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L-Proline: An Efficient Organocatalyst for the Synthesis of 5-Substituted 1*H*-Tetrazoles *via* [3+2] Cycloaddition of Nitriles and Sodium Azide

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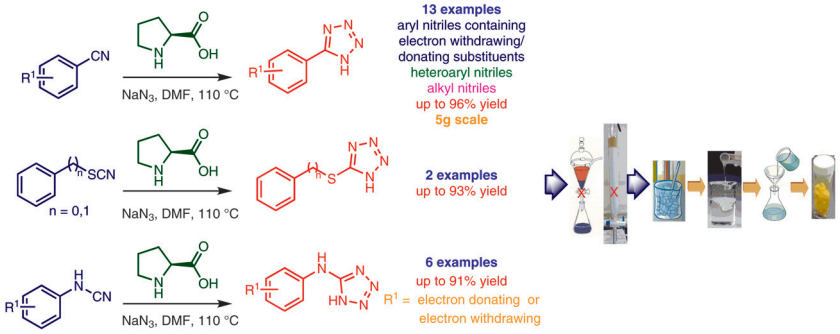

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Abstract A simple and efficient route for the synthesis of a series of 5-substituted 1*H*-tetrazoles using L-proline as a catalyst from structurally diverse organic nitriles and sodium azide is reported. The prominent features of this environmentally benign, cost effective, and high-yielding L-proline-catalyzed protocol includes simple experimental procedure, short reaction time, simple workup, and excellent yields making it a safer and economical alternative to hazardous Lewis acid catalyzed methods. The protocol was successfully applied to a broad range of substrates, including aliphatic and aryl nitriles, organic thiocyanates, and cyanamides.

Keywords 5-substituted 1*H*-tetrazoles, organic nitriles, thiocyanates, cyanamides, sodium azide, L-proline

Tetrazoles are an important class of nitrogen-containing heterocycles with numerous applications in a wide array of fields, including organic synthesis, medicinal chemistry, coordination chemistry, and material science.[1] The tetrazole functionality is found in anti-inflammatory, antihypertensive, anticancer, anti-allergic, antibiotic, diuretics, and receptor modulatory agents.[2] Tetrazoles serve as a non-classical bio-isosteres for the carboxylic acid moiety in drug design owing to their higher lipophilicity, metabolic stability, and increased absorption relative to the carboxylic acid.[3]

The tetrazole structural motif is a part of angiotensin II receptor antagonist belonging to the sartan family, for example, losartan, valsartan, candesartan, irbesartan, and BMS-183920, peptidase inhibitor CGS-26303, anti-arthritic drug indomethacin derivative, antiasthmatics drug tomelukast and pemirolast, phosphodiesterase inhibitor cilostazol, and anti-HIV drug candidates (Figure 1).[4]

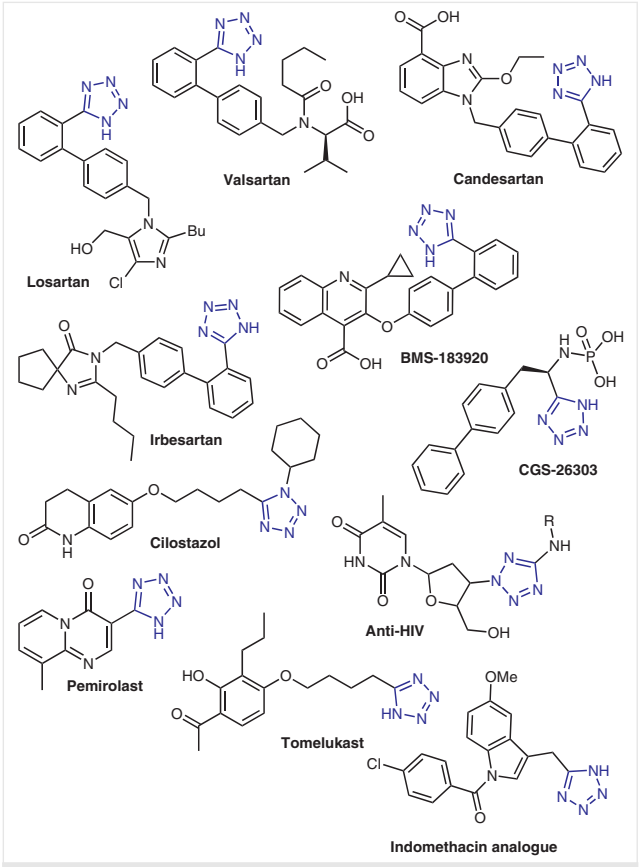


Figure 1 Biologically active agents containing the tetrazole moiety

The extensive utility of tetrazoles has prompted significant effort toward the development of several sophisticated strategies for their synthesis, however, the [3+2] cycloaddi-

tion of azide anion to corresponding organic nitriles remain by far the most direct and convenient method for the synthesis of 5-substituted 1*H*-tetrazoles.[5] A plethora of synthetic protocols and variations on this general route have been reported in the literature, which involve the use of various homogeneous catalytic system such as zinc(II) salts,[6] copper triflates,[7] $Fe(OAc)_2$,[8] various Lewis acid catalysts such as $AlCl_3$,[9] BF_3-OEt_2,[10] $FeCl_3$,[11] $CdCl_2$,[12] $InCl_3$,[13] Sb_2O_3,[14] TBAF,[15] I_2,[16] or heterogeneous catalysts such as mesoporous ZnS nanospheres,[17] nanocrystalline ZnO,[18] Cu–Zn alloy nanopowder,[19] $CuFe_2O_4$ nanoparticles,[20] CoY Zeolite,[21] Zn/Al hydrotalcite,[22] zeolite/sulfated zirconia,[23] phosphomolybdic acid,[24] $BaWO_4$ and other tungstates,[25] and amberlyst-15.[26]

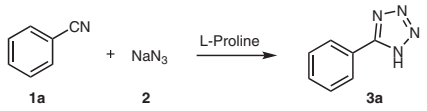
In spite of many pioneering methodologies explored for the synthesis of this versatile heterocyclic ring, their wide application still obviates the need for the development of alternate routes which eliminate the problems associated with the use of strong Lewis acids or expensive and toxic metal catalysts and reagents, stoichiometric amount of catalyst, drastic reaction conditions, water sensitivity, poor selectivity, or inferior yield of the desired product. This prompted us to develop a safe, metal-free, and environmentally benign protocol for the synthesis of 5-substituted 1*H*-tetrazoles.

Organocatalysis, use of metal-free small organic molecules as catalyst, has emerged as a rapidly growing research field for chemical synthesis due to good accessibility, environmental friendliness, and high efficiency.[27–29] Amongst them, L-proline is a readily available, safe, easy to handle, and inexpensive 'privileged catalyst' bringing about numerous chemical transformations in a rapid, selective, catalytic, and atom-economical fashion.[30] As a part of our ongoing research interest aimed at developing green and sustainable organocatalytic protocols and their subsequent application to access bioactive compounds, we envisioned the benign and metal-free L-proline-mediated one-pot synthesis of 5-substituted 1*H*-tetrazoles, via [3+2] cycloaddition reaction between organic nitriles and sodium azide, in high yields and purity.

To optimize the reaction conditions and evaluate the catalytic activity of L-proline for the [2+3] cycloaddition, the reaction between benzonitrile (**1a**) and sodium azide (**2**) was selected as a model reaction for the synthesis of 5-phenyl 1*H*-tetrazole (**3a**) using different reaction parameters, and the results are summarized in Table 1.

In the absence of catalyst at 110 °C, no reaction occurred even after 12 h (Table 1, entry 1). However, when benzonitrile (**1a**) was reacted with sodium azide (**2**) using 10 mol% L-proline in DMF at 110 °C, the product 5-phenyl 1*H*-tetrazole (**3a**) was isolated in 70% yield after 6 h (Table 1, entry 2). The yield was improved to 87% when the reaction was carried out in the presence of 20 mol% of L-proline (Table 1, entry 3). In an attempt to improve the conversion and yield, the reaction was repeated using 30 mol% of L-proline as a catalyst, gratifyingly, this resulted in complete conversion of benzonitrile into 5-phenyl 1*H*-tetrazole within 1 h in excellent yield (Table 1, entry 4). A further increase in the amount of catalyst had no significant effect on the yield and the reaction time (Table 1, entry 5). Further, a decrease in temperature to 80 °C had a detrimental influence on the yield of the product **3a** (Table 1, entry 6), while an increase in temperature from 110 °C to 120 °C gave no obvious improvement in the reaction (Table 1, entry 7). Subsequently, the reaction was carried out in different solvents and DMF as solvent provided higher yields than those using other common solvents, such as DMSO, *n*-propanol, and EtOH (Table 1, entries 8–10). Thus, the best result was achieved by carrying out the reaction with 1:1.25 molar ratios of benzonitrile and NaN_3 in the presence of 30 mol% L-proline in DMF at 110 °C for 1 h (Table 1, entry 4).

Table 1 Optimization of Reaction Conditions[a]



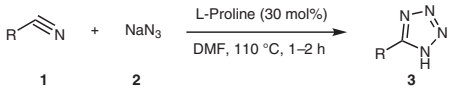
1a 2 3a

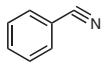
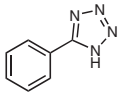
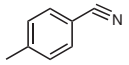
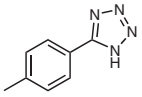
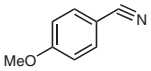
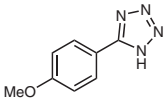
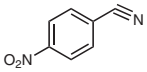
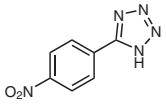
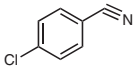
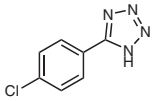
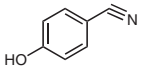
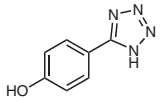
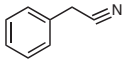
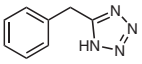
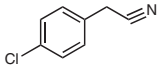
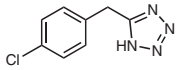
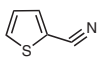
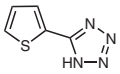
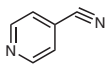
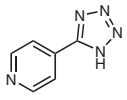
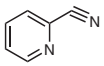
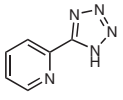
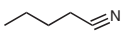
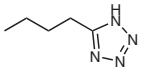
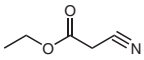
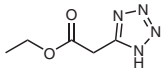
Entry	L-Proline (mol%)	Solvent	Temp (°C)	Yield (%)[b]
1	-	DMF	110	ND[c]
2	10	DMF	110	70
3	20	DMF	110	87
4	30	DMF	110	96
5	50	DMF	110	94
6	30	DMF	80	54
7	30	DMF	120	91
8	30	DMSO	110	47
9	30	*n*-PrOH	reflux	63
10	30	EtOH	reflux	15

[a] Reaction conditions: benzonitrile (**1a**, 1mmol), sodium azide (**2**, 1.25 mmol), and L-proline in solvent (5.0 mL).
[b] Yields of isolated products.
[c] ND = no desired product.

With the optimized conditions in hand, we next investigated the substrate scope and generality of the L-proline promoted [3+2] cycloaddition reaction to form 5-substituted 1*H*-tetrazoles, by employing a variety of structurally divergent benzonitriles possessing a range of activating and deactivating functional groups, a few heteroaromatic and aliphatic nitriles and the results are summarized in Table 2.

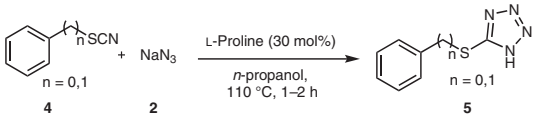
Table 2 Synthesis of 5-Substituted-1*H*-tetrazoles under Optimized Conditions Using L-Proline[a]



Entry	Organic nitriles **1**	Product **3**	Yield (%)[b]
1			96
2			91
3			89
4			90
5			94
6			83
7			84
8			89
9			92
10			94
11			92
12			71
13			78

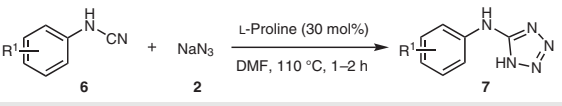
[a] Reaction conditions: nitrile (1.0 mmol), sodium azide (1.25 mmol), and L-proline (30 mol%) in DMF at 110 °C for 1–2 h.
[b] Isolated yields.

In all cases the conversion was completed within 1–1.5 h with good to excellent yields. The nature of the substituent on the benzonitrile did not affect the reaction time. In general, aromatic nitriles containing an electron-withdrawing substituent reacted slightly better than those containing an electron-donating ring substituent (Table 2, entries 2–6). The benzyl nitriles provided good yields of the corresponding products (Table 2, entries 7 and 8). The heteroaromatic nitriles such as 2-thiophenecarbonitrile, 4-pyridinecarbonitrile, and 2-pyridinecarbonitrile also underwent the conversion smoothly giving the corresponding tetrazoles in excellent yields (Table 2, entries 9–11). Among aliphatic nitriles, valeronitrile as well as ethyl cyanoacetate reacted under the optimized conditions to afford the corresponding tetrazoles in moderate yields (Table 2, entries 12 and 13). Aiming to extend the scope of this protocol, organic thiocyanates **4** were subjected to the present reaction conditions (Scheme 1). Gratifyingly, the corresponding thiotetrazoles **5** were obtained in excellent yield using *n*-propanol as a solvent (Table 3, entries 1 and 2).



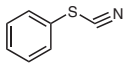
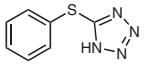
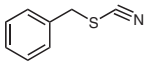
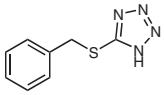
Scheme 1 A general scheme for the synthesis of thiotetrazoles

Further, to demonstrate the versatility of this protocol, we undertook the synthesis of arylaminotetrazole derivatives from the corresponding arylcyanamides (Scheme 2). Thus so far, it has been reported in the literature that the substitution pattern on the aryl ring of arylcyanamides appears to dictate the course of the reaction.[31]



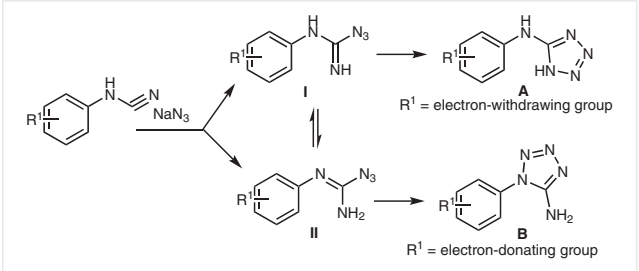
Scheme 2 Synthesis of arylaminotetrazoles from arylcyanamides

Table 3 L-Proline-Catalyzed Synthesis of Thiotetrazoles[a]

Entry	Organic thiocyanates **4**	Product **5**	Yield (%)[b]
1			87
2			93

[a]Reaction conditions: thiocyanates (1.0 mmol), sodium azide (1.25 mmol), L-proline (30 mol%) in *n*-propanol at reflux for 1–2 h.
[b] Isolated yields.

Generally, when the substitution on the aryl ring is electron withdrawing, the formation of 5-aryl-1-amino-1*H*-tetrazoles **A** is favored via guanidine azide intermediate **I** and as the electropositivity of substituent increases, the position of equilibrium shifts toward the isomer 1-aryl-5-amino-1*H*-tetrazoles **B** via guanidine azide intermediate **II**. This is due to the rearrangement of the intermediate as shown in the Scheme 3.[32]



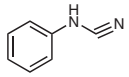
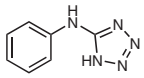
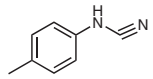
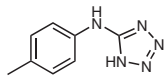
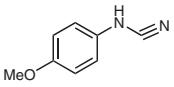
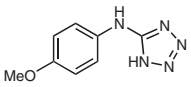
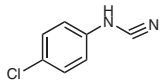
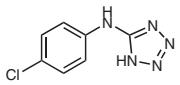
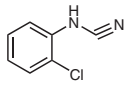
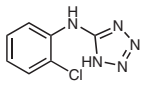
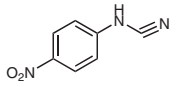
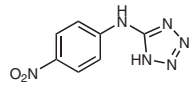
Scheme 3 The possible mechanism involving tautomerism for the synthesis of different aminotetrazoles

However, under the present reaction conditions, the electronic effect of the functional group present on the aryl ring of corresponding cyanamides had no significant impact on the type of product formed. In all the cases, using our developed protocol, and irrespective of the substitutent present, 5-aryl-1-amino 1*H*-tetrazole was formed alone selectively in excellent yield; no 1-aryl-5-amino-1*H*-tetrazole was observed in the reaction (Table 4, entries 1–6).

Further, to investigate the application feasibility of the developed protocol for large-scale synthesis and industry, a scale-up experiment was carried out. When 5 g benzonitrile (**1a**) was reacted with sodium azide (**2**) in DMF under the standard reaction conditions in the presence of L-proline, the reaction proceeded smoothly, providing the corresponding 5-phenyl-1*H*-tetrazole (**3a**) in 90% yield.

Based on the above findings and in accordance with previous literature reports,[33] a tentative mechanism is proposed as shown in Scheme 4. We presume that the nitrile

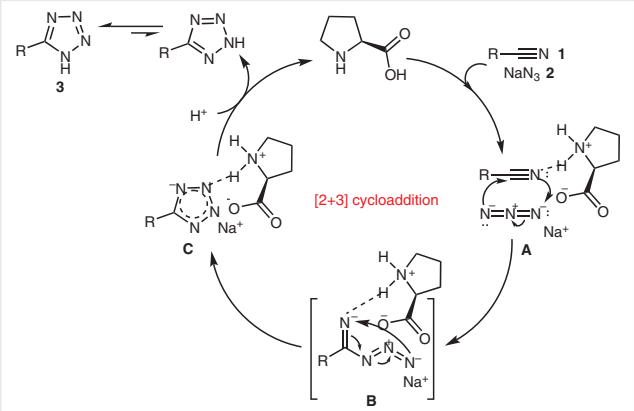
Table 4 Synthesis of 5-Aryl-1-amino-1*H*-tetrazole[a]

Entry	Organic cyanamides **6**	Product **7**	Yield (%)[b]
1			81
2			86
3			87
4			89
5			91
6			87

[a] Reaction conditions: cyanamide (1.0 mmol), sodium azide (1.25 mmol), and L-proline (30 mol%) in DMF at 110 °C for 1–2 h.
[b] Isolated yields.

functionality is activated through hydrogen-bond formation between L-proline and nitrogen atom of nitrile group to form the intermediate **A**. This accelerates the cyclization step by enhancing the electrophilic character of the cyanide group. The [3+2] cycloaddition between the C≡N bond of organic nitrile and azide ion takes place readily to form the intermediate **C**. The cycloaddition may be concerted or two step via formation of an imidoyl azide intermediate **B**. Further, protonation of intermediate **C** during the acid treatment results in the formation of 5-substituted 1*H*-tetrazole product **3**. Although the role of the CO_2^- is not clear, it may stabilize the transition state of the reaction through electrostatic interaction.

In summary, we have demonstrated an efficient and atom-economical synthesis of 5-substituted 1*H*-tetrazoles using organic nitriles and NaN_3 via [3+2] cycloaddition reaction in the presence of L-proline as an organocatalyst.[34] The general protocol described here can be applied to wide array of substrates including aryl and alkyl organic nitriles as well as organic thiocyanates and cyanamides affording in each case the corresponding 5-substituted 1*H*-tetrazoles in excellent yields. The selectivity of the protocol to afford 5-arylamino-1*H*-tetrazoles as product from aryl cyanamide irrespective of the substitution pattern is unique to this protocol. The low cost of reagents, nontoxic and environmentally benign catalyst, milder reaction conditions, short reaction times, broad substrate scope, good to excellent



Scheme 4 A plausible mechanism for the formation of tetrazoles

yields of the products, and good reproducibility are attractive features of this protocol. Moreover, in addition to the above, a simple and clean workup eliminating the need of sophisticated extraction and column chromatography to get the product in high purity makes the present method highly desirable.

Acknowledgment

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Supporting Information

Supporting information for this article (included are experimental details, ^{1}H NMR and ^{13}C NMR analysis of the synthesised compounds) is available online at https://doi.org/10.1055/s-0036-1591534.

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(34) **Typical Procedure for the Synthesis of 5-Substituted 1*H*-tetrazoles 3, 5, 7**

General Procedure for the Synthesis of 5-Aryl/Alkyl 1*H*-Tetrazoles 3

The mixture of organic nitrile (1 mmol), NaN_3 (1.25 mmol), and L-proline (30 mol%) in DMF (5 mL) was stirred at 110 °C for 1–2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The cooled reaction mixture was poured in ice water (15 mL) with stirring. The resulting mixture was acidified with dilute HCl under vigorous stirring. The solid product was filtered under suction and washed with sufficient cold water. The solid was air dried to obtain the pure product.

General Procedure for the Synthesis of 5-(Substituted Sulfanyl)-1*H*-tetrazoles 5

The mixture of appropriate thiocyanate (1 mmol), NaN_3 (1.25 mmol), and L-proline (30 mol%) in *n*-propanol (5 mL) was refluxed for 1–2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The cooled reaction mixture was poured in ice water (15 mL) with stirring. The resulting mixture was acidified with dilute HCl under vigorous stirring. The solid product was filtered under suction and washed with sufficient cold water. The solid was air dried to obtain the pure product.

General Procedure for the Synthesis of 5-Arylamino-1*H*-tetrazoles 7

The mixture of organic cyanamide (1 mmol), NaN_3 (1.25 mmol), and L-proline (30 mol%) in DMF (5 mL) was stirred at 110 °C for 1–2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. The cooled reaction mixture was poured in ice water (15 mL) with stirring. The resulting mixture was acidified with dilute HCl under vigorous stirring. The solid product was filtered under suction and washed with sufficient cold water. The solid was air dried to obtain the pure product.

5-Phenyl-1*H*-tetrazole (3a, Table 2 Entry 1)

Yield 96%, 140.3 mg; white solid; mp 214–216 °C (lit.[6a] 215–216 °C). IR (KBr): ν_{max} = 3207, 3075, 3051, 1610, 1565, 1491, 1466, 688 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 16.8 (br, NH), 8.03–8.01 (m, 2 H), 7.62–7.58 (m, 3 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.1, 131.2, 129.5, 126.8, 124.1 ppm. MS (ESI): *m/z* = 147 $[M + H]^+$.

5-(4-Pyridyl)-1*H*-tetrazole (3j, Table 2, Entry 10)

Yield 94%, 138.3 mg; white solid; mp 254–256 °C (lit.[21] 254–255 °C). IR (KBr): ν_{max} = 3485, 3264, 3099, 3040, 2966, 1621, 1580, 1450, 1388, 1123, 1096, 1042, 1022, 845, 784 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 16.30 (br s, 1 H), 8.51 (d, *J* = 7.6 Hz, 2 H), 7.78 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1, 149.9, 139.4, 120.9 ppm. MS (ESI): *m/z*: 148 $[M + H]^+$.

5-(Benzylsulfanyl)-1*H*-tetrazole (5b, Table 3, Entry 2)

Yield 93%, 178.8 mg; white solid; mp 133–135 °C (lit.[35] 134–135 °C). IR (KBr): ν_{max} = 3061, 2900, 2812, 2653, 2545, 2490, 1532, 1493, 1454, 1433, 1362, 1318, 1236, 1079, 1037, 980, 776, 704 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 16.45 (br s, 1 H), 7.40–7.38 (m, 2 H), 7.32–7.28 (m, 3 H), 4.50 (s, 2 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.2, 137.2, 129.5, 129.1, 128.2, 36.5 ppm. MS (ESI): *m/z* = 193 $[M + H]^+$.

5-(*p*-Tolyl)amino-1*H*-tetrazole (7b, Table 4, Entry 2)

Yield 86%, 150.7 mg; coffee colored solid; mp 200–202 °C (lit.[35] 201–203 °C). IR (KBr): ν_{max} = 3268, 3210, 3135, 3091, 1626, 1578, 1545, 1470, 1440, 1256, 1134, 1090, 1060, 835, 782, 730, 503 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 15.21 (br s, 1 H), 9.66 (s, 1 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 2.24 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.8, 138.1, 130.2, 124.0, 117.8, 20.3 ppm. MS (ESI): *m/z* = 176 $[M + H]^+$.

5-(4-Chlorophenyl)amino-1*H*-tetrazole (7d, Table 4, Entry 4)

Yield 89%, 174.1 mg; white solid; mp 227–229 °C (lit.[35] 226–228 °C). IR (KBr): ν_{max} = 3268, 3210, 3135, 3091, 1626, 1578, 1545, 1470, 1440, 1256, 1134, 1090, 1060, 835, 782, 730, 503 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 15.43 (br s, 1 H), 9.97 (s, 1 H), 7.56–7.53 (d, *J* = 11.9 Hz, 1 H), 7.38–7.35 (d, *J* = 11.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.1, 139.8, 129.3, 125.1, 118.7 ppm. MS (ESI): *m/z* = 196 $[M + H]^+$.

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