CH_2), 7.58−7.63 (m, 5H, Ph), 8.66 (br s, 2H, NH_2), 10.84 (br s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 12.7 ($\underline{C}H_3CH_2$), 22.7 ($\underline{C}H_3CO$), 38.8 ($CH_3\underline{C}H_2$), 125.1, 129.86, 129.87, 134.1 (carbons of Ph), 142.6 (C-3), 148.2 (C-5), 170.7 (CO). MS (EI, 70 eV), m/z (%): 246 (3) $[M - I^-]^+$, 245 (25) $[M - HI]^+$, 175 (100). Anal. Calcd for $C_{12}H_{16}N_5IO$: C, 38.62; H, 4.32; N, 18.77. Found: C, 38.29; H, 4.39; N, 18.48.

Acetyl(5-amino-4-benzyl-1-phenyl-4H-1,2,4-triazol-1-ium-3-yl)-azanide (16a). Yield 0.580 g (82%) of colorless crystals, mp 199−200 °C (from EtOH). IR (cm^{-1}): 3319, 3213, 3061, 1659, 1618, 1572, 1547, 1474, 1454, 1387, 1345, 1067, 1009, 993, 723. ^1H NMR (600 MHz, DMSO-d_6): δ 2.03 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.14−7.42 (m, 8H, Ar), 7.96−7.97 (m, 2H, Ar). ^{13}C NMR (150 MHz, DMSO-d_6): δ 22.6 (CH_3), 44.0 (CH_2), 118.5, 123.9, 127.1, 127.5, 128.5, 128.8, 135.9, 138.8 (carbons of benzene rings), 141.2 (C-3), 150.4 (C-5), 170.6 (CO). MS (EI, 70 eV), m/z (%): 307 (6) $[M]^+$, 91 (100). Anal. Calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.27; H, 5.49; N, 22.98.

Acetyl(5-amino-1,4-dibenzyl-4H-1,2,4-triazol-1-ium-3-yl)azanide (16b). Yield 0.480 g (65%) of colorless crystals, mp 182−183 °C (from EtOH). IR (cm^{-1}): 3331, 3236, 3060, 1659, 1617, 1572, 1546, 1475, 1386, 1345, 1067, 1009, 933, 744. ^1H NMR (600 MHz, DMSO-d_6): δ 1.87 (s, 3H, $C\underline{H}_3CO$), 4.81 (s, 2H, CH_2), 4.94 (s, 2H, CH_2), 7.25−7.32 (m, 10H, 2Ph). ^{13}C NMR (150 MHz, DMSO-d_6): δ 23.7 ($\underline{C}H_3CO$), 43.9 (4-CH_2), 48.8 (1-CH_2), 127.0, 127.3, 127.4, 128.3, 136.2, 136.7 (carbons of benzene rings), 144.4 (C-3), 150.5 (C-5), 171.6 (CO). MS (EI, 70 eV), m/z (%): 321 (3) $[M]^+$, 91 (100). Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 66.95; H, 5.78; N, 22.08.

Acetyl(4-benzyl-1-tert-butyl-4H-1,2,4-triazol-1-ium-3-yl)azanide (16c). Yield 0.626 g (72%) of colorless crystals, mp 253 °C with dec IR (cm^{-1}): 3321, 2977, 1590, 1503, 1376, 1213, 1119, 936, 709. ^1H NMR (500 MHz, DMSO-d_6): δ 1.52 (s, 9H, *tert*-Bu), 1.83 (s, 3H, $C\underline{H}_3CO$), 5.09 (s, 2H, CH_2), 7.29−7.36 (m, 5H, Ph), 9.51 s (1H, H-5). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.6 ($\underline{C}H_3CO$), 27.8 (3C, $C(\underline{C}H_3)_3$), 46.8 (CH_2), 60.3 ($\underline{C}(CH_3)_3$), 127.8, 128.0, 128.5 (carbons of Ph), 134.8 (C-5), 135.6 (Ph), 157.3 (C-3), 174.2 (CO). HRMS (ESI-TOF), m/z $[M + H]^+$ calcd for $C_{15}H_{20}N_4O$ 273.1710, found 273.1710.

4.8. General Procedure for the Synthesis of Compounds 10a,c−e, 5a. A mixture of the acetyl derivative **15a**, **15c**, and **16a−c**

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(1 mmol), ethanol (3 mL), and concentrated hydrochloric or hydrobromic acid (1 mL) was refluxed for 1 h and then evaporated to dryness at reduced pressure. To isolate **10c**, **10d**, and **5a**, acetonitrile (3 mL) was added to the residue and the precipitate formed was collected by filtration and recrystallized. To isolate **10a** and **10e**, a hot 50% water solution of KI (2 mL) was added to the residue. The solid that separated after cooling was collected by filtration and recrystallized.

*3,5-Diamino-4-methyl-1-phenyl-4H-1,2,4-triazol-1-ium Iodide (**10a**).* Yield 0.25 g (79%). The product obtained was identical in both its physical and spectral characteristics with the described above sample of compound **10a** obtained by direct alkylation of compound **22**.

*3,5-Diamino-4-benzyl-1-phenyl-4H-1,2,4-triazol-1-ium Bromide (**10d**).* Yield 0.325 g (94%) of yellowish crystals, mp 136−137 °C (from acetonitrile). IR (cm^{-1}): 3473, 3253, 3107, 1670, 1635, 1595, 1522, 1496, 1454, 1359, 1211, 1073, 735. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 5.34 (s, 2H, CH_2), 6.95 (s, 2H, 3-NH_2), 7.36−7.58 (m, 10H, 2Ph), 8.46 (s, 2H, 5-NH_2). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 44.6 (CH_2), 124.5, 126.9, 128.0, 128.7, 129.0, 129.7, 133.9, 134.8 (carbons of benzene rings), 146.6 (C-5), 150.4 (C-3). MS (EI, 70 eV), m/z (%): 266 (11) $[M - Br]^+$, 91 (100). Anal. Calcd for $C_{15}H_{16}N_5Br$: C, 52.04; H, 4.66; N, 20.23. Found: C, 51.81; H, 4.79; N, 19.84.

*3,5-Diamino-4-ethyl-1-phenyl-4H-1,2,4-triazol-1-ium Iodide (**10e**).* Yield 0.228 g (69%) of white crystals, mp 168−170 °C. IR (cm^{-1}): 3302, 3266, 3194, 3126, 2983, 1674, 1631, 1533, 1498, 1448, 1037, 762. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.23 (t, J = 7.1 Hz, 3H, CH_3), 3.94 (q, J = 7.1 Hz, 2H, CH_2), 6.78 (s, 2H, 3-NH_2), 7.47−7.58 (m, 5H, Ph), 8.24 (s, 2H, 5-NH_2). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 12.8 (CH_3), 37.2 (CH_2), 124.3, 128.8, 129.6, 134.8(carbons of Ph), 146.1 (C-5), 149.9 (C-3). Anal. Calcd for $C_{10}H_{14}N_5I$: C, 36.27; H, 4.26; N, 21.15. Found: C, 36.16; H, 4.38; N, 21.34.

*3,5-Diamino-1,4-dibenzyl-4H-1,2,4-triazol-1-ium Bromide (**10c**).* Yield 0.266 g (74%). Physical and spectral characteristics are identical to those of the above-described sample obtained by direct alkylation of the compound **3d**.

*3-Amino-4-benzyl-1-tert-butyl-4H-1,2,4-triazol-1-ium Bromide (**5a**).* Yield 0.193 g (62%). Physical and spectral characteristics are identical to those of the above-described sample obtained by direct alkylation of the compound **2c**.

4.9. 4-Benzyl-5-imino-1-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-3-amine (13). A 10% water solution of NH_3 (4 mL) was added to a solution of compound **10d** (0.5 g, 1.44 mmol) in 50% aqueous EtOH (2 mL). The precipitate formed was collected by filtration, washed with water, and dried at 100 °C. Yield 0.309 g (81%) of colorless crystals, mp 158−159 °C (from *i*-PrOH). IR (cm^{-1}): 3260, 3114, 3033, 1671, 1627, 1602, 1497, 1453, 1397, 1102, 949, 751, 720. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.88 (s, 2H, CH_2), 5.44 (s, 1H, NH), 6.19 (s, 2H, NH_2), 6.95−6.99 (m, 1H, Ar), 7.29−7.34 (m, 7H, Ar), 7.97 (2H, Ar). ^{13}C NMR (150 MHz, DMSO-d_6): δ 42.7 (Ph$\underline{C}H_2$), 117.3, 121.9, 127.0, 127.3, 128.43, 128.46, 136.4, 139.8 (carbons of benzene rings), 148.5 and 150.5 (carbons of triazole ring). MS (EI, 70 eV), m/z (%): 265 (61) $[M]^+$, 91 (100). Anal. Calcd for $C_{15}H_{15}N_5$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.81; H, 5.85; N, 26.34.

4.10. *N*-(1-*tert*-Butyl-1*H*-1,2,4-triazol-3-yl)acetamide (14c). A mixture of compound **2c** (2 g, 14 mmol), acetonitrile (2 mL), and acetic anhydride (2.14 g, 21 mmol) was refluxed for 2 h and then diluted with ethanol (4 mL). The resultant solution was evaporated almost to dryness, and the residue obtained was dissolved in water (10 mL). The resultant solution was neutralized by addition of $NaHCO_3$ to a pH 7−8 and extracted by $CHCl_3$ (4 × 5 mL). The extract was dried by Na_2SO_4 and evaporated to dryness. The residue formed was recrystallized from CCl_4 to give compound **14c**. Yield 2.09 g (82%), mp 142−144 °C. IR (cm^{-1}): 3315, 3222, 3123, 2836, 1714, 1633, 1574, 1529, 1364, 1255, 1228, 1006, 748. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.50 (s, 9H, *tert*-Bu), 1.99 (s, 3H, C$\underline{H}_3$CO), 8.36 (s, 1H, H-5), 10.15 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.9, 28.7, 57.7, 140.3, 155.5, 167.5. MS (EI, 70 eV), m/z (%): 182 (10) $[M]^+$, 140 (40), 84 (100). Anal. Calcd for $C_8H_{14}N_4O$: C, 52.73; H, 7.74; N, 30.75. Found: C, 52.59; H, 7.81; N, 30.57.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Discussion of medicinal applications of *C*-amino-1,2,4-triazoles, detailed results of quantum chemical calculations, copies of NMR and IR spectra, GC−MS chromatograms, and crystallographic data including CIF's for **6e** and **10a** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

‖Prof. Oleg V. Shishkin passed away unexpectedly on July 17, 2014. He had been fully in charge of this project.

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