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Article

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Construction of 5-Aminotetrazoles via In Situ Generation of Carbodiimidium ions from Ketones Promoted by $TMSN_3$/TfOH

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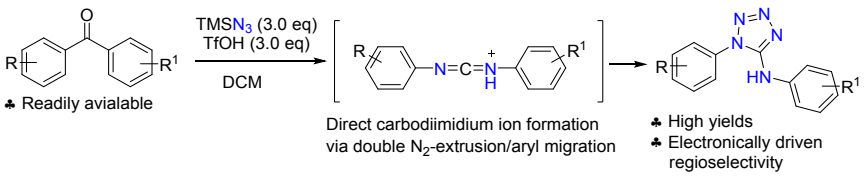


Abstract

A novel synthetic approach for the synthesis of 5-aminotetrazoles has been developed employing simple ketones as the substrates. This methodology involved the N_2-extrusion/aryl migration of azido complexes as the key step for the in situ generation of carbodiimidium ion which could further react with hydrazoic acid and cyclize intramolecularly to provide 5-aminotetrazoles in good to excellent yields. In addition, the regioselectivity of the reaction was studied and rationalized by DFT calculations.

■ INTRODUCTION

5-Substituted tetrazoles are ubiquitous structures found in many applications including pharmaceutical chemistry, organic and inorganic chemistry, and material sciences.[1] Several methods are available for the preparation of 5-substituted tetrazoles.[2] However, 5-aminotetrazoles are relatively much less accessible even though they are crucial core structures of many biologically active molecules.[3] In particular, this class of compounds shows several pharmacological properties such as anti-allergic,[3a] antitumor[3c] anti-inflammatory,[3d] anti-neoplastic,[3e-3f] antimicrobial[3g] and anti-HIV[3j] activities. They also have inhibitory effect in the secretion process of hepatitis B virus surface antigen (HBsAg)[3b] and could act as inhibitors of iNOS,[3h] HIF-2,[3i] and STAT3[3k] as shown in Figure 1. Besides the biological activities, 5-aminotetrazoles could also be utilized as an energetic material. Due to their importance, the development of efficient and practical methods for preparation of 5-aminotetrazoles continues to be vital. Some examples are depicted in Scheme 1.[4]

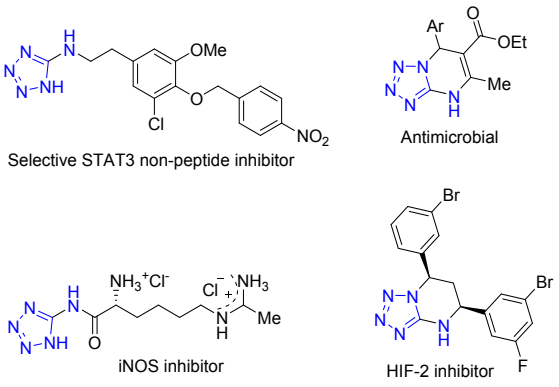
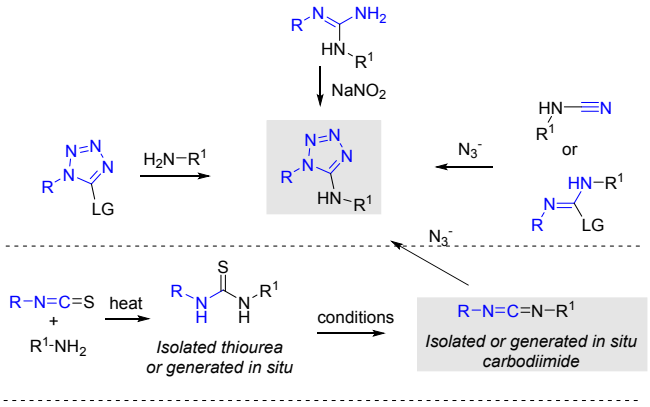


Figure 1. Bioactive compounds

Among a small number of synthetic methodologies, carbodiimide is the most important key intermediate for the preparation of 5-aminotetrazole analogues through nucleophilic addition of azide, followed by ring closure. The most prevalent precursors used

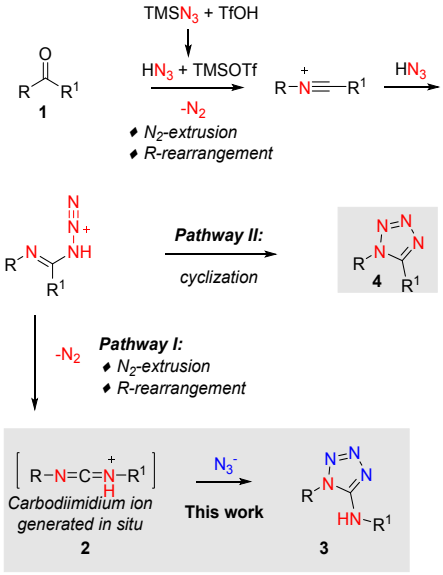
in the preparation of carbodiimides are thioureas which could be synthesized from isothiocyanates and amines.[5] In the synthesis of 5-aminotetrazoles using these methods, carbodiimide intermediate was generated in situ from the reaction of thiourea either with I_2/NEt_3 or hypervalent iodine/NEt_3[6] which further reacted with azide in a one-pot manner. In a related procedure, thioureas could be generated in situ from isothiocyanates and amines which could be directly converted to carbodiimides by treatment with $HgCl_2$ or CuBr in the presence of base.[7] However, the availability and variety of thiourea and isothiocyanate derivatives are rather limited. Therefore, the development of a novel method for the preparation of 5-aminotetrazoles using more readily available and structurally diverse substrates is highly beneficial.



Scheme 1. The reported methods for the synthesis of 5-aminotetrazole.

Herein, we report an alternative approach for the formation of 5-aminotetrazoles from simple ketone precursor (**1**) which is easily accessible from inexpensive and abundant materials. In this work, ketone substrate was converted to a carbodiimidium ion intermediate (**2**) using $TMSN_3$/TfOH via double rearrangement-nitrogen extrusion (Pathway **I**)[8] as shown in Scheme 2. Then, this intermediate was further reacted with HN_3 to provide 5-aminotetrazole product (**3**). However, the formation of tetrazoles could also compete with the

generation of carbodiimidium ion intermediate when the rate of R^1-migration is slower than the cyclization (Pathway **II**).

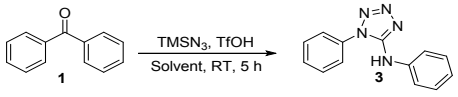


Scheme 2. Proposed synthetic methodology for the synthesis of 5-aminotetrazole.

■ RESULTS AND DISCUSSION

In our study, benzophenone (**1a**) was employed as the screening substrate to optimize reaction conditions as shown in Table 1. Based on the proposed strategy, at least 3.0 equivalents of $TMSN_3$ were required. Therefore, the combination of 3.0 equiv of $TMSN_3$ and 3.0 equiv of TfOH in dry DCM was examined in entry 1 to provide the desired product **3a** in 90%. Interestingly, reducing the reaction time could increase the yield of 5-aminotetrazole to 94% (entry 2) whereas reducing the amount of TfOH to 1.0 and 2.0 equivalents provided the desired product in lower yields (entries 3-4). Moreover, we investigated the effect of solvents such as DCE, toluene and CH_3CN (entries 5-7) and found that these solvents diminished the yields of 5-aminotetrazole. Therefore, using 3.0 equivalents each of TfOH and $TMSN_3$ in dry DCM at room temperature was the optimal conditions for the transformation.

Table 1. Screening for the optimal conditions.[a]



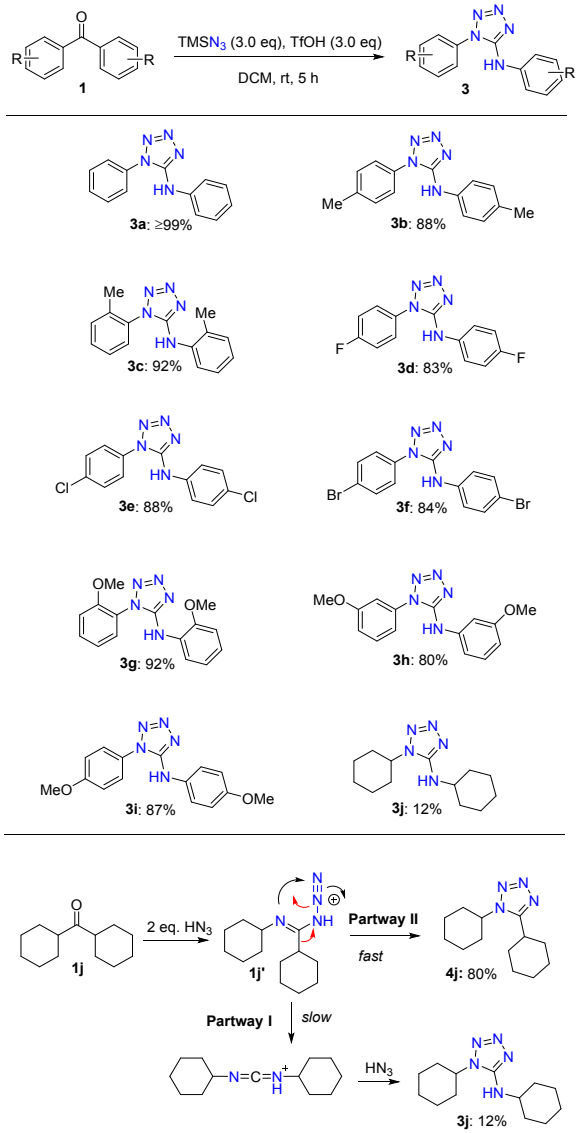
Entry	1 (eq)	$TMSN_3$ (eq)	TfOH (eq)	Solvent	Time (h)	Yield (%)
1	1.0	3.0	3.0	DCM	o/n	90
2	1.0	3.0	3.0	DCM	5	94
3	1.0	3.0	1.0	DCM	5	45
4	1.0	3.0	2.0	DCM	5	78[b]
5	1.0	3.0	3.0	DCE	5	71
6	1.0	3.0	3.0	$PhCH_3$	5	87
7	1.0	3.0	3.0	CH_3CN	5	88

[a] Isolated yields [b] 1,3-Diphenylurea was isolated in 8% yield.

To evaluate the generality of our protocol, a variety symmetrical ketone precursors was examined using the optimal conditions as shown in Table 2. The reaction of benzophenone (**1a**) provided the desired product in 94%. Other analogues of benzophenone were also smoothly converted to the desired products. The *para*-methylbenzophenone (**1b**) gave 5-aminotetrazole product **3b** in 88% yield whereas the *ortho*-methylbenzophenone (**1c**) furnished the corresponding product **3c** in slightly higher yield (92%). All *para*-halobenzophenone derivatives (**1d-1f**) were converted to the corresponding aminotetrazole products in good yields. Furthermore, regioisomeric methoxybenzophenone derivatives (**1g-1i**) were also investigated under these conditions. All three substrates provided the

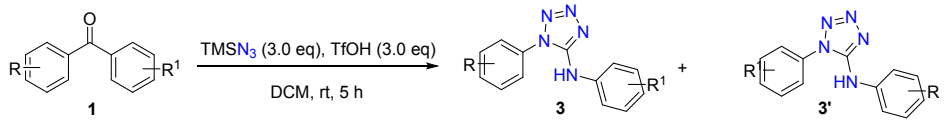
corresponding products in good to excellent yields with the *ortho*-methoxybenzophenone (**1g**) giving the desired product in highest yield among the three regioisomers. This was possibly due to the steric effect of the *ortho*-methoxy group in facilitating the rearrangement process. Unfortunately, the reaction of dicyclohexylketone (**1j**) provided tetrazole **4j** as the major product whereas the corresponding product **3j** was obtained in only 12% yield. This result demonstrated that dicyclohexylketone could be smoothly converted to azidonium imine (**1j'**) via cyclohexyl migration and nucleophilic addition of HN_3. However, the rate of cyclohexyl migration of this intermediate (Pathway **I**, Scheme 2) is slower than cyclization (Pathway **II**, Scheme 2) which led to the formation of 5-aminotetrazole **3j** as the minor product (12%) and tetrazole **4j** as the major product (80%).

Table 2. Synthesis of 5-aminotetrazoles from symmetrical ketones.[a]

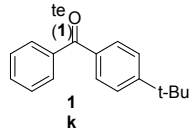
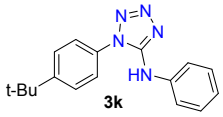
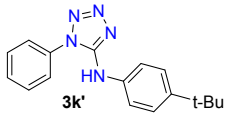
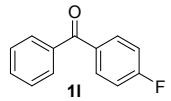
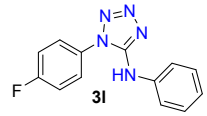
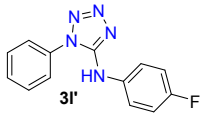
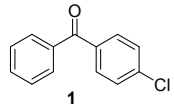
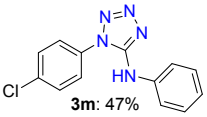
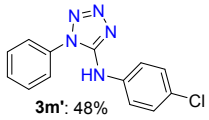
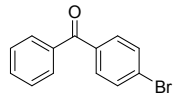
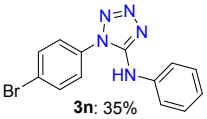
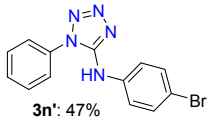
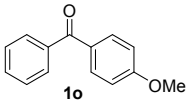
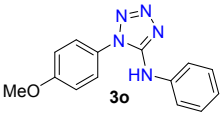
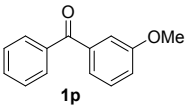
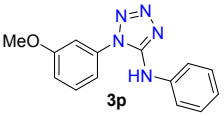
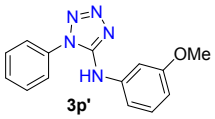
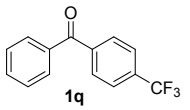
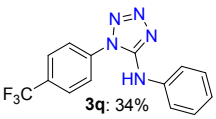
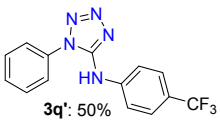
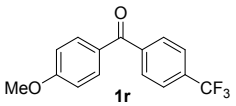
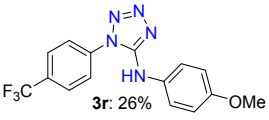
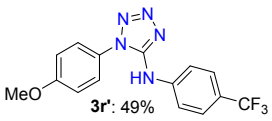
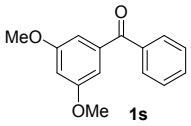
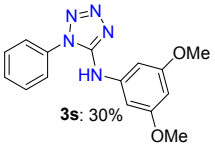
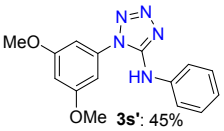
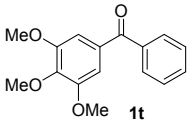
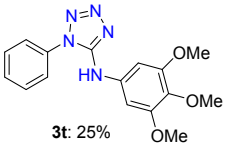
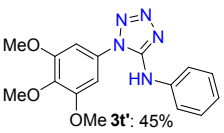


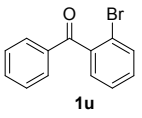
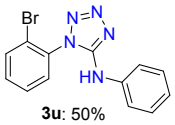
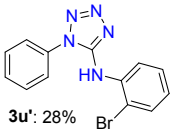
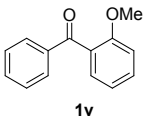
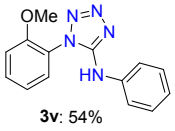
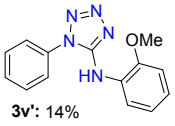
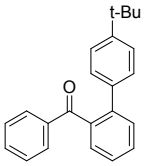
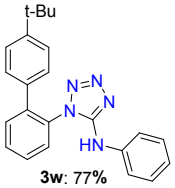
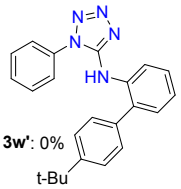
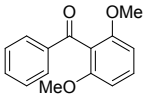
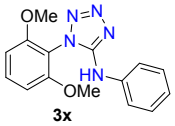
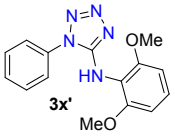
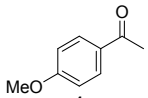
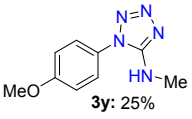
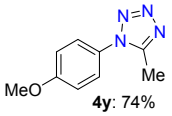
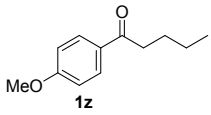
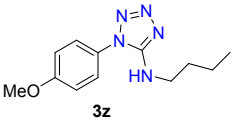
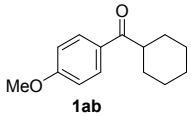
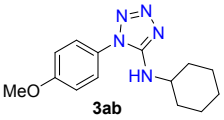
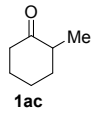
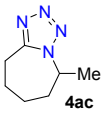
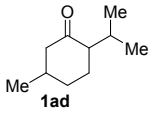
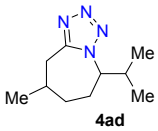
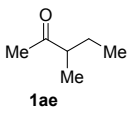
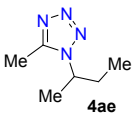
[a] Isolated yields

Table 3 Substrate Scope.[a]



1 3 3'

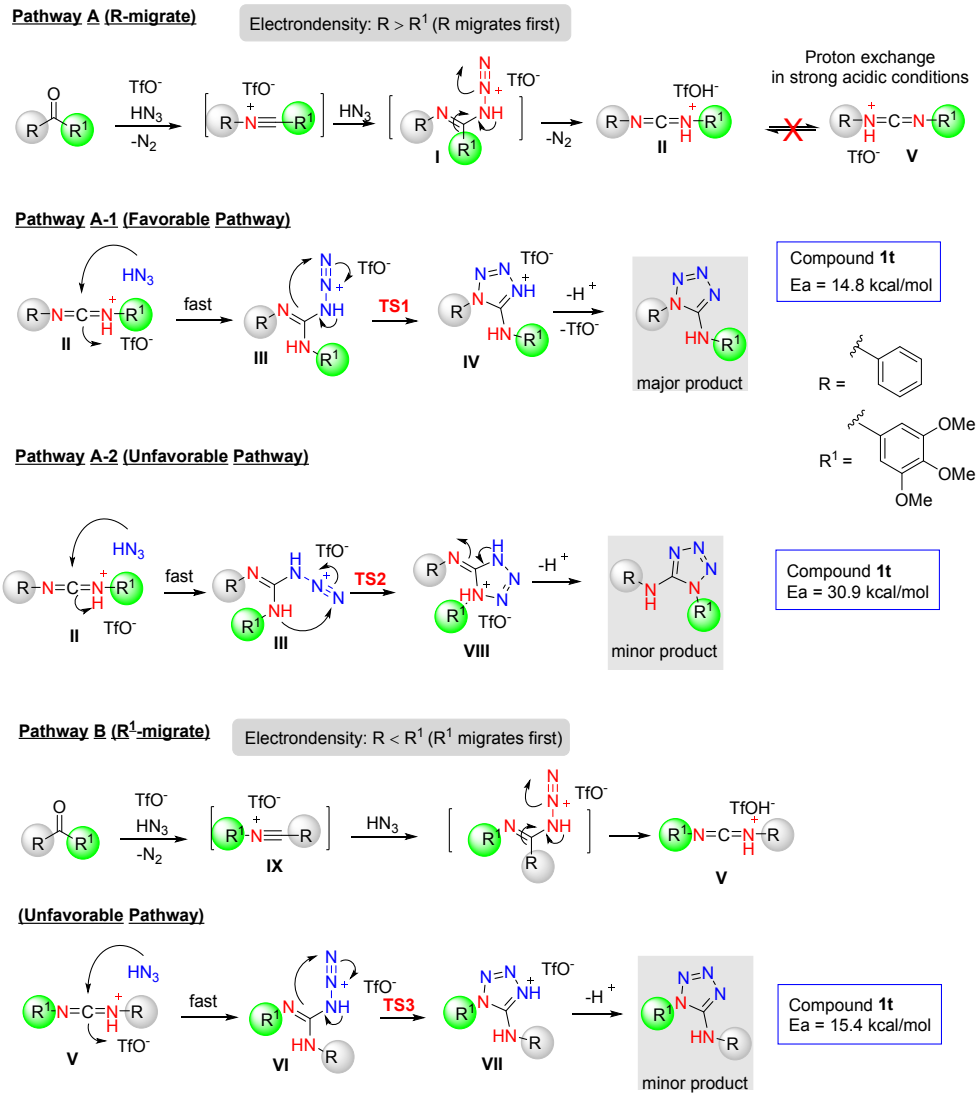
Entry	Substrate (1)	Product (3 and 3')	Yield (%) and ratio (3:3')
1	 1k	 3k  3k'	91% (55:45)[b]
2	 1l	 3l  3l'	90% (48:52)[b]
3	 1m	 3m: 47%  3m': 48%	95% (49:51)
4	 1n	 3n: 35%  3n': 47%	82% (43:57)
5	 1o	 3o  3o'	94% (48:52)[b]
6	 1p	 3p  3p'	94% (53:47)[b]
7	 1q	 3q: 34%  3q': 50%	84% (40:60)
8	 1r	 3r: 26%  3r': 49%	75% (35:65)
9	 1s	 3s: 30%  3s': 45%	91% (40:60)
10	 1t	 3t: 25%  3t': 45%	75% (28:72)

Entry	Substrate (**1**)	Product (**3** and **3'**)		Combined Yield (%) and ratio (3:3')
11	 **1u**	 **3u**: 50%	 **3u'**: 28%	78% (64:36)
12	 **1v**	 **3v**: 54%	 **3v'**: 14%	68% (79:21)
13	 **1w**	 **3w**: 77%	 **3w'**: 0%	77% (100:0)
14	 **1x**	 **3x**	 **3x'**	≥99% (55:45)[b]
15	 **1y**	 **3y:** 25%	 **4y**: 74%	-
16	 **1z**	 **3z**	–	77%
17	 **1ab**	 **3ab**	–	82%
18	 **1ac**	 **4ac**	–	64%
19	 **1ad**	 **4ad**	–	59%
20	 **1ae**	 **4ae**	–	69%

[a] Isolated yields [b] A mixture of inseparable products was isolated whose ratio was determined using ^{1}H NMR.

Next substrate scope study is shown in Table 3, unsymmetrical ketones were employed to generate unsymmetrical carbodiimidium ion intermediates which could lead to the formation of regioisomeric 5-aminotetrazole products. A number of substituents on unsymmetrical ketones was varied to study their influence on product distribution. Using 4-*tert*-butylbenzophenone (**1k**), the reaction provided aminotetrazole **3k** and **3k'** in an almost 1:1 ratio. Similarly, a series of 4-halobenzophenone (**1l-1n**) also gave the corresponding products as mixtures of regioisomeric products in ratios of nearly 1:1 in good combined yields. Next investigation, derivatives of methoxybenzophenone (**1o-1p**) were examined as shown in entries 5-6. Both *meta*- and *para*-methoxybenzophenone afforded mixtures of aminotetrazoles in almost 1:1 ratios with excellent combined yields in both cases. The regioselectivity for the formation of the two isomeric products was clearly observed when both aryl substituents of ketone have great difference in electron density. For example, compound **1q**, having electronically neutral phenyl ring and strong electron-withdrawing 4-trifluoromethylbenzene as substituents of ketone (entry 7), provided a mixture of 5-aminotetrazoles **3q** and **3q'** with a ratio of 40:60 in very good combined yield. The regioselective conversion was achieved based on ring closure of the nitrogen atom on the more electron-rich aniline moiety (phenyl ring) while the minor product was obtained from the ring closure of nitrogen atom on the less electron-rich aniline unit (*para*-trifluoromethylbenzene). Furthermore, substrates having higher difference in electron density on both aromatic rings were examined in entries 8-10. To increase the difference in electron density on both aryl rings of ketone substrate, we then employed compound **1r** containing *para*-methoxybenzene and *para*-trifluoromethylbenzene as the ketone substituents (entry 8). In this case, the improvement in regioselectivity was observed to give a mixture of 5-aminotetrazoles **3r** and **3r'** with a 35:65 ratio in good combined yield. In comparing entries 6 and 9, the substrate with one more methoxy group (entry 9), 1,3-dimethoxybenzene, could

improve the regioselectivity providing a mixture of compounds **3s** and **3s'** with a 40:60 ratio in 91% combined yield. In addition, the result from entry 10 with 3,4,5-trimethoxybenzene as the substituent provided even better regioselectivity with a 28:72 ratio of the corresponding products **3t** and **3t'** in good combined yield. From all results, the regioselective conversion was achieved via cyclization of the nitrogen atom on the more electron rich aniline moiety while the minor product was obtained via cyclization of the nitrogen atom on the lower electron density aniline unit. These results also implied that when the electron densities on both aryl rings were obviously different, the migratory aptitude of aryl rings were distinct such that the corresponding products were obtained regioselectively. The reaction mechanism was proposed in Scheme 3.



Scheme 3. Proposed reaction mechanism.

The ketone substrate reacted with HN_3, which was generated in situ, to give nitrilium ion intermediate following one of the two possible N_2-extrusion/migration Pathways, **A** and **B**, depending on the migratory aptitude of R and R^1 groups. In Pathway **A**, the higher electron density aryl ring (R group) underwent the first aryl migration to give the nitrilium ion intermediate. Then, this intermediate reacted with the second equivalent of HN_3 to provide intermediate **I**. The reaction subsequently underwent another nitrogen extrusion/aryl migration of R^1 (lower electron density) to generate carbodiiminium ion intermediate **II.** According to experiments in the literature regarding rate of proton exchange, the NH exchange rate was very slow under strong acidic conditions.[10] Therefore, the proposed mechanism for the generation of carbodiiminium ion intermediate **V** via proton exchange of intermediate **II** could be ruled out. The proposed mechanism for the generation of major product was proposed in Pathway **A-1**. The intermediate **II** could react with the third equivalent of HN_3 and immediately cyclize to obtain the major product. An alternative route was the cyclization using N-6 atom of **III** to give the intermediate **VIII** as shown in Pathway **A-2**. However, Pathway **A-1** could give the more stable intermediate **IV** due to its higher aromatic character and being less strained compared to intermediate **VIII**. Another competitive mechanism is Pathway **B** which is the competing R^1 aryl ring migration resulting in the formation of minor product. In this pathway, the lower electron density (R^1) underwent aryl migration in the first step to obtain the nitrillium ion **IX** which further reacted with HN_3 to give carbodiimidium ion intermediate **V**. Next, this intermediate reacted with another HN_3 and directly cyclized to provide the aminotetrazole salt which could give the desired product as the minor product after work up.

The steric effect of *ortho* substituents on aryl ketone substrate was investigated. With bromo substituent **1u**, the reaction gave a mixture of the corresponding products **3u** and **3u'**

in 78% yield with a ratio of 64:36. Increasing the size of substituents, the reaction could significantly affect the regioselectivity of the corresponding products. Substrates **1v** containing *ortho*-methoxy substituent gave the desired products with high regioselectivity (**3v:3v'**; 79:21). Interestingly, the regioselectivity of this reaction was opposite to the reported method from which compound **3v** was obtained as the minor product.[6a] Having more steric hindrance in substrate **1w**, containing *ortho*-(4-^{t}Bu-phenyl) group gave a single product **3w** in 77% yield. These results indicated that the steric bulkiness of *ortho* substituent could significantly increase a migratory aptitude of the aryl ring to provide high regioselectivity for the formation of 5-aminotetrazole products. The results from entries 7-13 clearly showed that the regioselectivity of the reaction depended on the migratory aptitude of the aryl groups. Aryl ring with higher electron density and steric hindrance has lower migratory. Surprisingly, low regioselectivity was observed with the substrate having symmetrical 2,6-dimethoxyphenyl groups **1x** which offered the corresponding products in an almost 1:1 ratio (55:45) in excellent yield. The results from the reactions of alkylarylketones in entries 15-17 were strongly supportive of our proposed mechanism. In case of methylarylketone (**1y**), the reaction gave compound **3y** in only 25% yield while longer side chain, butylarylketone, provided a single regioisomer of compound **3z** in 77% yield. In case of compound **1ab** containing cyclohexyl group as the substituent, the reaction smoothly provided aminotetrazole **3ab** as a single isomer in 82% yield. The results from entries 15-17 demonstrated that the order of migratory aptitude as aryl ring> bulky alkyl group > less bulky alkyl group leading to the formation of a single regioisomeric product. These results further confirmed that proton exchange under strong acidic conditions could be ruled out as intermediate **V** was formed as only single regioisomeric products were obtained (Pathway **A-1**).

Furthermore, ketone substrates having dialkyl substituents were examined in entries 18-20. Unfortunately, 5-aminotetrazole products could not be generated; only the formation of tetrazoles was resulted in all cases. These results implied that the migratory aptitude of ketone substituents played an important role on the outcome of reactions. In case of ketone having alkyl substituent on both sides, the reaction readily underwent cyclization after the first alkyl migration and nucleophilic addition by HN_3 at the nitrilium ion intermediate to provide tetrazole products.

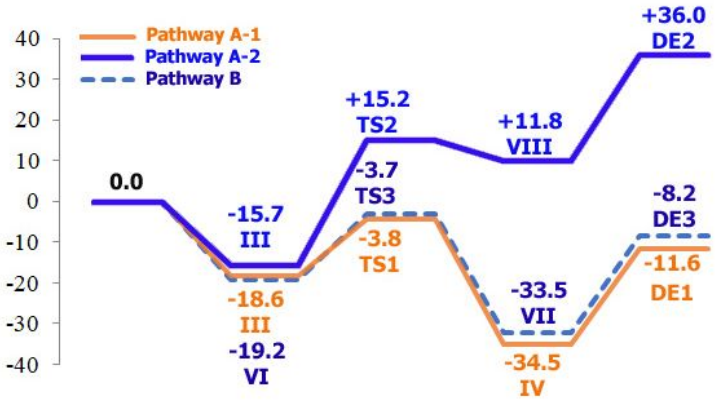


Figure 2. The potential energy diagram of the reaction of compound **1t** via Pathways A-1, A-2, and B calculated with MP2/6-311+G(2df,2p) on the optimized structures with M06-2X/6-311+G(2df,2p). Energies are in kcal/mol.

In this work, a computational study was also performed to assist in understanding the regioselectivity of the reaction. The molecular structure and the reaction mechanism to produce compound **1t** were studied as a representative case using density functional theory (DFT).[11] The reaction mechanism in Pathway **A-1** to produce compound **3t'** was studied as shown in Figure 2. The formation of intermediate **IV** was a strongly exothermic reaction with relative energy of -34.5 kcal/mol. This pathway led to the lowest activation energy (14.8 kcal/mol). The activation energy of Pathway **A-2** was highest (30.9 kcal/mol) among the

three pathways. Therefore, this was an unfavorable reaction pathway to form 5-aminotetrazole product. For the formation of compound **3t** (minor product, Pathway **B**), the total activation energy of the pathway was 15.4 kcal/mol. The activation energy for **TS3** was higher than **TS1** of 0.6 kcal/mol while the stability of the product **VII** is less stable than **IV** by 1.0 kcal/mol. Product **3t'** was predicted to be the major product while product **3t** was the minor product. In summary, the results from computational study of a model system using the reaction of compound **1t** illustrated that the activation energy of the reaction in Pathway **A-1** is lower than the reaction of Pathway **A-2** and **B**. Therefore, Pathway **A-1** became a more favorable pathway in term of both kinetic and thermodynamic properties resulting in the cyclization of nitrogen on electron-rich aniline unit to give the major product. The results from the computational study corroborated well to our experimental results. Therefore, we concluded that regioselectivity outcome of 5-aminotetrazoles depended on the difference in migratory aptitude of ketone substituents. This implied that the more highly differentiated electron density between the two aryl substituents would result in better regioselectivity in products as summarized in Pathway **A-1**.

■ CONCLUSIONS

We have developed a new method for the synthesis of 5-aminotetrazoles employing ketone precusors. This method involved N_2-extrusion/aryl migration of ketone compounds to generate carbodiimidium ion as the key intermediate, followed by cyclization with HN_3 to obtain 5-aminotetrazoles in good to excellent yields. The regioselectivity of this conversion was controlled by the migratory aptitude of ketone substituents. A good regioselectivity could be obtained when both substituents of ketone have a significant difference in migratory aptitude. This method has the advantages in the ease of access to starting materials from commercially available precursors, metal-free conditions and a broad range of substrate scope.

■ EXPERIMENTAL SECTION

General Procedure. The commercial grade chemicals were used without further purification, unless otherwise specified. All solvents used were purified by the solvent purification system. The oven-dried glassware (110 °C at least for 2 h) was used for all reactions. Crude reaction mixtures were concentrated under reduced pressure by removing organic solvent with the rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.06−0.2 mm; 70−230 mesh ASTM). Analytical thin layer chromatography (TLC) was performed with silica gel 60 F254 aluminum sheets. The nuclear magnetic resonance (NMR) spectra were recorded in deuterochloroform ($CDCl_3$), deuterated acetone (acetone-d_6) and deuterated dimethyl sulfoxide (DMSO-d_6, 2.50 ppm) with 300, 400 and 600 MHz spectrometers. Chemical shifts for ^1H and ^{13}C NMR spectra were reported in part per million (ppm, δ), relative to tetramethylsilane (TMS, 0.00 ppm) as the internal reference. Coupling constants (J) were reported in hertz (Hz). Infrared spectra were measured using an FT-IR spectrometer and were reported in cm^{-1}. High resolution mass spectra (HRMS) were obtained using time-of-flight (TOF).

General procedure for the synthesis of aminotetrazole: compound **1a** (506.1 mg, 2.7775 mmol, 1.0 equiv) was dissolved in dry DCM (7.4 mL/mmol) under argon. A solution was added $TMSN_3$ (1.10 mL, 8.3324 mmol, 3.0 equiv), followed by TfOH (730 μL, 8.3324 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 5 hr. After completion, the reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide crude product which was purified on silica gel (EtOAc/Hexane: 1:1) to yield *N,1-diphenyl-1H-tetrazol-5-amine* (**3a**) 617.5 mg. (94%, white solid); mp 163-164 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3200, 3052, 2922, 1605, 1571, 1496, 1317, 1089, 751 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.33 (s, 1H), 7.69-7.62 (m, 7H), 7.35-7.30 (m, 2H), 7.01 (t, 1H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.3, 139.8, 133.1, 130.0, 129.9, 128.8, 125.5, 122.1, 118.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{12}N_5$ 238.1087; found 238.1083.

1,3-Diphenylurea:[12] white solid; mp 237-239 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.64 (s, 2H), 7.44 (dd, 4H, J = 8.7, 1.2 Hz), 7.30-7.25 (m, 4H), 6.99-6.93 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.5, 139.6, 128.7, 121.7, 118.1.

N,1-dip-tolyl-1H-tetrazol-5-amine (**3b**): Yield 118.1 mg (88%, white solid); mp 207-208 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3180, 3021, 1603, 1562, 1508, 1389, 1231, 1079, 824, 808 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.41 (m, 6H), 7.16-7.13 (m, 2H), 6.29 (s, 1H), 2.48 (s, 3H), 2.31 (s. 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 151.8, 141.0, 135.6, 133.0, 131.1, 130.1, 129.8, 124.7, 118.2, 21.3, 20.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}N_5$ 266.1400; found 266.1401.

N,1-dio-tolyl-1H-tetrazol-5-amine (**3c**): Yield 90.5 mg (92%, pale yellow solid); mp 148-149 °C (3/7 EtOAc/hexane); IR (neat): υ_{max} 3154, 2985, 2911, 1600, 1564, 1493, 1465, 1086, 746 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.55-7.40 (m, 4H), 7.31 (d, 1H, J = 7.2 Hz), 7.22-7.06 (m, 3H), 2.16 (s, 3H), 2.14 (s. 3H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 154.2, 137.5, 135.3, 132.4, 132.0, 131.4, 130.7, 130.6, 127.6, 127.3, 126.3, 125.3, 124.7, 17.8, 17.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}N_5$ 266.1400; found 266.1394.

N,1-bis(4-fluorophenyl)-1H-tetrazol-5-amine (**3d**): Yield 110.8 mg (88%, pale yellow solid); mp 179-180 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3268, 3060, 1617, 1577, 1503, 1418, 1238, 1222, 1089, 822 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.80-7.66 (m, 4H), 7.48-7.40 (m, 2H), 7.14-7.06 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 164.1

(d, J_{CF} = 246 Hz), 160.7, 155.6 (d, J_{CF} = 296 Hz), 136.9 (d, J_{CF} = 2.3 Hz), 140.4 (d, J_{CF} = 2.4 Hz), 129.5 (d, J_{CF} = 9 Hz), 120.8 (d, J_{CF} = 8 Hz), 117.7 (d, J_{CF} = 24 Hz), 116.1 (d, J_{CF} = 22 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{10}F_2N_5$ 274.0899; found 274.0891.

N,1-bis(4-chlorophenyl)-1H-tetrazol-5-amine (**3e**): Yield 102.2 mg (≥83%, pale yellow solid); mp 194-195 °C (2/8 EtOAc/hexane); IR (neat): υ_{max} 3267, 3064, 1606, 1563, 1490, 1089, 802 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.73-7.65 (m, 6H), 7.38 (d, 2H, J = 8.4 Hz); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.7, 139.2, 135.3, 132.2, 130.4, 129.1, 128.3, 126.2, 120.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{10}Cl_2N_5$ (Cl-35) 306.0308; found 306.0297.

N,1-bis(4-bromophenyl)-1H-tetrazol-5-amine (**3f**): Yield 91.3 mg (84%, white solid); mp 175-176 °C (3/7 EtOAc/hexane); IR (neat): υ_{max} 3262, 3190, 3043, 1606, 1561, 1492, 1070, 824, 804 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 7.85 (dd, 2H, J = 8.4, 1.8 Hz), 7.62 (td, 4H, J = 8.7, 2.1 Hz), 7.49 (dd, 2H, J = 9.0, 2.1 Hz); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.2, 139.2, 133.0, 132.2, 131.6, 128.0, 123.6, 120.3, 113.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{10}Br_2N_5$ (Br-79) 393.9298; found 393.9304.

N,1-bis(2-methoxyphenyl)-1H-tetrazol-5-amine (**3g**): Yield 100.5 mg (97%, pale yellow solid); mp 99-100 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3353, 2943, 2843, 1612, 1574, 1506, 1464, 1249, 1024, 749 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.80 (d, 1H, J = 7.8 Hz), 7.64-7.53 (m, 2H), 7.34 (d, 1H, J = 8.4 Hz), 7.18 (t, 1H, J = 7.8 Hz), 7.07-6.93 (m, 3H), 3.89 (s, 3H), 3.80 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.7, 152.6, 148.9, 132.1, 128.1, 127.7, 123.6, 121.2, 121.1, 120.6, 119.4, 113.0, 111.0, 56.1, 55.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}N_5O_2$ 298.1299; found 298.1309.

N,1-bis(3-methoxyphenyl)-1H-tetrazol-5-amine (**3h**): Yield 83.4 mg (80%, white solid); mp 129-130 °C (2/8 EtOAc/hexane); IR (neat): υ_{max} 3078, 2997, 2835, 1608, 1575, 1490, 1158, 869, 794 cm^{-1}; ^1H NMR (300 MHz, Acetone-d_6) δ 8.48 (s, 1H), 7.56 (t, 1H, J = 8.1 Hz), 7.42 (d, 1H, J = 2.1 Hz), 7.26-7.16 (m, 5H), 6.61 (dt, 1H, J = 6.6, 2.4 Hz), 3.91 (s, 3H), 3.78 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, Acetone-d_6) δ 161.5, 161.2, 153.1, 141.8, 135.0, 131.7, 130.4, 118.5, 117.0, 112.0, 111.2, 108.5, 104.9, 56.0, 55.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}N_5O_2$ 298.1299; found 298.1293.

N,1-bis(4-methoxyphenyl)-1H-tetrazol-5-amine (**3i**): Yield 79.2 mg (87%, pale yellow solid); mp 137-138 °C (3/7 EtOAc/hexane); IR (neat): υ_{max} 3259, 3104, 2835, 1612, 1578, 1508,

1464, 1244, 1235, 1031, 837 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.57-7.52 (m, 4H), 7.17 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 9.0 Hz), 3.86 (s, 3H), 3.72 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 160.3, 154.6, 152.9, 133.0, 127.5, 125.6, 120.1, 115.0, 113.9, 55.6, 55.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}N_5O_2$ 298.1299; found 298.1298.

N,1-dicyclohexyl-1H-tetrazol-5-amine (**3j**): Yield 12.7 mg (12%, pale yellow solid); mp 182-183 °C (2/8 EtOAc/hexane); IR (neat): υ_{max} 3313, 3261, 2926, 2852, 1594, 1448, 1101, 894 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 6.50 (d, 1H, J = 7.4 Hz), 4.16 (tt, 1H, J = 11.5, 3.8 Hz), 1.95-1.58 (m, 11H), 1.39-1.12 (m, 10H); $^{13}C\{1H\}$ NMR (125 MHz, DMSO-d_6) δ 154.0, 53.7, 52.7, 32.4, 31.6, 25.2, 24.7, 24.64, 24.55; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{24}N_5$ 250.2026; found 250.2027.

1,5-dicyclohexyl-1H-tetrazole (**4j**): Yield 80.3 mg (80%, pale yellow solid); mp 171-172 °C (2/8 EtOAc/hexane); IR (neat): υ_{max} 2936, 1450, 1265, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.16-4.09 (m, 1H), 2.81-2.73 (m, 1H), 2.11-1.72 (m, 14H), 1.51-1.21 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 57.3, 33.4, 33.1, 31.4, 25.8, 25.4, 25.3, 24.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{23}N_4$ 235.1917; found 235.1917.

1-(4-tert-butylphenyl)-N-phenyl-1H-tetrazol-5-amine (**3k**)*, N-(4-tert-butylphenyl)-1-phenyl-1H-tetrazol-5-amine* (**3k'**): Yield 129.1 mg (91%, ratio 55:45, white solid); mp 154-155 °C (1/19 to 3/7 EtOAc/hexane); IR (neat): υ_{max} 3265, 3053, 2963, 1604, 1567, 1499, 1088, 837, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ .7.68-7.52 (m, 5H, 4.1H minor), 7.48-7.44 (m, 2H, 1.64H minor), 7.39-7.32 (m, 2H, 1.64H minor), 7.12-7.06 (m, 1H), 6.35 (s, 1H), 6.31 (s, 0.82H minor), 1.40 (s, 9H), 1.31 (s, 7.38H minor); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.2, 151.9, 151.6, 146.7, 138.1, 135.4, 132.8, 130.6, 130.4, 129.95, 129.4, 127.6, 126.2, 124.8, 124.5, 123.4, 118.2, 118.1, 35.1, 34.3, 31.4, 31.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}N_5$ 294.1713; found 294.1721.

1-(4-fluorophenyl)-N-phenyl-1H-tetrazol-5-amine (**3l**)*, N-(4-fluorophenyl)-1-phenyl-1H-tetrazol-5-amine* (**3l'**): Yield 41.5 mg (90%, ratio 48:52, light yellow solid); mp 180-181 °C (2/8 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 2924, 2854, 1618, 1572, 1509, 1499, 1224, 746 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.36 (br s, 1H), 9.29 (br s, 0.91H minor), 7.76-7.74 (m, 1.82H minor), 7.68-7.61 (m, 7H, 1.82H minor), 7.53-7.48 (m, 1.82H minor), 7.35-7.30 (m, 1.82H minor), 7.20-7.14 (m, 2H), 7.03-6.98 (m, 1.82H minor); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 162.7 (d, J_{CF} = 246 Hz), 157.5 (d, J_{CF} = 237 Hz), 152.5, 152.4, 139.7, 136.2,

133.0, 130.1, 129.9, 129.4, 128.8, 128.6 (d, J_{CF} = 9 Hz), 125.6, 122.1, 120.2 (d, J_{CF} = 8 Hz), 118.2, 116.8 (d, J_{CF} = 24 Hz), 115.3 (d, J_{CF} = 23 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{11}FN_5$ 256.0993; found 256.0995.

1-(4-chlorophenyl)-N-phenyl-1H-tetrazol-5-amine (**3m**): Yield 37.2 mg (47%, white solid); mp 165-166 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3253, 3054, 2921, 2851, 1610, 1571, 1534, 1496, 1092, 1013, 831, 737 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.72 (s, 4H), 7.61 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 7.8 Hz), 7.01 (t, 1H, J = 7.2 Hz); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.4, 139.7, 134.7, 131.8, 129.9, 128.8, 127.7, 122.1, 118.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{13}H_{10}ClN_5Na$ (Cl-35) 294.0517; found 294.0509.

N-(4-chlorophenyl)-1-phenyl-1H-tetrazol-5-amine (**3m'**): Yield 38.2 mg (48%, white solid); mp 195-196 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 2925, 1607, 1565, 1490, 1242, 1089, 804, 771, 691 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.68-7.66 (m, 7H), 7.38 (d, 2H, J = 7.2 Hz); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.1, 138.8, 132.9, 130.1, 129.9, 128.6, 125.7, 125.6, 119.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{13}H_{10}ClN_5Na$ (Cl-35) 294.0517; found 294.0516.

1-(4-bromophenyl)-N-phenyl-1H-tetrazol-5-amine (**3n**): Yield 41.5 mg (35%, white solid); mp 164-165 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3185, 3030, 2916, 1601, 1563, 1487, 1068, 834, 746 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.56 (s, 1H), 7.88-7.83 (m, 2H), 7.79-7.66 (m, 4H), 7.33 (t, 2H, J = 7.5 Hz), 7.03 (t, 1H, J = 7.2 Hz); $^{13}C\{1H\}$ NMR (75 MHz, acetone-d_6) δ 140.6, 134.0, 133.5, 129.7, 128.8, 124.5, 123.2, 118.96, 118.89; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{11}BrN_5$ (Br-79) 316.0192; found 316.0206.

N-(4-bromophenyl)-1-phenyl-1H-tetrazol-5-amine (**3n'**): Yield 57.3 mg (47%, white solid); mp 181-182 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3258, 3083, 1606, 1563, 1486, 1238, 1073, 823, 762, 686 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.66 (s, 1H), 7.70-7.63 (m, 7H), 7.51-7.46 (m, 2H); $^{13}C\{1H\}$ NMR (75 MHz, acetone-d_6) δ 140.2, 134.2, 132.6, 131.2, 130.9, 126.7, 120.9, 120.8, 115.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{11}BrN_5$ (Br-79) 316.0192; found 316.0206.

1-(4-methoxyphenyl)-N-phenyl-1H-tetrazol-5-amine (**3o**)*, N-(4-methoxyphenyl)-1-phenyl-1H-tetrazol-5-amine* (**3o'**): Yield 123.2 mg (94%, ratio 48:52, orange solid); mp 178-179 °C (2/8 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3079, 2836, 1603, 1570, 1511, 1497, 1236 cm^{-1}; ^1H

NMR (300 MHz, DMSO-d_6) δ 9.14 (s, 0.94H minor), 9.06 (s, 1H), 7.60-7.45 (m, 6H, 5.64H minor), 7.26 (t, 2H, J = 7.8 Hz), 7.13 (d, 1.88H, J = 8.7 Hz minor), 6.94 (t, 1H, J = 7.2 Hz), 6.86 (d, 1.88H, J = 9.0 Hz minor), 3.81 (s, 2.82H minor), 3.68 (s, 3H); ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ 160.9, 155.3, 153.2, 153.0, 140.4, 133.6, 133.4, 130.4, 129.2, 128.0, 126.03, 125.95, 122.4, 122.1, 120.9, 118.6, 115.5, 114.4, 56.1, 55.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}N_5O_1$ 268.1193; found 268.1194.

1-(3-methoxyphenyl)-N-phenyl-1H-tetrazol-5-amine (**3p**)*, N-(3-methoxyphenyl)-1-phenyl-1H-tetrazol-5-amine* (**3p'**): Yield 123.2 mg (94%, ratio 53:47, white solid); mp 157-158 °C (2/8 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3078, 2998, 1604, 1571, 1495, 1269 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.30 (s, 0.88H mimor), 9.27 (s, 1H), 7.67-7.61 (m, 5H), 7.56 (t, 1H, J = 8.1 Hz), 7.34 (t, 2H, J = 5.4 Hz), 7.29-7.17 (t, 1H, J = 7.2 Hz), 6.62-6.55 (m, 0.88H minor), 3.84 (s, 3H), 3.73 (s, 2.64H minor); ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 160.1, 159.7, 152.3, 152.2, 141.0, 139.8, 133.9, 133.0, 130.7, 130.1, 139.9, 129.6, 128.8, 125.6, 122.1, 118.4, 117.6, 116.0, 111.2, 110.6, 107.7, 104.1, 55.6, 55.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{14}H_{13}N_5ONa$ 290.1012; found 290.1018.

N-phenyl-1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-amine (**3q**): Yield 34.0 mg (34%, pale yellow solid); mp 155-156 °C (1/9 EtOAc/hexane); IR (neat): υ_{max} 3359, 2921, 2851, 1606, 1575, 1523, 1422, 1327, 1177, 1107, 1068, 846, 751 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.05 (d, 2H, J = 8.7 Hz), 7.95 (d, 2H, J = 8.4 Hz), 7.62 (d, 2H, J = 7.8 Hz), 7.34 (t, 2H, J = 7.8 Hz), 7.02 (t, 1H, J = 7.5 Hz); ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 152.4, 139.6, 136.5, 130.0 (q, J_{CF} = 32 Hz), 128.8, 127.1 (q, J_{CF} = 56 Hz), 126.4, 123.8 (q, J_{CF} = 272 Hz), 122.3, 118.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}F_3N_5$ 306.0961; found 306.0960.

1-phenyl-N-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-amine (**3q'**): Yield 49.5 mg (50%, pink solid); mp 184-185 °C (1/9 EtOAc/hexane); IR (neat): υ_{max} 3261, 2926, 1610, 1570, 1530, 1499, 1325, 1111, 1068, 839, 760, 687 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 7.84 (d, 2H, J = 8.7 Hz), 7.70-7.65 (m, 7H); ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 152.8, 143.4, 132.8, 130.2, 129.9, 126.0 (q, J_{CF} = 4 Hz), 125.5, 124.5 (q, J_{CF} = 269 Hz), 122.0 (q, J_{CF} = 32 Hz), 117.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}F_3N_5$ 306.0961; found 306.0962.

N-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-amine (**3r**): Yield 24.7 mg (26%, white solid); mp 176-177 °C (1/9 EtOAc/hexane); IR (neat): υ_{max} 3311, 2925, 2854,

1604, 1508, 1325, 1139, 1125, 1071, 1033, 1014, 845, 829 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.02 (d, 2H, J = 8.5 Hz), 7.92 (d, 2H, J = 8.4 Hz), 7.50-7.49 (m, 2H), 6.92-6.90 (m, 2H), 3.72 (s, 3H); $^{13}C\{1H\}$ NMR (150 MHz, DMSO-d_6) δ 155.0, 152.8, 136.5, 132.7, 129.9 (q, J_{CF} = 32 Hz), 127.1 (q, J_{CF} = 4 Hz), 126.2, 123.8 (q, J_{CF} = 271 Hz), 120.6, 114.1, 55.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}F_3N_5O$ 336.1067; found 336.1070.

1-(4-methoxyphenyl)-N-(4-(trifluoromethyl)phenyl)-1H-tetrazol-5-amine (**3r'**): Yield 46.2 mg (49%, pale yellow solid); mp 174-175 °C (1/9 EtOAc/hexane); IR (neat): υ_{max} 3260, 2927, 2854, 1609, 1571, 1514. 1323, 1252, 1112, 1068, 834 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 9.63 (s, 1H), 7.80 (d, 2H, J = 8.5 Hz), 7.66 (d, 2H, J = 8.7 Hz), 7.55 (d, 2H, J = 8.9 Hz), 7.16 (d, 2H, J = 8.9 Hz), 3.84 (s, 3H); $^{13}C\{1H\}$ NMR (125 MHz, DMSO-d_6) δ 160.7, 152.2, 143.6, 127.7, 126.2 (q, J_{CF} = 4 Hz), 125.4, 124.6 (q, J_{CF} = 270 Hz), 122.2 (q, J_{CF} = 32 Hz), 118.0, 115.2, 55.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}F_3N_5O$ 336.1067; found 336.1064.

N-(3,5-dimethoxyphenyl)-1-phenyl-1H-tetrazol-5-amine (**3s**): Yield 33.9 mg (30%, white solid); mp 134-135 °C (2/8 EtOAc/hexane); IR (neat): υ_{max} 3278, 2938, 1608, 1572, 1153, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.69-7.63 (m, 5H), 6.90 (d, 2H, J = 2.0 Hz), 6.16 (t, 1H, J = 2.0 Hz), 3.71 (s, 6H); $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6) δ 160.6, 152.1, 141.4, 133.0, 130.1, 129.9, 125.7, 96.6, 94.2, 55.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}N_5O_2$ 298.1298; found 298.1296.

1-(3,5-dimethoxyphenyl)-N-phenyl-1H-tetrazol-5-amine (**3s'**): Yield 50.8 mg (45%, white solid); mp 149-150 °C (2/8 EtOAc/hexane); IR (neat): υ_{max} 3259, 2938, 1570, 1158, 749 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 7.65 (d, 2H, J = 8.0 Hz), 7.32 (t, 2H, J = 7.6 Hz), 7.01 (t, 1H, J = 7.6 Hz), 6.84 (d, 2H, J = 2.0 Hz), 6.74 (t, 1H, J = 2.4 Hz), 3.82 (s, 6H); $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6) δ 161.1, 152.2, 139.8, 134.4, 128.8, 122.1, 118.4, 104.0, 102.0, 55.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}N_5O_2$ 298.1298; found 298.1296.

1-phenyl-N-(3,4,5-trimethoxyphenyl)-1H-tetrazol-5-amine (**3t**): Yield 31.5 mg (25%, white solid); mp 185-186 °C (3/7 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3270, 2924, 2850, 1608, 1570, 1453, 1226, 1128, 1002, 693 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.66-7.62 (m, 5H), 7.02 (s, 2H,), 3.74 (s, 6H), 3.61 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz,

DMSO-d_6) δ 153.2, 152.7, 136.1, 133.2, 133.0, 130.6, 130.4, 126.0, 96.8, 60.6, 56.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{16}H_{17}N_5O_3Na$ 350.1224; found 350.1228.

N-phenyl-1-(3,4,5-trimethoxyphenyl)-1H-tetrazol-5-amine (**3t'**): Yield 82.1 mg (66%, white solid); mp 172-173 °C (3/7 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3316, 2926, 2854, 1600, 1571, 1499, 1232, 1126, 1087, 751 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.66 (d, 2H, J = 7.8 Hz), 7.32 (t, 2H, J = 7.8 Hz), 7.03-6.99 (m, 3H), 3.82 (s, 6H), 3.76 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.6, 152.5, 139.8, 138.6, 128.8, 128.3, 122.2, 118.5, 104.1, 60.2, 56.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}N_5O_3$ 328.1404; found 328.1401.

1-(2-bromophenyl)-N-phenyl-1H-tetrazol-5-amine (**3u**): Yield 47.8 mg (50%, pale yellow solid); mp 157-158 °C (1/9 EtOAc/hexane); IR (neat): υ_{max} 3169, 3039, 2997, 1615, 1575, 1530, 1486, 1083, 748 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.36 (s, 1H), 7.96 (d, 1H, J = 7.2 Hz), 7.79 (d, 1H, J = 7.5 Hz), 7.70-7.61 (m, 4H), 7.33 (t, 2H, J = 7.2 Hz), 7.01 (t, 1H, J = 7.2 Hz); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.8, 139.6, 133.7, 133.0, 131.9, 130.6, 129.3, 128.8, 122.2, 121.8, 118.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{11}BrN_5$ (Br-79) 316.0192; found 316.0195.

N-(2-bromophenyl)-1-phenyl-1H-tetrazol-5-amine (**3u'**): Yield 26.7 mg (28%, yellow solid); mp 137-138 °C (1/9 EtOAc/hexane); IR (neat): υ_{max} 3368, 3065, 2921, 1595, 1562, 1522, 1448, 1314, 1089, 1024, 748 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.73-7.58 (m, 7H), 7.36 (td, 1H, J = 7.5, 1.2 Hz), 7.11 (td, 1H, J = 8.1, 1.5 Hz); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.8, 137.7, 133.2, 133.0, 129.9, 129.8, 128.6, 126.3, 124.7, 124.5, 117.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{11}BrN_5$ (Br-79) 316.0192; found 316.0196.

1-(2-methoxyphenyl)-N-phenyl-1H-tetrazol-5-amine (**3v**): Yield 79.4 mg (54%, reddish solid); mp 121-122 °C (2/8 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3396, 3058, 2943, 1610, 1572, 1489, 1247, 1106, 1022, 745 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.67-7.61 (m, 3H), 7.54 (dd, 1H, J = 7.8, 1.5 Hz), 7.34-7.29 (m, 3H), 7.17 (td, 1H, J = 7.5, 0,9 Hz), 6.99 (t, 1H, J = 7.2 Hz), 3.79 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 154.6, 153.0, 139.8, 132.4, 128.9, 128.8, 122.0, 120.98, 120.89, 118.2, 113.2, 56.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}N_5O$ 268.1193; found 268.1202.

N-(2-methoxyphenyl)-1-phenyl-1H-tetrazol-5-amine (**3v'**): Yield 20.9 mg (14%, brown solid); mp 130-131 °C (2/8 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3251, 3087, 2840, 1612, 1573, 1499, 1280, 1020, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.75 (dd, 1H, J = 8.0, 1.6 Hz), 7.68-7.56 (m, 5H), 7.08-6.94 (m, 3H), 3.74 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.4, 149.6, 133.2, 129.9, 129.8, 128.0, 124.5, 124.0, 120.6, 120.2, 111.3, 55.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{14}N_5O$ 268.1193; found 268.1196.

1-(4'-(tert-butyl)-[1,1'-biphenyl]-2-yl)-N-phenyl-1H-tetrazol-5-amine (**3w**): Yield 70.9 mg (77%, pale yellow solid); mp 167-168 °C (1/9 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3240, 3038, 2963, 2866, 1602, 1572, 1486, 1271, 1088, 742 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.99 (s, 1H), 7.77-7.71 (m, 1H), 7.69-7.62 (m, 3H), 7.29-7.16 (m, 6H), 6.97-6.89 (m, 3H), 1.14 (s, 9H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 152.7, 150.0, 139.4, 138.98, 134.0, 131.2, 131.1, 130.3, 128.8, 128.5, 128.4, 127.7, 125.1, 121.8, 118.0, 34.1, 30.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{24}N_5$ 370.2026; found 370.2028.

1-(2,6-dimethoxyphenyl)-N-phenyl-1H-tetrazol-5-amine and N-(2,6-dimethoxyphenyl)-1-phenyl-1H-tetrazol-5-amine (**3x**): Yield 68.6 mg (≥99%, white solid); mp 248-249 °C (3/7 EtOAc/hexane); IR (neat): υ_{max} 3258, 1604, 1575, 1489, 1265, 1114, 1024, 777, 755 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.48 (s, 1H), 7.66 (d, 2H, J = 8.1 Hz), 7.59 (t, 1H, J = 8.4 Hz), 7.46-7.42 (m, 5H), 7.31 (t, 2H, J = 7.5 Hz), 7.07 (t, 1H, J = 8.4 Hz), 6.98 (t, 1H, J = 7.2 Hz), 6.91 (d, 2H, J = 8.4 Hz), 6.55 (d, 2H, J = 8.4 Hz), 3.76 (s, 6H), 3.67 (s, 6H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 156.4, 155.1, 154.0, 153.3, 139.8, 133.4, 132.7, 129.1, 128.7, 127.0, 124.2, 121.8, 118.0, 115.6, 109.2, 104.9, 104.2, 56.2, 55.7; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{15}N_5O_2Na$ 320.1118; found 320.1116.

1-(4-methoxyphenyl)-5-methyl-1H-tetrazole (**4y**): Yield 98.1 mg (74%, white solid); mp 91-92 °C (1/1 EtOAc/hexane) IR (neat): υ_{max} 2924, 2851, 1607, 1523, 1509, 1449, 1273, 1254, 1021, 830 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.60-7.54 (m, 2H), 7.21-7.16 (m, 2H), 3.92 (s, 3H), 2.55 (s, 3H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 161.7, 152.8, 127.8, 127.2, 115.6, 56.1, 9.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_9H_{11}N_4O$ 191.0927; found 191.0920.

1-(4-methoxyphenyl)-N-methyl-1H-tetrazol-5-amine (**3y**): Yield 35.7 mg (25%, white solid); mp 145-146 °C (1/1 EtOAc/hexane); IR (neat): υ_{max} 3333, 2923, 2853, 1609, 1518, 1463, 1247, 1017, 835 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.48-7.43 (m, 2H), 7.16-7.11 (m, 2H), 6.71 (d, 1H, J = 4.8 Hz), 3.83 (s, 3H), 2.85 (d, 3H, J = 4.8 Hz); $^{13}C\{1H\}$ NMR (75

MHz, DMSO-d_6) δ 159.9, 155.8, 126.5, 125.8, 115.0, 55.6, 30.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_9H_{12}N_5O$ 206.1036; found 206.1041.

N-butyl-1-(4-methoxyphenyl)-1H-tetrazol-5-amine (**3z**): Yield 82.6 mg (77%, white solid); mp 113-114 °C (2/8 EtOAc/hexane); IR (neat): υ_{max} 3270, 2937, 1605, 1519, 1256, 836, 735 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.47-7.42 (m, 2H), 7.17-7.12 (m, 2H), 6.79 (t, 1H, J = 5.7 Hz), 3.84 (s, 3H), 3.25 (q, 2H, J = 6.9 Hz), 1.31 (quint, 2H, J = 7.2 Hz), 1.30-1.24 (m, 2H), 0.88 (t, 3H, J = 7.2 Hz); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 159.9, 155.3, 126.5, 125.9, 115.0, 55.6, 43.3, 30.8, 19.4, 13.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{18}N_5O$ 248.1506; found 248.1502.

N-cyclohexyl-1-(4-methoxyphenyl)-1H-tetrazol-5-amine (**3ab**): Yield 93.5 mg (82%, white solid); mp 158-159 °C (2/8 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 3264, 2922, 2854, 1595, 1577, 1516, 1450, 1251, 1090, 838 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.43 (d, 2H, J = 8.7 Hz), 7.13 (d, 2H, J = 8.7 Hz), 6.59 (d, 1H, J = 7.5 Hz), 3.83 (s, 3H), 3.48 (s, 1H), 1.90 (s, 2H), 1.71 (s, 2H), 1.6-1.56 (m, 1H), 1.35-1.20 (m, 4H), 1.09-1.06 (m, 1H); $^{13}C\{1H\}$ NMR (75 MHz, DMSO-d_6) δ 159.8, 154.6, 126.6, 126.0, 114.9, 55.6, 53.2, 32.2, 25.2, 24.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{20}N_5O$ 274.1662; found 274.1660.

5-Methyl-6,7,8,9-tetrahydro-5H-tetrazolo[1,5-a]azepine (**4ac**): Yield 97.7 mg (64%, colorless oil); (3/7 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 2937, 1450, 1428, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85-4.75 (m, 1H), 3.15-2.99 (m, 2H), 2.08-1.66 (m, 6H), 1.61 (d, 3H, J = 7.0 Hz); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.6, 55.9, 33.5, 25.9, 24.5, 24.0, 18.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_7H_{13}N_4$ 153.1135; found 153.1133.

5-Isopropyl-8-methyl-6,7,8,9-tetrahydro-5H-tetrazolo[1,5-a]azepine (**4ad**): Yield 87.8 mg (59%, colorless oil) (3/7 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 2969, 1523, 1403, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42-4.35 (m, 1H), 3.10 (d, 2H, J = 4.5 Hz), 2.52-2.42 (m, 1H), 2.17-2.11 (m, 2H), 2.06-1.84 (m, 2H), 1.70-1.60 (m, 1H), 1.10 (d, 3H, J = 6.6 Hz), 0.89 (d, 3H, J = 6.9 Hz), 0.83 (d, 3H, J = 6.6 Hz); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.8, 65.4, 31.2, 29.8, 28.5, 28.2, 23.5, 19.6, 18.5, 18.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{19}N_4$ 195.1604; found 195.1602.

*1-(sec-Butyl)-5-methyl-1H-tetrazole (***4ae**): Yield 117.7 mg (69%, colorless oil) (3/7 to 1/1 EtOAc/hexane); IR (neat): υ_{max} 2969, 1523, 1403, 1384, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38-4.26 (m, 1H), 2.56 (s, 3H), 2.14-1.78 (m, 2H), 1.59 (d, 3H, J = 6.9 Hz), 0.84

(t, 3H, J = 7.5 Hz); $^{13}C\{1H\}$ NMR (75 MHz, $CDCl_3$) δ 150.8, 56.2, 29.4, 20.4, 10.3, 8.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_6H_{13}N_4$ 141.1135; found 141.1133.

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■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of all prepared products. This material is available free of charge via the Internet at http://pubs.acs.org/.

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