Synthesis of thiotetrazoles and arylaminotetrazoles using rutile TiO_2 nanoparticles as a heterogeneous and reusable catalyst

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A novel method is described to prepare rutile TiO_2 nanoparticles which are reusable and efficient heterogeneous catalysts for the synthesis of thiotetrazoles and arylaminotetrazoles – compounds widely used in medicinal and coordination chemistry. This procedure has the advantages of good to excellent yields of products, elimination of homogeneous catalysts and toxic and explosive reagents, simple methodology, easy work up and the reusability of the heterogeneous catalyst.

Keywords: rutile TiO_2 nanoparticles, thiotetrazole, arylaminotetrazole, sodium azide, heterogeneous catalyst

Tetrazoles are well-documented compounds of synthetic importance that have been widely used in coordination and medicinal chemistry and in the synthesis of pharmaceutically important compounds and nitrogen-containing molecules.[1–6]

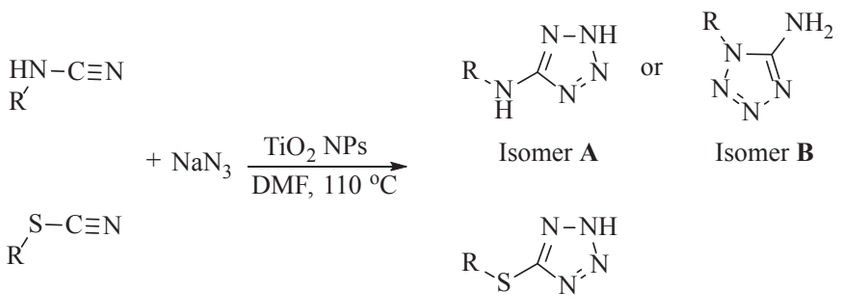
Tetrazoles are conventionally synthesised by the reaction of harmful hydrazoic acid or azide ions with nitriles, thiocyanates or cyanamides in the presence of homogeneous catalysts.[3–11] However, these procedures suffer from disadvantages such as environmentally unpleasant use of toxic reagents or stoichiometric amounts of homogeneous mediators, long reaction times, harsh reaction conditions, tedious isolation steps and low yields of the products. This has limited the large-scale applications of tetrazoles in industry. Recently tetrazoles have been prepared from the reaction between thiocyanates or nitriles with NaN_3 and NH_4Cl as a substitute for HN_3.[1] However, combining sodium azide with ammonium chloride as an acid may yield gaseous HN_3 which is potentially toxic.

Heterogeneous catalysts have attracted attention in the past few years due to their potential in organic synthesis[12] and they often permit easier separations from reaction mixtures. However, heterogeneous catalysts are increasingly used in the form of nanoparticles due to their small size and large surface areas.[9–13] Nanosized TiO_2 has created much interest; its small size and large specific surface area mean it has certain unusual physico-chemical properties.[13] In continuation of our research on natural products, tetrazoles and application of heterogeneous catalysts,[14,15] we now report a simple method for the synthesis of thiotetrazoles and aminotetrazoles using rutile TiO_2 nanoparticles (NPs) as novel and stable heterogeneous catalysts under thermal conditions (Scheme 1).

Results and discussion

There are three mineral phases namely, anatase, rutile and brookite for TiO_2. TiO_2 nanoparticles were prepared by the Degussa Company with an average particle size of 30 nm with an anatase/rutile phase ratio of 80/20. These data are in good agreement with the X-ray diffraction analysis (Fig. 1). The phase transformation of TiO_2 nanoparticles occurs at temperatures higher than 600 °C. Clearly, heating the TiO_2-Degussa nanoparticles up to 600 °C did not bring about any phase transition. Rutile TiO_2 nanoparticles can be obtained by thermal treatment of TiO_2-Degussa nanoparticles at 900 °C. As shown in Fig. 1, at 900 °C temperature the TiO_2 phase is completely rutile (Fig. 1). A typical TEM image of rutile TiO_2 nanoparticles made from TiO_2 nanoparticles with the thermal method at 900 °C is shown in Fig. 2. We decided to study the behaviour of rutile TiO_2 nanoparticles in the synthesis of thiotetrazoles and aminotetrazoles.

Initially, we employed benzylthiocyanate and sodium azide as model substrates for the development of the optimised conditions. Several solvents such as water, toluene, MeCN, DMF and DMSO were examined. Control experiments show that there is no reaction without a catalyst (Table 1, entry 1). However, addition of a catalyst to the mixture rapidly increased the formation of 5-benzylthiotetrazole in high yields. The results indicated that solvent had a significant effect on the yield of product (Table 1, entry 2). A decrease in the catalyst loading from 0.05 to 0.03 g afforded the 5-benzylthiotetrazole in lower yield (Table 1, entry 7). No significant improvement in the yield was observed using higher amounts of the catalyst and 0.05 g of the rutile TiO_2 NPs was found to be optimum. The best result



Scheme 1 Synthesis of thiotetrazoles and aminotetrazoles.

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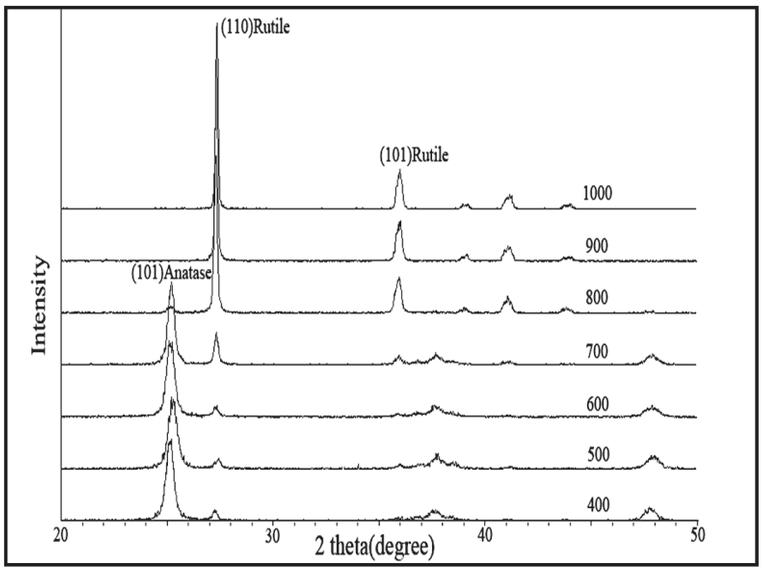


Fig. 1 X-ray diffraction of TiO_2 nanoparticles at 400–1000 °C.

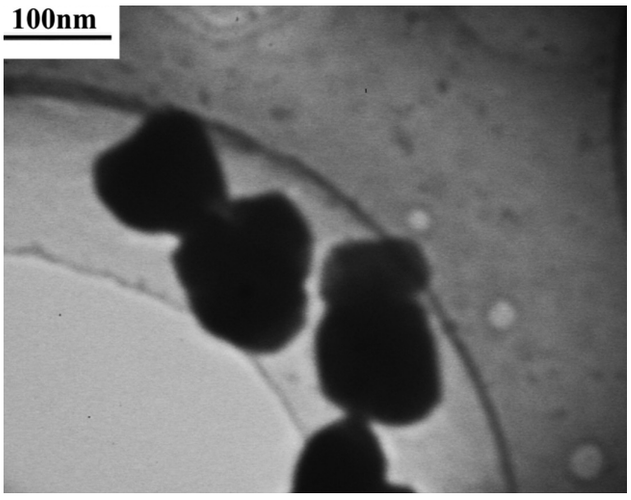
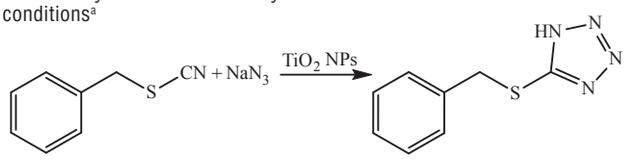


Fig. 2 TEM image of rutile TiO_2 NPs.

Table 1 Synthesis of 5-benzylthiotetrazole under different reaction conditions[a]



Entry	Rutile TiO_2 NPs/g	Solvent	Yield/%[b]
1	0	DMF	0
2	0.05	DMF	90
3	0.05	DMSO	83
4	0.05	CH_3CN	73
5	0.05	H_2O	12
6	0.05	Toluene	74
7	0.03	DMF	60
8	0.07	DMF	90
9	0.10	DMF	89

[a]Reaction conditions: sodium azide (3 mmol), phenylthiocyanate (2 mmol), DMF (6 mL), 110 °C, 20 h.
[b]Isolated yield.

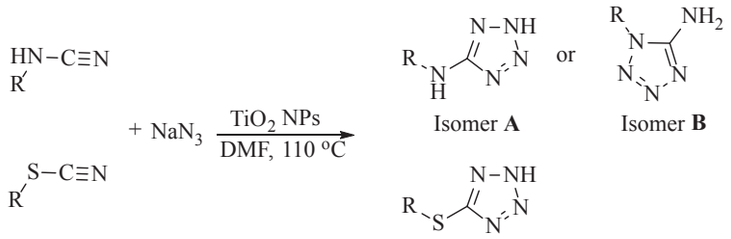
was obtained with 2.0 mmol of benzylthiocyanate, 3.0 mmol of sodium azide, 0.05 g of catalyst and 6.0 mL of DMF as solvent at 110 °C, which gave the product in an excellent yield.

Next, the reactivity of several thiocyanates and cyanamides were tested in the cycloaddition reaction at 110 °C and the results are indicated in Table 2. In all cases, tetrazoles were prepared in good to excellent yields on heating (Table 2). As shown in Table 2, cyanamides having the electron releasing groups on the rings (entries 10–13) were completely reacted at 110 °C after 60 min, while the examples bearing the electron withdrawing species (entries 5–9) require higher reaction times. The influences of various substituents in different *ortho*, *meta* or *para* positions on the type of products were examined. Generally, when the substituent on the aryl ring of the cyanamide is electron-releasing, formation of a 1-aryl-5-amino-1*H*-tetrazole (isomer **B**) is favoured (entries 10–13, Table 2), and as the electronegativity of the substituent is increased, the product is shifted toward 5-arylamino-1*H*-tetrazoles (isomers **A**) (entries 5–9, Table 2).

From an economic point of view, the stability and sustained activity of the catalysts are of great importance. Thus, the recovery and reusability of the rutile TiO_2 NPs were examined by the analysis of the reaction of benzylthiocyanate with sodium azide (Table 2, entry 3). After the first run was completed, the rutile TiO_2 nanoparticles were easily separated by using centrifugation. Next, the catalyst was washed with H_2O and ethyl acetate and dried at 120 °C for 3 h in a hot air oven and employed for the next cycle of the reaction. The catalytic activity did not decrease considerably after five catalytic cycles.

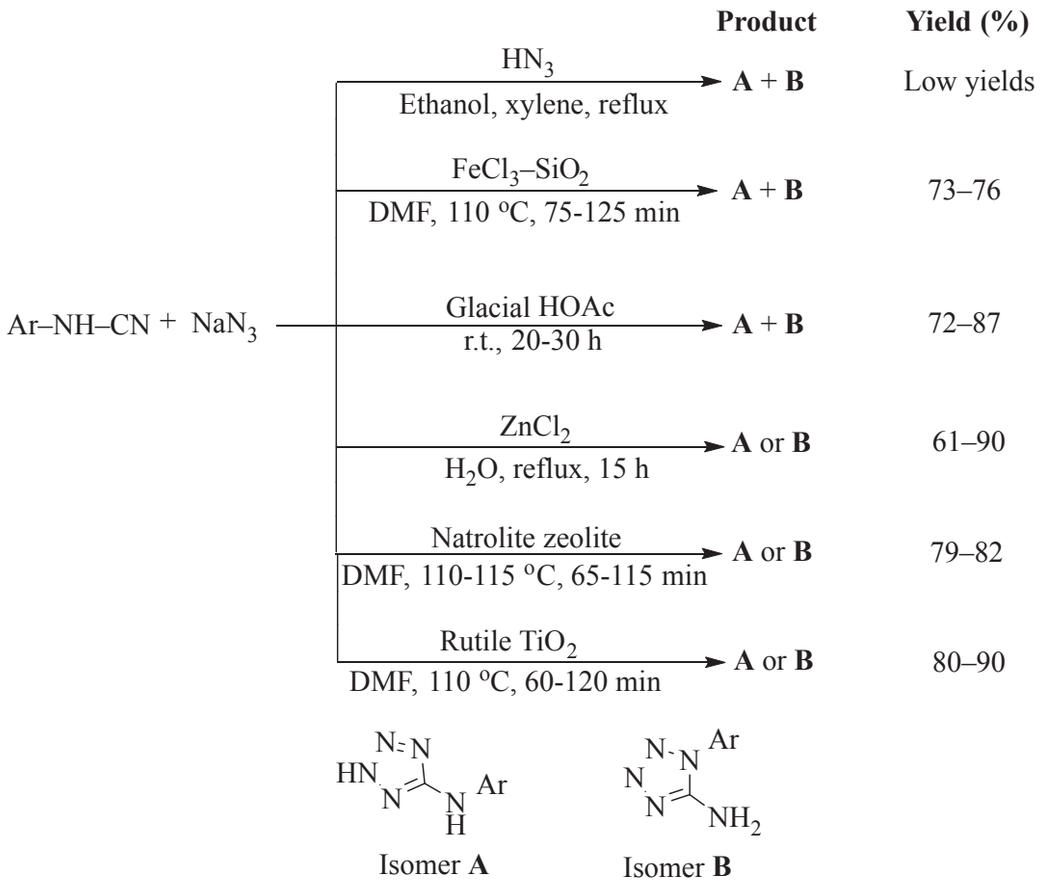
To show the merits of rutile TiO_2 nanoparticles in comparison with other reported catalysts, we summarised some of results in Scheme 2, which show that rutile TiO_2 is an equally or more efficient catalyst with respect to reaction time and yield than those previously reported. As shown in Scheme 2, a rutile TiO_2 nanoparticle is an effective catalyst since the products are regiospecific, whereas with hydrazoic acid,[16] $FeCl_3$–SiO_2[17] and glacial acetic acid,[7] a mixture of isomers are produced. If hydrazoic acid is used, care must be taken by monitoring the

Table 2 Formation of thiotetrazoles and aminotetrazoles



Entry	RXCN	Product	Time/h	Yield/%[a]
1	MeSCN	MeSTet	20	91
2	$Me(CH_2)_3SCN$	$Me(CH_2)_3STet$	20	90
3	$PhCH_2SCN$	$PhCH_2STet$	20	87, 84[b]
4	4-OH,2-Me,5-IsopropylC_6H_2SCN	4-OH,2-Me,5-IsopropylC_6H_2STet	17	95
5	4-$NO_2C_6H_4NHCN$	4-$NO_2C_6H_4NHTet$ (isomers **A**)	2	80
6	2-ClC_6H_4NHCN	2-ClC_6H_4NHTet (isomers **A**)	2	83
7	2,5-$(Cl)_2C_6H_3NHCN$	2,5-$(Cl)_2C_6H_3NHTet$ (isomers **A**)	2	80
8	4-AcC_6H_4NHCN	4-AcC_6H_4NHTet (isomers **A**)	2	81
9	3-$CF_3C_6H_4NHCN$	3-$CF_3C_6H_4NHTet$ (isomers **A**)	2	82
10	2-MeC_6H_4NHCN	2-$MeC_6H_4TetNH_2$ (isomers **B**)	1	84
11	4-MeC_6H_4NHCN	4-$MeC_6H_4TetNH_2$ (isomers **B**)	1	87
12	4-$OMeC_6H_4NHCN$	4-$OMeC_6H_4TetNH_2$ (isomers **B**)	1	90
13	2,6-$(Me)_2C_6H_3NHCN$	2,6-$(Me)_2C_6H_3TetNH_2$ (isomers **B**)	1	81

[a]Yields are after work-up.
[b]Yield after the fifth cycle.



Scheme 2 Various methods for the synthesis of arylaminotetrazoles.

concentration of hydrazoic acid in the reaction mixture to avoid an explosion. $ZnCl_2$[18] is homogeneous and cannot be separated from the reaction mixture, while rutile TiO_2 nanoparticle is heterogeneous and can easily be recovered and reused. Natrolite zeolite[19] is a good and local catalyst, but there are difficulties in the preparation and availability of this catalyst.

The products were characterised by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and melting points. The disappearance of one strong and sharp absorption band (CN stretching band) in the IR spectra, and the appearance of an NH stretching band in the IR and ^{1}H NMR spectra, were evidence for the formation of tetrazoles. The ^{13}C NMR spectra displayed signals about δ = 154–157.5 ppm for C5 of the tetrazole ring.[19]

The two **A** and **B** isomers, have different chemical properties. 5-arylamino-1*H*-tetrazoles, isomers (**A**) are acidic substances, while 1-aryl-5-amino-1*H*-tetrazoles, isomers (**B**) have basic properties due to their NH_2 functional group. 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*-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 an 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 stabilise a negative charge by electron delocalisation.[16–20] In general, tetrazolic acids exhibit physical characteristics similar to carboxylic acids. Thus, the signal of the NH proton of the tetrazole ring (NH^T) is shifted downfield. Indeed, ^{1}H NMR spectra showed signals at δ = 9–10 ppm indicative of NH^A in 5-arylamino-1*H*-tetrazoles isomers (**A**), whereas ^{1}H NMR spectra of 1-aryl-5-amino-1*H*-tetrazoles isomers (**B**) showed one peak at δ = 5–7 ppm indicative of the NH_2 group.

Conclusion

In conclusion we have shown that the rutile TiO_2 nanoparticles, easily prepared in the laboratory, can afford an effective solid catalyst for the synthesis of thiotetrazoles and aminotetrazoles. The catalyst was characterised by XRD and TEM. The protocol offers several merits such as generality and simplicity, high yields and elimination of homogeneous catalysts and dangerous and toxic reagents. Furthermore, the catalytic activity of rutile TiO_2 nanoparticles did not decrease considerably after five catalytic cycles.

Experimental

All the purchased solvents and reagents were of the highest commercial quality and were used without further purification. All reaction mixtures were stirred magnetically and were monitored by TLC using 0.25 mm E-Merck silica gel 60 F254 pre-coated glass plates, which were visualised with UV light and then developed by using iodine mixed with silica gel 60–120 mesh. Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR 240-C spectrophotometer using KBr optics. NMR spectra were recorded on Bruker Avance 300, 400 and 500 MHz spectrometers in acetone and DMSO using TMS as the internal standard, with chemical shifts being given in ppm with respect to internal TMS and *J* values quoted in Hz. The catalyst was prepared by thermal treatment of TiO_2-Degussa nanoparticles at 900 °C.

Synthesis of thiotetrazoles and aminotetrazoles; general procedure

Rutile TiO_2 NPs (0.05 g) was added to the mixture of thiocyanates or cyanamide (2 mmol) and NaN_3 (3 mmol) in DMF (6 mL). The mixture was heated and stirred at 110 °C for the appropriate time (Table 2). After completion of the reaction, rutile TiO_2 NPs as catalyst was separated *via* centrifugation. The centrifuged catalyst was washed with H_2O and EtOAc. Next, it was diluted with HCl (5 M, 20 mL) and extracted three times with EtOAc (25 mL each). The organic layer was concentrated under reduced pressure to afford the crude product which was recrystallised from aqueous ethanol. Most tetrazoles were known and were characterised by melting points, IR, ^{1}H NMR, ^{13}C NMR and CHN analyses.[17–20]

5-(Methylthio)tetrazole (Table 2, entry 1): M.p. 150–152 °C (lit.[20] 150–151 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.70 (s, 3H).

5-(Butylthio)tetrazole (Table 2, entry 2): M.p. 96–98 °C (lit.[20] 95–97 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.89 (t, *J* = 8.0 Hz, 3H), 1.40 (m, *J* = 8.0 Hz, 2H), 1.83 (m, *J* = 7.4 Hz, 2H), 3.33 (t, *J* = 7.0 Hz, 2H).

5-Benzylthiotetrazole (Table 2, entry 3): M.p. 132–134 °C (lit.[20] 132–133 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.53 (s, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 2H).

5-(4'-Hydroxy-2'-methyl-5'-isopropylphenylthio)tetrazole (Table 2, entry 4): M.p. 165–167 °C (lit.[20] 165–166 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.13 (d, *J* = 7.1 Hz, 6H), 2.23 (s, 3H), 3.13 (m, *J* = 7.4 Hz, 1H), 6.81 (s, 1H), 7.31 (s, 1H), 9.88 (s, 1H).

5-(4-Nitrophenyl)amino-1H-tetrazole (Table 2, entry 5): M.p. 218–220 °C (lit.[11] 218–220 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.78 (d, *J* = 8.3 Hz, 2H), 8.22 (d, *J* = 8.3 Hz, 2H), 10.97 (br, 1H).

5-(2-Chlorophenyl)amino-1H-tetrazole (Table 2, entry 6): M.p. 228–230 °C (lit.[11] 228–230 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.05 (t, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 8.3 Hz 1H), 9.13 (s, 1H), 14.87 (br, 1H).

5-(2,5-Dicholorophenyl)amino-1H-tetrazole (Table 2, entry 7): M.p. 273–275 °C (lit.[11] 272–274 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.09 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 8.20 (s, 1H), 9.59 (br, 1H), 14.50 (br, 1H).

5-(4-Acetylphenyl)amino-1H-tetrazole (Table 2, entry 8): M.p. 216–218 °C, IR (KBr disk, cm^{-1}) 3403, 3282, 3177, 3024, 2978, 2839, 2780, 2440, 1651, 1627, 1605, 14579, 1470, 1426, 1364, 1285, 1258, 1195, 1055, 1024, 962, 885, 865, 835, 733, 592; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.38 (s, 1H), 7.92 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H,), 1.10 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 196.7, 145.3, 130.4, 130.1, 116.2, 116.1, 26.8. Anal. calcd for $C_9H_9N_5O$: C, 53.20; H, 4.46; N, 34.47; found: C, 53.25; H, 4.51; N, 34.52%.

5-[3-Trifluoromethyl)phenyl]amino-1H-tetrazole (Table 2, entry 9): M.p. 70–72 °C, IR (KBr, cm^{-1}) 3296, 3170, 3024, 2978, 2839, 2781, 2440, 1660, 1620, 1601, 1556, 1470, 1407, 1334, 1260, 1234, 1186, 1175, 1129, 1099, 1072, 1057, 1024, 984, 917, 885, 867, 797, 782, 762, 728, 697, 675, 665, 612; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 7.23 (d, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 8.70 (s, 1H), 10.40 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 141.65, 130.63, 130.43, 130.01, 120.76, 117.63, 112.89, 34.58. Anal calcd for $C_8H_6F_3N_5$: C, 41.93; H, 2.64; N, 30.56; found: C, 41.99; H, 2.69; N, 30.63%.

1-(2-Methylphenyl)-5-amino-1H-tetrazole (Table 2, entry 10): M.p. 191–192 °C (lit.[19] 191–192 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.52–7.34 (m, 4H), 6.79 (s, 2H), 2.05 (s, 3H).

1-(4-Methylphenyl)-5-amino-1H-tetrazole (Table 2, entry 11): M.p. 177–179 °C (lit.[19] 178–179 °C); ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 7.45 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 6.82 (s, 2H), 2.37 (s, 3H).

1-(4-Methoxyphenyl)-5-amino-1H-tetrazole (Table 2, entry 12): M.p. 212–214 °C (lit.[19] 211–213 °C); ^{1}H NMR (500 MHz, acetone-d_6): δ_H 7.50 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.20 (s, 2H), 3.85 (s, 3H).

1-(2,6-Dimethyphenyl)-5-amino-1H-tetrazole (Table 2, entry 13): M.p. 147–149 °C; FT-IR (KBr, cm^{-1}): 3441, 3383, 3351, 2952, 2921, 1697, 1651, 1604, 1583, 1558, 1526, 1486, 1442, 1247, 1228, 1194, 1168, 1032, 987, 938, 780; ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 7.05 (s, 3H), 5.26 (s, 2H), 2.24 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 157.4, 137.0, 136.5, 128.2, 126.2, 18.5. Anal calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01; found: C, 57.16; H, 5.92; N, 37.06%.

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