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Synthesis of 5-Arylamino-1*H*(2*H*)-tetrazoles and 5-Amino-1-aryl-1*H*-tetrazoles from Secondary Arylcyanamides in Glacial Acetic Acid: A Simple and Efficient Method

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A simple and efficient method for the preparation of 5-arylamino-1*H* (2*H*)-tetrazoles (**3a-i**) and 5-amino-1-ary-1*H*−tetrazoles (**4a-i**), with excellent yields and high purity, from secondary arylcyanamides (**1a-i**) at room temperature in glacial acetic acid is described. Tautomers **3a-i** were separated from tautomers **4a-i** by crystallization in ethanol. A mechanism was introduced in glacial acetic acid. The ratio of isomers is described based on the electronic and steric effects of various substituents. The electron withdrawing group (-NO_2) increased the ratio of **4:3**. The rate of product formation was enhanced by introducing electron donating substituents. ^{1}H-NMR and ^{13}C-NMR chemical shifts and multiplicities are also discussed.

Key Words: 5-Arylamino-1*H*(2*H*)-tetrazoles, 5-amino-1-aryl-1*H*-tetrazoles, arylcyanamides, guanyl azides, glacial acetic acid.

Introduction

The tetrazole ring system has attracted considerable attention in recent years,[1−8] especially among medicinal chemists, as a potential surrogate for *cis*-peptide linkage[1,9−12] and carboxylic acids.[1,13,14] Indeed, the number of patent claims and publications related to the medicinal use of tetrazoles continue to grow rapidly and encompass a wide range of applications. Tetrazoles are reported to exhibit antihypertensive, anti-allergic, and antibiotic activity;[15−22] for example, they are currently used as activator[23−25] and anticonvulsants,[1,26] as well as in cancer[27−29] and AIDS treatment.[1,30,31] Furthermore, aminotetrazole derivatives have been patented

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for their muscle relaxation, anti-inflammatory, anti-arthritic, analgesic, ulcer therapeutic, and coccidiostatic properties. Tetrazoles are also used as plant growth regulators, herbicides, and fungicides in agriculture,[32,33] as stabilizers in photography and photo imaging,[32,34] and as explosives in rocket propellants.[35–37] Another important application of tetrazoles is in the preparation of imidoylazides.[38–43]

The addition of azide anion to nitriles, cyanates, and cyanamides is the most common method of preparing 5-substituted tetrazoles, 5-aryl/alkyl oxytetrazoles, and 5-aryl/alkyl aminotetrazoles, respectively.[1–7,38–45] In most cases the reaction actually proceeds in solutions of hydrazoic acid in such solvents as benzene, toluene, xylene, and chloroform. When hydrazoic acid is used care must be taken to monitor the concentration of hydrazoic acid in the reaction mixture in order to avoid an explosion.[1–7,32,45,46] A substitute for hydrazoic acid is a mixture of sodium azide and ammonium chloride, with dimethylformamide as the solvent.[1–7,17,32,45,47] In dimethylformamide, the reaction mixture must be heated to ∼150 °C for several hours to several days. An additional disadvantage of dimethylformamide is its solubility in both organic solvents and water. Thus, removing DMF from tetrazole is difficult. To resolve this problem, the reaction was carried out in several solvents that allowed the temperature to be elevated to the degree necessary to enhance the reaction.[32,45,47]

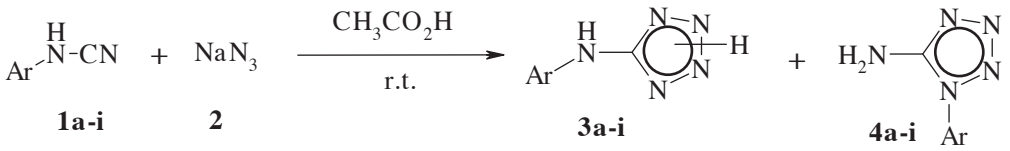
Miller et al. recently reported the synthesis of some amino-1*H*-tetrazoles in low yield (4%-59%) from the treatment of amino(imino)methanesulfonic acid derivatives with sodium azide in acetic acid at 50 °C.[48]

Another possible method for obtaining 5-monoalkylaminotetrazoles is an adaption of the von Braun degradation of tertiary amines with cyanogens bromide. In this way it might be possible to eliminate an alkyl group from 5-dialkylaminotetrazoles.[49,50]

Moreover, 5-monosubstituted amino-1*H*-tetrazoles were synthesized by thermal isomerization of 5-amino-1-substituted-1*H*-tetrazoles in boiling ethylene glycol, or melt state (180-200 °C).[51,52]

These methods suffer from one or more disadvantages, such as low yield, long reaction time, harsh reaction conditions, difficult to obtain and/or prepare starting materials, use of expensive and toxic reagents, and the hydrazoic acid generated in situ is highly toxic and explosive.

In light of the importance of amino tetrazoles and amino imidoyl azides,[38–43] we want to report a facile, effective, and less hazardous method for the synthesis of 5-arylamino-1*H*-tetrazoles (**3a-i**) and 5-amino-1-aryl-1*H*-tetrazoles (**4a-i**) in quantitative yields from secondary arylcyanamides (**1a-j**) (based on TLC and NMR) in glacial acetic acid (Scheme 1). Additionally, to the best of our knowledge this is the first reported use of CH_3COOH as both solvent and proton donor source for monosubstituted arylamino-1*H*-tetrazoles synthesis.



1a-i **2** **3a-i** **4a-i**

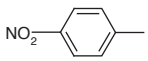
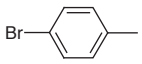
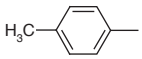
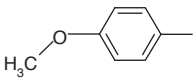
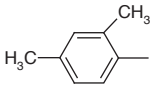
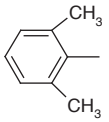
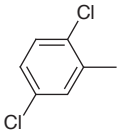
Scheme 1.

Results and Discussion

Cyanamides **1a-i** were prepared according to previous reports.[53,54] In order to gain insight into the electronic and steric effects, mono-aryl (*ortho*, *meta*, and *para*)-substituted cyanamides **1a-i** were studied (Table 1).

Mono-alkyl-substituted cyanamides readily trimerize into triazines and other defined polymeric substances, while mono-aryl-substituted cyanamides **1a-i** are more stable.[54]

Table 1. Preparation of 5-arylamino-1 *H*-tetrazoles (**3a-i**) and 5-amino-1-aryl-1*H*-tetrazoles (**4a-i**) from secondary arylcyanamides at room temperature in glacial acetic acid.

mp (°C) of Isomers	Ratio of isomers (**4:3**)[b]	Yield (%)[a]	Reaction time (h)	Ar	Compound	Entry
3a: 218-220 **4a**: 187-188, lit[51] 185-187	4.6	80	24		**3a, 4a**	1
3b: 245-247 **4b**: 239-240	1.3	87	30		**3b, 4b**	2
3c: 202-204, lit[51] 200-201 **4c**: 176-178, lit[51] 175-177	1.0	83	20		**3c, 4c**	3
3d: 200-202, lit[51] 200-202 **4d**: 211-213	2.0	78	20		**3d, 4d**	4
3e: 201-203	**3e** (100%)	82	20		**3e, 4e**	5
3f: 190-192 **4f**: 196-198, lit[51] 199-201	1.1	81	20		**3f, 4f**	6
3g: 245-247	**3g** (100%)	84	20		**3g, 4g**	7
3h: 227-229 **4h**: 187-189, lit[51] 185-190	0.5	86	24		**3h, 4h**	8
3i: 272-274 **4i**: 260-262	1.6	72	30		**3i, 4i**	9

[a]Yields given are after work up. [b]The ratio of **4**:**3** was measured by ^{1}H-NMR.

Perhaps the most remarkable feature of the reaction of mono-substituted cyanamides with hydrazoic acid is the unidirectional character of their cyclization.[1−7,50,51] The nature of the substituent appears to play an important role in directing the course of the reaction. Furthermore, substituents have different electronic effects, as the methyl- and para-nitrophenyl groups permit the formation of the same type of compound, presumably through the intermediate formation of a guanyl azide. Surprisingly, ring closure of the substituted guanyl azide in all of these methods yields 1-alkyl- or 1-aryl-5-amino–1*H*-tetrazole as the major product (as much as 95% in certain cases). No serious consideration appears to have been given by previous researchers to the isolation or detection of the other isomers, although Stolle and Heintz reported the isolation of 5-anilinotetrazole in very small yield from the reaction of phenylthiourea with lead oxide and sodium azide.[55]

In attempts to find a facile and less hazardous method for preparing 5-arylamino-1*H*-tetrazoles in quantitative yields from cyanamides and sodium azide, we discovered that the reaction was completed quantitatively (based on TLC and NMR) in glacial acetic acid at ambient temperature using 3.0 equivalent of sodium azide overnight (Scheme 1 and Table 1). Evaporation of acetic acid under vacuum followed by the addition of water gave a white precipitate that is a pure mixture of isomeric tetrazoles **3** and **4**. Since isomers **4a-i** are not soluble in spirit alcohol they are easily separated from isomers **3a-i** via a simple procedure (see experimental section).

All products are known compounds and were identified by comparison of some of their spectral data (IR, and ^{1}H- and ^{13}C-NMR) and physical properties with those of authentic samples.[48,50−52,56] Melting points, and a complete list of carbon and proton chemical shifts for the 2 isomers are presented in Tables 1 and 2. ^{13}C-NMR spectra displayed signals of about δ = 155-157 ppm for C5 of the tetrazole ring.[57,58] A comparison of ^{1}H-NMR spectra revealed that 5-arylamino-1*H*-tetrazoles **3a-i** generally show a large separation in the chemical shifts of the *ortho*-, *meta*-, and *para*-aryl protons when there is a strong interannular conjugation, with the exception of isomers **3b** and **3g**, for which a sharp 4- and 3-proton singlet were observed for the aryl ring protons, respectively (Table 2 and Figure 1 [top]). Isomers **4a-i** had a small separation of the aryl ring protons. Indeed, signals of the aryl ring protons of isomers **4a-i** contracted their multiplicities and shifted downfield; for example, see Figure 1 (bottom) for **3b** and **4b** in acetone.[58]

X-ray analysis of 5-amino-1-phenyltetrazoles and 1-aryl-5-alkyltetrazoles has previously been reported, showing that the tetrazole rings and aryl fragments are not coplanar, while the corresponding dihedral angles are about 50° and 90°, respectively.[59,60] This means that coplanarity of the phenyl and tetrazole rings cannot be achieved due to the repulsive interaction between the *ortho*-phenyl hydrogens and the amino group. Thus, isomers **4a-i**, in contrast to isomers **3a-i**, cannot be coplanar, and the chemical shifts of the aryl ring protons are similar in value to those of isomers **3a-i**. It is more likely that for isomers **4a-i** the tetrazole ring rotated significantly out of the plane of the aryl ring, and that the principle difference in the chemical shifts of the aryl ring protons was due to inductive and anisotropic effects, and the lack of resonance effects. This indicates that the free electron pair of the amine nitrogen must have effectively participated in the conjugated aryl ring of isomers **3a-i**, whereas there was no such interaction between the tetrazole nitrogens and the aryl ring of isomers **4a-i** (a reason for non co-planarity between the tetrazole and aryl ring). A similar effect has been observed in 5-*ortho*-substituted aryltetrazoles.[57a]

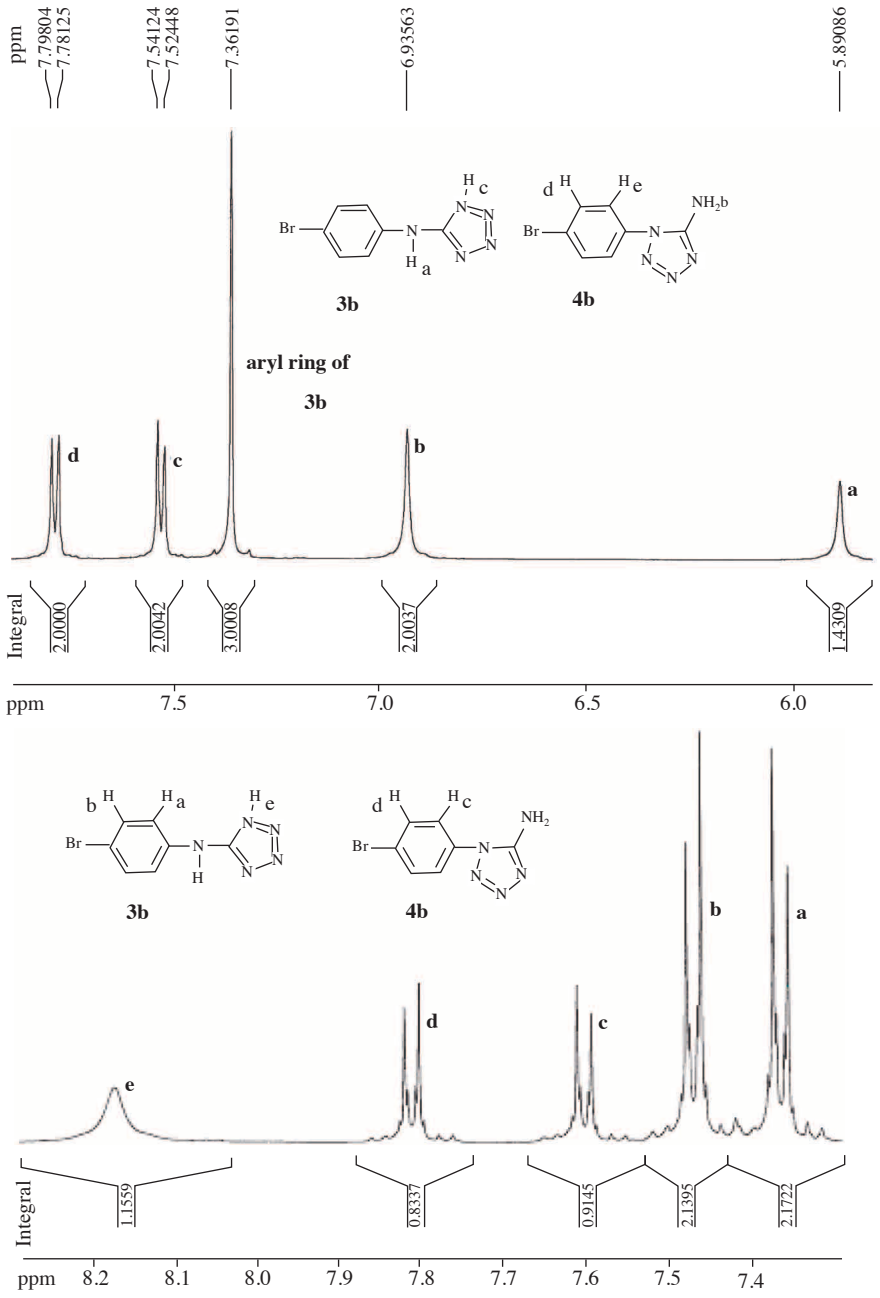
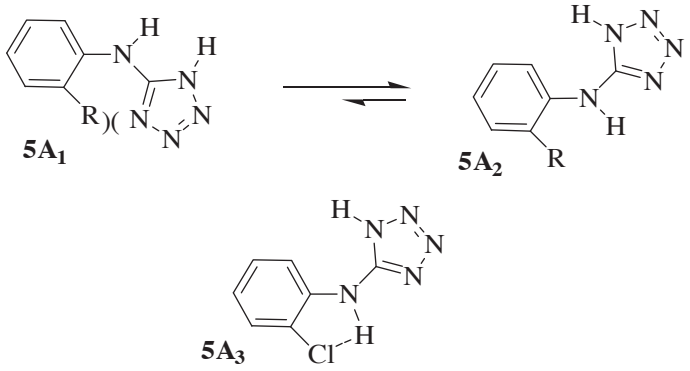


Figure 1. Portion of the ^{1}H-NMR spectrum (500 MHz) of 5-(4-bromophenyl) amino-1*H*-tetrazole **3b** and 5-amino-1-(4-bromophenyl)-1*H*-tetrazole **4b** in DMSO-d$_6$ (top), and in acetone-d$_6$ (bottom), with a reaction time of 30 h at 25 and 65 °C, respectively.

The steric effects of the *ortho*-substituent might be expected to increase the dihedral angle between the rings of the 2 *ortho*-substituents in the 5-aryl ring of isomers **3a-i** and isomers **4a-i**, resulting in the reduction or complete loss of interannular conjugation in these compounds. For example, for compounds **3g** and **4g** the 2 *ortho*-methyls of the 5-aryl ring were undoubtedly lying orthogonally (confirmed by ^{13}C-NMR for 1,5-

disubstituted amino tetrazoles[58]); thus, the difference in the chemical shifts of the aryl ring protons was due to inductive and anisotropic effects, and the lack of resonance effects, and so they should be equivalent to show a singlet for aryl ring protons (Table 2). It seems likely that the electron withdrawing of the aminotetrazole fragment was counterbalanced by the electron donating of the 2 methyl groups.

Nonetheless, the presence of an *ortho*-substituent in the aryl ring of isomer $\mathbf{5A}_1$ cannot be responsible for the loss of interannular conjugation, because the tetrazole ring and aryl fragment are coplanar for the most stable conformer ($\mathbf{5A}_2$) (Scheme 2). This is demonstrated by **3h** and **4h**, and **3i** and **4i**, in which the intramolecular hydrogen bonding and strong interannular conjugation enforces co-planarity, which for $\mathbf{5A}_3$ is shown in Scheme 2.



Scheme 2.

At the present time we do not have sufficient data to explain why compound **3b** showed a singlet for the aryl ring protons (Figure 1 [top]). One explanation is that the electronegativity of the aminotetrazole fragment could be equal to the bromine atom.[61]

The sharp singlet signals of the NH protons of arylamine and -NH_2, or the somewhat broad NH (1*H*/2*H*) of the tetrazole ring are consistent with rapid tautomeric equilibrium on the NMR timescale. This prohibits the identification of the individual tautomers[62] (Figure 1 and Table 2).

The observed chemical shifts in DMSO were not equivalent to those observed in acetone. This general medium effect in ^{1}H-NMR causes a large separation of aryl ring proton shifts in acetone, as compared with DMSO, for compounds **3b** and **4b** (Figure 1).

The following important results were extracted from data in Table 1 and compared to those reported in the literature.[50–52]

1. In general, when the substitution was electron-donating the group reaction was completed in less time (starting cyanamide **1a-i** is consumed faster) than when the substitution was electron-withdrawing (compare entries 1, 2, 8, and 9 with 3, 4, 5, 6, and 7 in Table 1). Entries 5 (20 h), 8 (24 h), and 9 (30 h) confirm this result. The rate of reaction decreased with increasing electronegativity of the substituent on the aryl group along the indicated series (*ortho*-Me and *ortho*-Cl in compounds **3g, 4g**, **3h,** and **4h,** and 2 chlorine atoms in the *ortho* and *meta* positions in compounds **3i** and **4i**, respectively). These results contradict what was reported for nitriles.[45,64,65]

Table 2. ^{1}H- and ^{13}C-NMR chemical shifts of 5-arylamino-1*H*-tetrazoles (3a-i)

Compound	^{1}H-NMR (δppm)[a]	^{13}C-NMR (δ ppm) aryl ring	C5 of tetrazole
3a	(DMSO-d_6, 500 MHz), 7.71 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H), NH^A; -, NH^T; 10.72 (s, 1H). (Acetone-d_6, 500 MHz), 7.77 (d, J = 9.2 Hz, 2H), 8.14 (d, J = 9.2 Hz, 2H), NH^A; 5.94 (s, br, 1H), NH^T; 9.16 (s, br, 1H).	(DMSO-d_6, 125 MHz), 147.2, 140.4, 124.9, 116.8.	155.2
4a	(DMSO-d_6, 500 MHz), 7.91 (d, J = 7.2 Hz, 2H), 8.43 (d, J = 7.2 Hz, 2H), NH_2; 7.19 (s, 2H). (Acetone-d_6, 500 MHz), 8.01 (d, J = 7.2 Hz, 2H), 8.49 (d, J = 7.2 Hz, 2H), NH_2; 6.58 (s, br, 2H).	(DMSO-d_6, 125 MHz), 147.1, 138.6, 125.3, 124.6.	155.0
3b	(DMSO-d_6, 500 MHz), 7.36 (s, 4H), NH^A; 5.90 (s, 1H), NH^T; 8.66 (s, 1H). (Acetone-d_6, 500 MHz), 7.37 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 8.9 Hz, 2H), NH^A; 5.52 (s, br, 1H), NH^T; 8.17 (s, br, 1H).	(DMSO-d_6, 125 MHz), 140.0, 131.4, 119.7, 112.5.	155.0
4b	(DMSO-d_6, 500 MHz), 7.54 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), NH_2; 6.97 (s, 2H). (Acetone-d_6, 500 MHz), 7.60 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), NH_2; 6.33 (s, br, 2H).	(DMSO-d_6, 125 MHz), 133.4, 132.9, 126.7, 123.0.	155.4
3c	(DMSO-d_6, 300 MHz), 2.19 (s, 3H), 6.99 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), NH^A; 5.74 (s, 1H), NH^T; 8.37 (s, 1H).	(DMSO-d_6, 75 MHz), 138.1, 130.2, 124.0, 117.8, 20.3.	154.9
4c	(DMSO-d_6, 500 MHz), 2.38 (s, 3H), 7.39 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), NH_2; 6.80 (s, 2H). ($CDCl_3$, 500 MHz), 2.46 (s, 3H), 7.38 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), NH_2; 5.23 (s, br, 2H).	(DMSO-d_6, 75 MHz), 139.0, 131.0, 129.6, 129.0 20.7. , (DMSO-d_6, 125 MHz), 139.8, 131.8, 131.1, 124.8, 21.6.	156.2 155.8
3d	(DMSO-d_6, 500 MHz), 3.67 (s, 3H), 6.78 (d, J = 8.7 Hz, 2H), 7.26 (d, J =8.7 Hz, 2H), NH^A; 5.70 (s, 1H), NH^T; 8.33 (s, 1H).	(DMSO-d_6, 125 MHz), 153.9, 133.7, 119.4, 113.8, 55.1.	156.2
4d	(DMSO-d_6, 500 MHz), 3.81 (s, 3H), 7.11 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), NH_2; 6.73 (s, 2H). (Acetone-d_6, 500 MHz), 3.89 (s, 3H), 7.14 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 8.9 Hz, 2H), NH_2; 6.14 (s, br, 2H).	(DMSO-d_6, 125 MHz), 159.7, 126.1, 126.1, 114.9, 55.6. (Acetone-d_6, 125 MHz), 161.5, 127.7, 127.1, 116.0, 56.2.	155.1 156.2
3e	(DMSO-d_6, 500 MHz), 2.17 (s, 3H), 6.87 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.1 HZ, 1H), NH^A; 5.99 (s, 1H), NH^T; 7.69 (s, 1H).	(DMSO-d_6, 125 MHz), 138.2, 130.1, 127.2, 126.0, 122.2, 121.1, 17.9.	156.3

Table 2. Continued

Compound	^{1}H-NMR (δppm)[a]	C-NMR (δ ppm) aryl ring	C-NMR (δ ppm) C5 of tetrazole
3f	(DMSO-d_6, 500 MHz), 2.15 (s, 3H), 2.21 (s, 3H), 6.89 (d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), NH^A; 5.92 (s, 1H), NH^T; 7.61 (s, br, 1H).	(DMSO-d_6, 125 MHz), 135.5, 130.9, 130.5, 127.4, 126.4, 121.4, 20.3, 17.8.	156.3
	(acetone-d_6, 500 MHz), 2.17 (s, 3H), 2.22 (s, 3H), 6.91 (d, J = 8.1 Hz, 1H), 6.93 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), NH^A; 5.47 (s, br, 1H), NH^T;-.	(acetone-d_6, 75 MHz), 136.3, 134.1, 132.2, 129.9, 128.1, 121.8, 20.7, 17.9.	156.6
	(acetone-d_6, 300 MHz), 2.29 (s, 6H), 6.98 (d, J = 7.9 Hz, 1H), 7.04 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), NH^A; - NH^T; 8.30 (s, br, 1H).		
4f	(DMSO-d_6, 500 MHz), 2.01 (s, 3H), 2.38 (s, 3H), 7.21 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), NH_2; 6.68 (s, 2H).	(DMSO-d_6, 125 MHz), 140.1, 135.0, 131.8, 129.5, 127.7, 127.3, 20.7, 16.8.	155.7
	(acetone-d_6, 500 MHz), 2.07 (s, 3H), 2.40 (s, 3H), 7.21-7.27 [m (d+s), 3H], NH_2; 6.08 (s, br, 2H).		
3g	(DMSO-d_6, 500 MHz), 2.15 (s, 6H), 7.00 (s, 3H), NH^A; 5.74 (s, br, 1H), NH^T; 7.74 (s, br, 1H),	(DMSO-d_6, 125 MHz), 136.3, 136.2, 127.6, 125.6, 18.3.	156.9
	(acetone-d_6, 500 MHz), 2.25 (s, 6H), 7.03 (s, 3H), NH^A; 5.24 (s, br, 2H).	(acetone-d_6, 125 MHz), 137.1, 136.6, 128.3, 126.3, 18.6.	157.5
3h	(acetone-d_6, 500 MHz), 6.96 (t, J = 7.7 Hz, 1H), 7.24 (t, J = 8.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), NH^A; 5.98 (s, br, 1H), NH^T;-.	(acetone-d_6, 125 MHz), 137.8, 131.6, 129.4, 123.4, 121.9, 121.78.	156.3
4h	(acetone-d_6, 500 MHz), 7.58-7.73 (m, 4H), NH_2; 6.33 (s, br, 2H).	(acetone-d_6, 125 MHz), 133.1, 132.7, 132.0, 130.6, 129.7, 128.1.	156.8
3i	(DMSO-d_6, 500 MHz), 7.09 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 8.29 (s, 1H), NH^A; 6.53 (s, br, 1H), NH^T; 8.20 (s, 1H).	(DMSO-d_6, 125 MHz), 138.0, 131.8, 130.3, 121.8, 119.6, 119.4	155.3
	(acetone-d_6, 500 MHz), 6.98 (dd, J = 8.6 Hz, J = 2.5 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), NH^A; 6.12 (s, br, 1H), NH^T; 7.88 (s, br, 1H).		
4i	(DMSO-d_6, 500 MHz), 7.73 (dd, J = 8.7 Hz, J = 2.1 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), NH_2; 6.97 (s, br, 2H).	(DMSO-d_6, 125 MHz), 132.5, 132.2, 131.8, 131.7, 130.3, 130.0.	155.7
	(acetone-d_6, 500 MHz), 7.70 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 2.4 Hz, 1H), NH_2; 6.46 (s, br, 2H).		

[a]The NH^A and NH^T are NH of the amine attached to the aryl group and NH of the tetrazole ring, respectively.

2. When the substitution was strongly electron withdrawing, the position of equilibrium shifted toward 5-amino-1-aryl-1*H*-tetrazoles **4a-i** (Table 1, entry 1). This is in contrast to the substituent effect on the aryl ring of the proposed mechanism reported by Henry et al. for the thermal isomerization of **3a-i** and **4a-i**.[50,51]

3. There was a lack of sufficient evidence to permit evaluation of steric effects in the *ortho*-substituted arylaminotetrazoles, although structurally the steric hindrance should have favored the formation of 5-arylamino-1*H*-tetrazoles **3a-i**. This effect was observed for compounds **3e** and **4e**, and **3g** and **4g**, but not for **3f**, **4f**, **3h**, and **4h**, or **3i** and **4i**. We do not have sufficient data to explain why compounds **3f** and **4f** did not follow the same trend as compounds **3e** and **4e**, and **3g** and **4g**. Perhaps the hyperconjugative effect influenced the observed selectivity. Henry et al.[50,51] also reported that 5-amino-1-(2,6-dimethylphenyl)-1*H*-tetrazole **4g** shows less of a tendency to isomerize to 5-(2,6-dimethylphenyl) amino-1*H*-tetrazole **3g** than does 5-amino-1-(2-methylphenyl)-1*H*-tetrazole **4e**, although the former is more sterically hindered (as described above for chemical shifts). The comparison of **3i** and **4i** (2 chlorine atoms at *ortho* and *meta* positions) with **3h and 4h** (1 chlorine atom at *ortho* positions) indicates that the inductive effect of the second chlorine at the *meta* position slightly favored the formation of isomer **4i**.

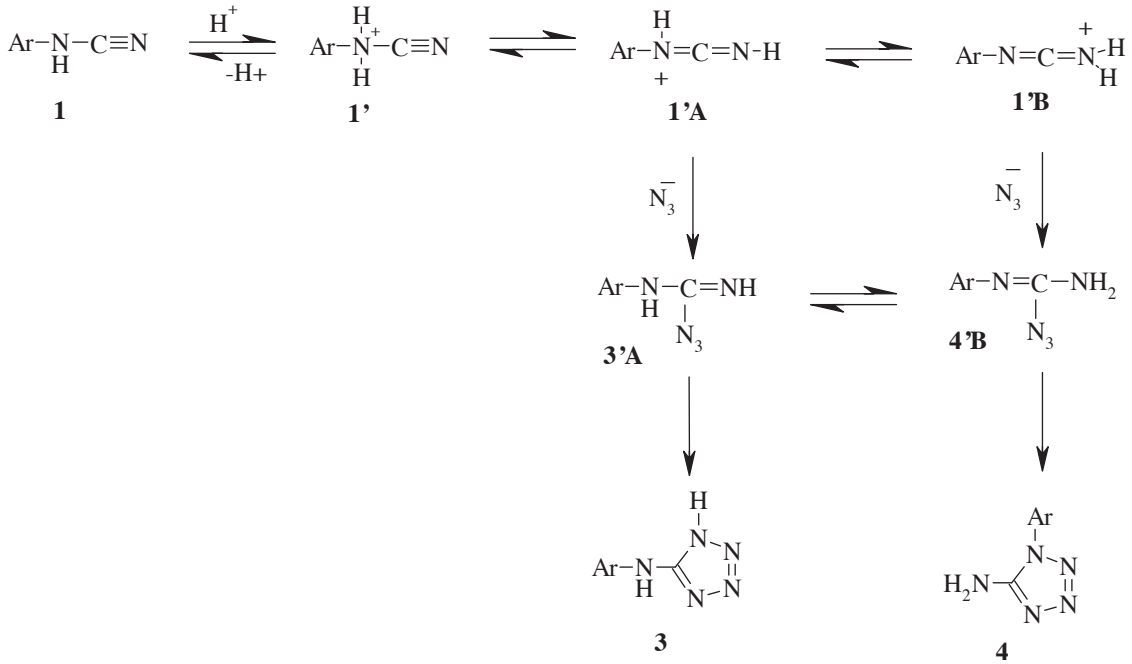
According to the above results, we formulated the possible mechanism as shown in Scheme 3. First, arylcyanamides **1a-i** are protonated to form 3 tautomeric forms: **1′**, **1′A,** and **1′B**.[66] These tautomers combined with the azide ion to form the arylguanyl azides **3′A** and **4′B**.[50,51,66] Arylguanyl azides were unstable intermediates under the reaction conditions (unless they carry strongly electron withdrawing groups) and immediately cyclized to give 2 tautomeric 5-arylamino-1*H*-tetrazoles **3a-i** or 5-amino-1-aryl-1*H*-tetrazole **4a-i**.[6,38−43,67,68] The product ratio of **4**:**3** depended on the individual reaction rates (Scheme 3).

When substitution on the aryl ring is electron donating in arylcyanamides **1a-i**, the nitrogen attached to the aryl ring has more power basicity than the terminal unsubstituted nitrogen. This makes the formation of **1′A** favorable, and hence promotes formation of guanyl azide **3′A**, rather than **4′B**. On the other hand, the electron-donating group acts to increase the electron density on the azomethine N atom attached to the aryl group, and thus assists in the cyclization of guanyl azide **4′B** to give 5-amino-1-aryl-1*H*-tetrazoles **4a-i**. The reverse of this electronic effect would shift the equilibrium toward the opposite direction. Indeed, the electronic effects of the aryl substituents have opposite effects on the cyclization of guanyl azides **3′A** and **4′B**, and on the formation of the protonated carbodiimides **1′A** and **1′B**. In addition, there are other factors that affect the rate and selectivity of the reaction; however, the time to complete the reaction at 25 °C (Table 1) is a good indication that the first step, addition of hydrogen ion to arylcyanamides **1a-i** to give the protonated carbodiimides **1′A** and **1′B**, is probably the most important step or the rate-determining step of the reaction, because when the substitution was electron donating, the reaction was completed in less time (compare entries 1, 2, 8, and 9 with 3, 4, 5, 6, and 7 in Table 1, as explained above).

Nonetheless, the possibility of a concerted cycloaddition [2 + 3] mechanism should not be ignored.[45,65] We intend to examine the subject in greater detail later.

Other effects, of course, such as the relative stability of the intermediates of the guanyl azides **3′A** and **4′B**, stereochemistry of the C=N bond,[69] and the relative rates of their cyclization could profoundly influence the course of the reaction.

Unfortunately, the available data did not permit evaluation of these effects. The current data are sufficient to emphasize, however, that, one can obtain isomers **3a-i** (5-arylamino-1*H*-tetrazoles) from arylcyanamides that carry electron-donating substituents on the aryl ring. Further studies are in progress.



Scheme 3.

Conclusions

A facile, convenient, and less hazardous synthetic method for the synthesis of 5-arylamino-1*H*-tetrazoles **3a-i** and 5-amino-1-aryl-1*H*-tetrazoles **4a-i**, with quantitative yields (based on TLC and NMR) and high purity, from arylcyanamides in glacial acetic acid was achieved, without involvement of expensive reagents or the formation of undesirable byproducts.

Furthermore, a method for separation of tautomers **3a-i** and **4a-i**, as well as a mechanism in glacial acetic acid were introduced.

This method did not require purification, separation (most importantly by column chromatography), or use of high temperatures that could initiate an explosion. Moreover, our experimental condition led to significant improvement in the process, in terms of safety and hygienic conditions for the operators.[46]

The rate of product formation was enhanced by introduction of electron-donating substituents. The electron withdrawing group (-NO_2) increased the ratio of **4:3**. Electron-donating groups and a steric effect produced unpredictable selectivity.

Experimental Section

CAUTION: Although aminotetrazoles are kinetically stable and, in most cases, are insensitive to electrostatic discharge, friction, and impact, they are nonetheless energetic materials and appropriate safety precautions should be taken, especially when these compounds are prepared on a larger scale. Hydrazoic acid is an unstable component, which may decompose violently, forming nitrogen and hydrogen. Depending on the literature

source, an explosive gas mixture can be formed with air or nitrogen above a concentration of 8%-15%.[46]

All of the products are known compounds and were identified by comparison of some of their spectral data (IR, ^{1}H-, and ^{13}C-NMR) and physical properties with those of authentic samples.[48,50−52,56−58] All starting materials and solvents were purified with the proper purification techniques before use, when necessary.[70] Cyanamides **1a-i** were prepared according to previous reports.[53,54]

Typical Experimental Procedure for the Preparation of 5-Arylamino-1*H*-tetrazoles 3a-i and 5-Amino-1-aryl-1*H*-tetrazoles 4a-i, using Glacial Acetic Acid

To a solution of the cyanamide (1 mmol) in glacial acetic acid (3 mL), was added sodium azide (3 mmol) at 25 °C and the reaction mixture was then stirred at this temperature until all the cyanamide was consumed (monitored by TLC and IR, usually 20-30 h). The reaction mixture was also concentrated under reduced pressure. The residue was dissolved in water and stirred for 5 min and the solid residue was filtered from the mixture. Desired pure products were characterized by IR and NMR spectra, and melting points (Tables 1 and 2).

As isomers **4a-i** were not soluble in spirit alcohol, they were separated from isomers **3a-i** via a simple procedure. Isomers **4a-i** precipitated from spirit alcohol and were easily collected on filter paper. The filtrates contained a small amount of isomers **4a-i** and residue of isomers **3a-i**. The remaining isomers **4a-i** in the stock solution were precipitated and removed by adding EtOH/H_2O (3:1). The filtrate solution contained only isomers **3a-i**. Removing the solvents gave pure isomers **3a-i**.

Melting points, and ^{1}H-NMR and ^{13}C-NMR data are shown in Tables 1 and 2, respectively.

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