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Efficient synthesis of arylaminotetrazoles in water

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ABSTRACT

Arylaminotetrazole derivatives are synthesized efficiently by the reaction of arylcyanamides and sodium azide in the presence of $ZnCl_2$ under aqueous conditions at reflux. Generally, isomer of 5-arylamino-1*H*-tetrazole can be obtained from arylcyanamides carrying electron-withdrawing substituent on aryl ring and as the electropositivity of substituent is increased, the product is shifted toward the isomer of 1-aryl-5-amino-1*H*-tetrazole.

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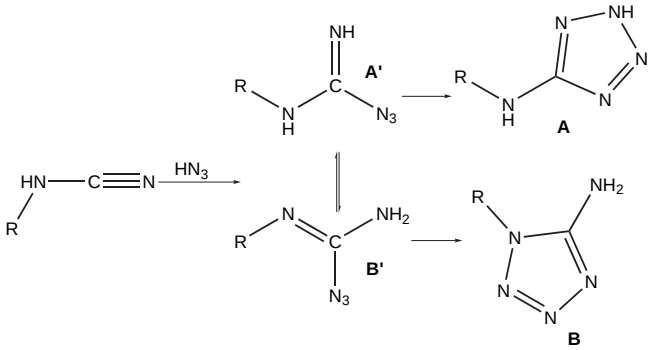
1. Introduction

5-Substituted tetrazoles (RCN_4H) may serve as a non-classical isostere for the carboxylic acid moiety (RCO_2H) in biologically active molecules.[1–7] Hansch has shown that anionic tetrazoles are almost 10 times more lipophilic than corresponding carboxylates, which is an important factor to bear in mind when designing a drug molecule to pass through cell membranes.[8] There is considerable interest in the medicinal and biological applications of tetrazoles,[4,6] including 5-aminotetrazoles, due to their reported *anti*-allergic and *anti*-asthmatic,[9,10] antiviral and *anti*-inflammatory,[11] *anti*-neoplastic,[12] and cognition disorder activities.[13] Tetrazoles are also applied as ligands in coordination chemistry,[14–16] as explosives and rocket propellants.[17–19] Another important application of tetrazoles is the preparation of imidoylazides.[20]

The earliest published methods for the preparation of aminotetrazole derivatives were reactions including the following: (1) addition of $NaNO_2$ to aminoguanidine[21] (2) addition of NaN_3 to carbodiimides[21c] or cyanamides[22] (3) reactions of amines with a leaving group in the tetrazoles 5-position[23] (4) nucleophilic substitution by N_3^- of (a) chlorine in α-chloroformamidines[24] and (b) sulfur from thioureas in the presence of mercury[25,26] or lead salts.[21a]

The addition of the azide anion to nitriles, cyanates, and cyanamides is the most common route for preparing 5-substituted tetrazoles, 5-aryl/alkyl oxytetrazoles, and 5-aryl/alkyl aminotetrazoles, respectively.[3,4,20,27–29a,29b] In most of them, the reaction actually proceeds in solutions of hydrazoic acid in solvents such as benzene, toluene, xylene, and chloroform. Herbst and Garbrecht have shown that cyanamides may be converted to aminotetrazoles using hydrazoic acid, which often result in a mixture of isomers (Scheme 1).[22b]



Scheme 1.

Previously, the 5-monosubstitutedamino-1*H*-tetrazoles were synthesized by thermal isomerization of 1-substituted-5-amino-1*H*-tetrazoles in boiling ethylene glycol or in melt state (180–200 °C).[21a,30] Later, Congreve has reported a two-step synthesis of

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1-aryl-5-amino-1*H*-tetrazoles from the corresponding 1-aryltetrazoles via cyanamide intermediates.[31] The reaction suffers from some drawbacks such as harsh reaction conditions, low temperatures (−70 °C), use of large excess of sodium azide and organolithium reagents that are potentially dangerous. Vorobiov and co-workers published a three-step synthesis of 1-aryl-5-amino-1*H*-tetrazoles, which proceeded in low yields from the corresponding aromatic amines via isolation of intermediate cyanamides.[32] Unfortunately, this approach is not well developed due to the insufficient stability of the intermediate cyanamides. In most cases, *N*-arylureas and other by-products were mostly formed and the intermediate cyanamides were not stable enough to be isolated. Therefore, the 1-aryl-5-amino-1*H*-tetrazoles were produced in low yields. The above mentioned syntheses require the use of highly toxic and explosive hydrazoic acid. On the other hand, in most cases only the 1-aryl-5-amino-1*H*-tetrazoles or mixture of isomers (5-arylamino-1*H*-tetrazole and 1-aryl-5-amino-1*H*-tetrazoles) was obtained.

Due to safety considerations, we required a method that did not use of hydrazoic acid or an azide source that produced hydrazoic acid in situ because of the associated hazards. If hydrazoic acid is used, care must be taken by monitoring the concentration of hydrazoic acid in the reaction mixture to avoid an explosion.[3,4,17,29]A substitute for hydrazoic acid is a mixture of sodium azide and ammonium chloride, with dimethylformamide as the solvent.[17,27c] 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. Therefore, it is desirable to develop a more efficient and convenient method for the regiospecific synthesis of arylaminotetrazoles.

In continuation of our recent work on the synthesis of heterocycles,[33] we herein report the synthesis of arylaminotetrazoles **3a**–**j** from a wide variety of arylcyanamides **1a**–**j** with sodium azide **2** under thermal conditions in H_2O using $ZnCl_2$ (Table 1 and Scheme 2).

Table 1
Synthesis of arylaminotetrazoles **3a**–**j** in the presence of $ZnCl_2$ by reaction between sodium azide **2** and arylcyanamides **1** under reflux conditions

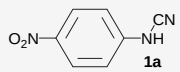
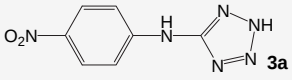
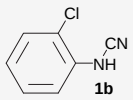
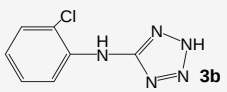
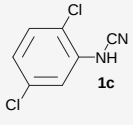
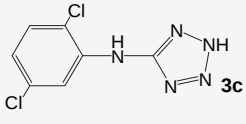
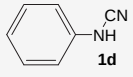
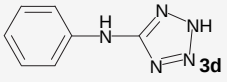
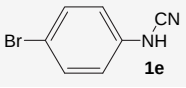
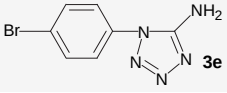
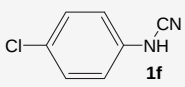
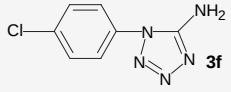
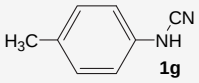
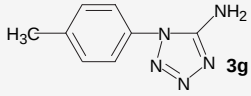
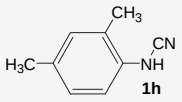
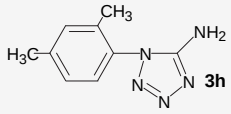
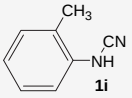
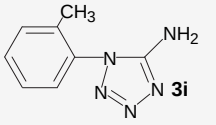
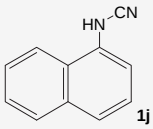
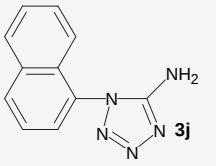
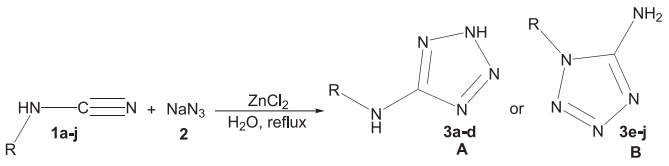
Entry	Substrate	Product	Yield[a] %
1	 **1a**	 **3a**	80
2	 **1b**	 **3b**	88
3	 **1c**	 **3c**	84
4	 **1d**	 **3d**	61
5	 **1e**	 **3e**	90

Table 1 (*continued*)

Entry	Substrate	Product	Yield[a] %
6	 **1f**	 **3f**	85
7	 **1g**	 **3g**	84
8	 **1h**	 **3h**	86
9	 **1i**	 **3i**	89
10	 **1j**	 **3j**	83

[a] Yields refer to pure isolated products.



Scheme 2.

2. Result and discussion

The cyanamides **1a**–**j** were prepared according to literature.[34] In order to include a reasonable range of electrical and steric effects, the arylsubstituted cyanamides **1a**–**j** studied included various groups in *ortho*, *meta*, and *para* positions, Table 1. Several aromatic cyanamides carrying either electron-donating or electron-withdrawing substituents reacted and gave the products in good yields (Table 1).

The following important results can be extracted from the data collected in Table 1:

1. In this work, we have observed that the process was completely regiospecific, Table 1. This is in contrast with the report that was presented for the synthesis of aminotetrazoles using hydrazoic acid, which often results in mixture of regio isomers **A** and **B**.[22b]

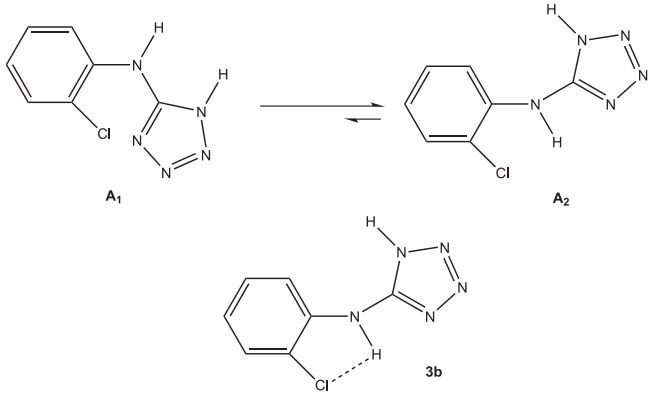
2. Perhaps the most remarkable feature of the reaction of the monosubstituted cyanamides with hydrazoic acid is the unidirectional character of the cyclization step.[3,4,21a,22b,27,30,35] The substituent identity appears to play at best a minor role in directing the course of the reaction. Substituents as different in their electrical effects as the methyl group and the *p*-nitrophenyl group 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 the 1-alkyl- or 1-aryl-5-aminotetrazole as major products (as much as 95% in certain cases). No serious consideration appears to have been given by previous workers to the isolation or detection of the

other regio isomer, 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.[36]

In contrast with the reports that have previously been published, in our methods, a clear distinction is that tetrazoles **3** are affected by the substituents in arylcyanamides **1a**–**j**, and isomer **A** or **B** is obtained, Table 1. In other words, there is an excellent correlation exclusively between the effect of substitution on the benzene ring and the major product. Generally, when the substitution on the aryl ring is electron-donating in arylcyanamides **1a**–**j**, the formation of 1-aryl-5-amino-1*H*-tetrazoles (**B**) is favored via guanidine azide intermediate **B′** (Table 1 and entries 6–9) and as the electronegativity of substituent is increased, the product is shifted toward the 5-arylamino-1*H*-tetrazole (**A**) (Table 1 and entries 1,2). In other words, if cyclization were to involve the nitrogen carrying the aryl substituent in guanidine azide intermediate **B′**, 1-aryl-5-amino-1*H*-tetrazoles (**B**) would result. On the other hand, involvement of the terminal unsubstituted nitrogen in the cyclization would result in 5-arylamino-1*H*-tetrazoles (**A**) via guanidine azide intermediate **A′**. This is similar to the substituent effect on the aryl ring of mechanism that was presented by Henry and coworkers for thermal isomerization.[30]

3. It is interesting to note that in the reaction between sodium azide with secondary arylcyanamides in the presence of zinc(II) chloride in water at reflux, the results obtained from the entries 5 and 6 are not as same as the results in entries 1–3. This observation is due to the presence of halogen groups (–Cl and –Br) on the benzene ring in the 4-position which exerts a *para* orienting influence. So, the resonance effects of the *p*-Cl and *p*-Br groups cause the nitrogen atom carrying the aryl substituent to become more negative and the formation of 1-aryl-5-amino-1*H*-tetrazoles isomer (**B**) is favored.

A comparison of **3b** (chlorine atom at *ortho* position) with **3f** (chlorine atom at *para* position) indicates that the intramolecular hydrogen bonding in **3b** favored the formation of 5-arylamino-1*H*-tetrazole isomer (**A**) (Scheme 3). As shown in Scheme 3, in the conformer $\mathbf{A_2}$ both the tetrazole ring and aryl fragment are coplanar.



Scheme 3.

In all cases, the products were characterized by ^{1}H NMR, ^{13}C NMR, IR, FTIR, elemental analysis (CHN), and melting points. The disappearance of one strong and sharp absorption band (CN stretching band), and the appearance of an NH stretching band in the IR spectra, provided clear evidence for the formation of arylaminotetrazoles. ^{13}C NMR spectra displayed signals at δ=154–157.5 ppm indicative of C5 in the tetrazole ring.[37] On the basis of ^{1}H NMR spectra we have considered two possible structures **A** and **B**. A comparison of ^{1}H NMR spectra revealed that 5-arylamino-1*H*-tetrazole (**A**) generally show a wide separation in the chemical shifts of the *ortho*-, *meta*-, and *para*-aryl protons, while 1-aryl-5-amino-1*H*-tetrazoles isomers (**B**) had a narrow separation of the aryl ring protons (Figs. 1 and 2). On the other hand, 5-arylamino-1*H*-tetrazoles isomers (**A**) contain two NH bonds (NH of the amine attached to the aryl group (NH^A) and NH of the tetrazole ring (NH^T)) and 1-aryl-5-amino-1*H*-tetrazoles isomers (**B**) contain a NH_2 bond. The free N–H bond of tetrazoles (NH^T) makes them acidic molecules, and not surprisingly it has been shown that both the aliphatic and aromatic heterocycles have pK_a values that are similar to the corresponding carboxylic acids, due to the ability of the moiety to stabilize a negative charge by electron delocalization.[6,38] In general, tetrazolic acids exhibit physical characteristics similar to carboxylic acids. Thus, signal of the NH proton of the tetrazole ring (NH^T) shifted downfield (see Fig. 1 and ^{1}H NMR data of **3a**–**d**). Indeed, ^{1}H NMR spectra showed signals at δ=9–10 ppm indicative of NH^A in 5-arylamino-1*H*-tetrazoles isomers (**A**) (Fig. 1), whereas ^{1}H NMR spectra of 1-aryl-5-amino-1*H*-tetrazoles isomers (**B**) showed one peak at δ=6.6–7 ppm indicative of the NH_2 group (Figs. 2 and 3).

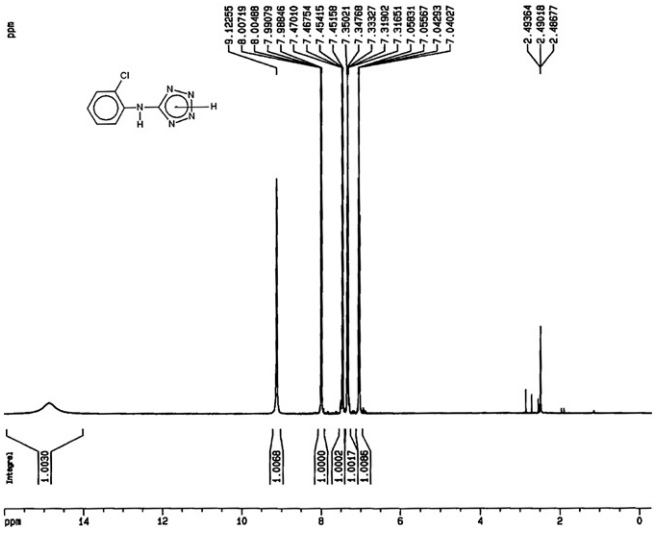


Figure 1. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) 5-(2-chlorophenyl)amino-1*H*-tetrazole (**3b**).

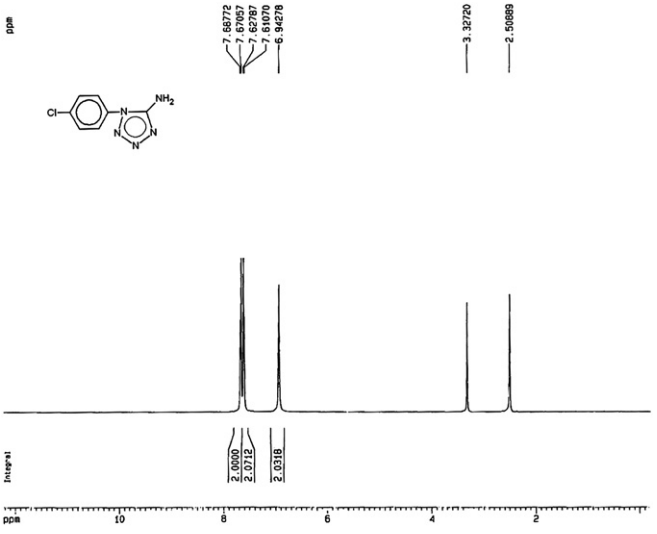


Figure 2. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) 1-(4-cholorophenyl)-5-amino-1*H*-tetrazole (**3f**).

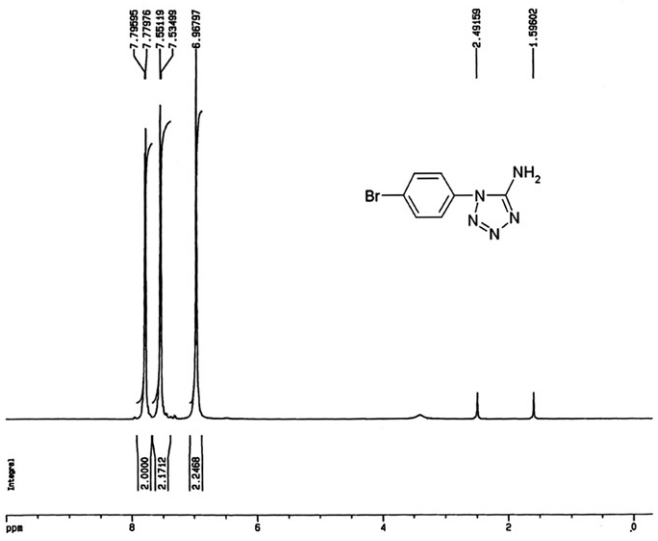


Figure 3. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) 5-(4-bromophenyl)amino-1*H*-tetrazole (**3e**).

3. Conclusions

In conclusion, we have reported an effective methodology for the preparation of substituted arylaminotetrazoles. The significant advantages of this methodology are high yields, simple methodology, a simple work-up procedure and no chromatographic separation or crystallization is necessary to get obtain pure compounds. The use of water as the solvent suggests good prospects for the applicability of this process.

4. Experimental

4.1. General

All reagents were purchased from Merck and Aldrich and used without further purification. Products were characterized by spectroscopy data (IR, FTIR, ^{1}H NMR, and ^{13}C NMR spectra), elemental analysis (CHN) and melting points. The NMR spectra were recorded in DMSO. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 300 and 500 MHz instruments. The chemical shifts (δ) are reported in parts per million relative to the TMS as internal standard. *J* values are given in Hertz. ^{13}C NMR spectra were recorded at 125 and 75 Hz. IR (KBr) and FTIR (KBr) spectra were recorded on a Shimadzu 470 and Perkin-Elmer 781 spectrophotometer, respectively. Melting points were taken in open capillary tubes with a BUCHI 510 melting point apparatus and were uncorrected. The elemental analysis was performed using Heraeus CHN-O-Rapid analyzer. TLC was performed on silica gel polygram SIL G/UV 254 plates.

4.2. Preparation of the arylcyanamides

The cyanamides **1a–j** were prepared according to literature.[34]

*4.2.1. 1-Naphthylcyanamide (**1j**, Table 1).* ^{1}H NMR (DMSO-d_6, 300 MHz): δ=7.21 (d, *J*=7.4 Hz, 1H), 7.47 (t, *J*=7.8 Hz, 1H), 7.54–7.59 (m, 3H), 7.89–7.93 (m, 1H), 8.09–8.12 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ=136.4, 134.4, 128.7, 127.0, 126.6, 126.3, 124.1, 122.8, 121.7, 114.3, 111.5; FTIR (KBr): ν 3382, 3165, 3079, 2961, 2897, 2226, 1613, 1515, 1436, 1409, 1302, 1256, 1181, 1108, 1016, 859, 835, 811, 771 cm^{-1}; Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.65. Found: C, 78.66; H, 4.90; N, 16.53.

4.3. Typical procedure for preparation of arylaminotetrazoles 3

To a 50 mL round-bottomed flask, the cyanamide **1** (2 mmol), sodium azide **2** (3 mmol), zinc(II) chloride (3 mmol) and of water (16 mL) were added. The reaction mixture was stirred at reflux for 15 h. After consumption of cyanamide **1**, the mixture was cooled to room temperature, the solid residue was filtered from the reaction mixture and then was washed with water. In continuation of work-up, the solid residue was treated with 3 N HCl (4 mL), the desired pure products were then filtered and characterized by ^{1}H NMR, ^{13}C NMR, IR, FTIR, elemental analysis (CHN), and melting points. This method did not require any further purification. No side product was observed under the reaction conditions.

The spectral data of ten representative arylaminotetrazoles are given below:

*4.3.1. 5-(4-Nitrophenyl)amino-1H-tetrazole (**3a**, Table 1, entry 1).* Mp 218–220 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=7.76 (d, *J*=7.3 Hz, 2H), 8.21 (d, *J*=7.3 Hz, 2H), 10.96 (s, br, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=116.8, 124.9, 140.4, 147.2, 155.2; IR (KBr) 3550, 3235, 3100, 1635, 1572, 1488, 1337, 1290, 1257, 1111, 1052, 839, 745 cm^{-1}; Anal. Calcd for $C_7H_6N_6O_2$: C, 40.78; H, 2.93; N, 40.77. Found: C, 40.90; H, 3.03; N, 40.64.

*4.3.2. 5-(2-Chlorophenyl)amino-1H-tetrazole (**3b**, Table 1, entry 2).* Mp 228–230 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=7.04 (t, *J*=7.7 Hz, 1H,), 7.33 (t, *J*=8.4 Hz, 1H), 7.46 (d, *J*=7.9 Hz 1H), 8.00 (d, *J*=8.2 Hz, 1H), 9.12 (s, 1H), 14.86 (s, br, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=120.2, 122.6, 123.5, 127.9, 129.6, 136.7, 154.8; IR (KBr) 3260, 3210, 3140, 3100, 1626, 1573, 1551, 1470, 1440, 1286, 1233, 1134, 1052, 796, 742, 674, 633 cm^{-1}; Anal. Calcd for $C_7H_6N_5Cl$: C, 42.98; H, 3.09; N, 35.80. Found: C, 43.10; H, 3.19; N, 35.68.

*4.3.3. 5-(2,5-Dichlorophenyl)amino-1H-tetrazole (**3c**, Table 1, entry 3).* Mp 272–274 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=7.06 (d, *J*=8.5 Hz, 1H), 7.48 (d, *J*=8.6 Hz, 1H), 8.19 (s, 1H), 9.38 (s, 1H), 14.72 (s, br, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=118.7, 120.3, 122.5, 130.8, 132.3, 137.8, 154.4; IR (KBr) 3245, 3184, 3156, 3115, 1620, 1592, 1569, 1544, 1467, 1411, 1090, 1054, 1038, 836, 799, 772, 664, 563, 538 cm^{-1}; Anal. Calcd for $C_7H_5N_5Cl_2$: C, 36.52; H, 2.17; N, 30.43. Found: C, 36.66; H, 2.22; N, 30.56.

*4.3.4. 5-Phenylamino-1H-tetrazole (**3d**, Table 1, entry 4).* Mp 215–217 °C (lit.[10] 211–212 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ=6.93 (t, *J*=7.3 Hz, 1H), 7.29 (t, *J*=7.9 Hz, 2H), 7.49 (d, *J*=8.2 Hz, 2H), 9.74 (s, 1H), 15.33 (s, br, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=116.7, 121.0, 128.9, 140.3, 155.8; IR (KBr) 3325, 3220, 1620, 1580, 1533, 1498, 1243, 1053, 785, 742, 735, 688, 660 cm^{-1}.

*4.3.5. 1-(4-Bromophenyl)-5-amino-1H-tetrazole (**3e**, Table 1, entry 6).* Mp 239–240 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=6.97 (s, 2H), 7.54 (d, *J*=8.1 Hz, 2H), 7.78 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=123.0, 126.7, 132.9, 133.4, 155.4; IR (KBr) 3340, 3140, 1647, 1588, 1570, 1489, 1449, 1400, 1319, 1139, 1104, 1096, 1065, 1004, 833, 815, 516 cm^{-1}; Anal. Calcd for $C_7H_6N_5Br$: C, 35.02; H, 2.52; N, 29.17. Found: C, 35.08; H, 2.60; N, 29.21.

*4.3.6. 1-(4-Chlorophenyl)-5-amino-1H-tetrazole (**3f**, Table 1, entry 5).* Mp 217–219 °C (lit.[30a] 215–217 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ=6.94 (s, 2H), 7.62 (d, *J*=8.6 Hz, 2H), 7.68 (d, *J*=8.6 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=126.9, 130.6, 133.2, 134.6, 155.8; FTIR (KBr) 3345, 3141, 1651, 1593, 1577, 1499, 1450, 1410, 1324, 1144, 1095, 1074, 1010, 838, 819, 734, 630, 557, 513, 471 cm^{-1}.

*4.3.7. 1-(4-Methylphenyl)-5-amino-1H-tetrazole (**3g**, Table 1, entry 7).* Mp 178–179 °C (lit.[30a] 175.5–177 °C); ^{1}H NMR (DMSO-d_6,

500 MHz): δ=2.38 (s, 3H), 6.80 (s, 2H), 7.39 (d, J=7.8 Hz, 2H), 7.43 (d, J=8.3 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=21.6, 124.8, 131.1, 131.8, 139.8, 155.8; FTIR (KBr) 3306, 3141, 1655, 1594, 1572, 1519, 1467, 1320, 1306, 1142, 1090, 1017, 839, 818, 618, 545, 483 cm^{-1}.

*4.3.8. 1-(2,4-Dimethylphenyl)-5-amino-1H-tetrazole (**3h**, Table 1, entry 8).* Mp 199–201 °C (lit.[11] 199–201 °C); ^{1}H NMR (DMSO-d_6, 500 MHz): δ=1.99 (s, 3H), 2.36 (s, 3H), 6.63 (s, 2H), 7.19 (d, J=8.3 Hz, 1H), 7.22 (d, J=8.1 Hz, 1H), 7.28 (s, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=16.7, 20.6, 127.1, 127.6, 129.4, 131.7, 134.9, 140.0, 155.6; IR (KBr) 3310, 3150, 1651, 1573, 1506, 1458, 1377, 1312, 1134, 1088, 1027, 868, 823, 614, 562 cm^{-1}.

*4.3.9. 1-(2-Methylphenyl)-5-amino-1H-tetrazole (**3i**, Table 1, entry 9).* Mp 191–192 °C (lit.[11] 191–192 °C); ^{1}H NMR (DMSO-d_6, 300 MHz): δ=2.06 (s, 3H), 6.74 (s, 2H), 7.36–7.51 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ=17.4, 127.7, 127.9, 130.9, 131.8, 132.5, 135.8, 156.1; FTIR (KBr) 3323, 3158, 1655, 1593, 1575, 1503, 1473, 1313, 1126, 1091, 1026, 772, 757, 715, 673, 564 cm^{-1}; Anal. Calcd for $C_8H_9N_5$: C, 54.84; H, 5.18; N, 39.98. Found: C, 54.92; H, 5.07; N, 40.11.

*4.3.10. 1-(1-Naphthyl)-5-amino-1H-tetrazole (**3j**, Table 1, entry 10).* Mp 220–221 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ=6.78 (s, br, 2H), 7.28 (d, J=8.3 Hz, 1H), 7.62–7.74 (m, 4H), 8.14 (d, J=8.2 Hz, 1H), 8.22 (d, J=7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ=157.3, 134.8, 131.6, 129.9, 129.8, 129.3, 128.8, 127.9, 126.7, 126.6, 122.7; FTIR (KBr) 3322, 3139, 1655, 1598, 1577, 1509, 1483, 1397, 1085, 806, 772, 662 cm^{-1}; Anal. Calcd for $C_{11}H_9N_5$: C, 62.56; H, 4.26; N, 33.17. Found: C, 62.64; H, 4.38; N, 33.29.

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