Note

Sequential Pd(0)/Fe(III) catalyzed azide-Isocyanide Coupling/ Cyclization Reaction: One-pot synthesis of Aminotetrazoles

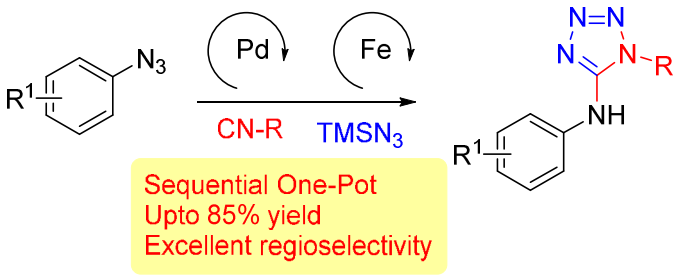
RAMDAS S. PATHARE, Arshad J Ansari, Sarika Verma, Anand Maurya, Antim K Maurya, Vijai K Agnihotri, Ashoke Sharon, Ram T. Pardasani, and Devesh M Sawant

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01261 • Publication Date (Web): 24 Jul 2018

Sequential Pd(0)/Fe(III) catalyzed azide-Isocyanide Coupling/Cyclization Reaction: One-pot synthesis of Aminotetrazoles

Ramdas S. Pathare,[a] Arshad J. Ansari,[a] Sarika Verma,[b] Anand Maurya,[a] Antim K. Maurya,[c] Vijai K. Agnihotri,[c] Ashoke Sharon,[b] Ram. T. Pardasani[a] and Devesh M. Sawant*[a]

[a] School of Chemical Sciences and Pharmacy, Central University of Rajasthan, NH-8, Bandarsindri, Ajmer-305817, Rajasthan, India, email: dms@curaj.ac.in
[b] Department of Chemistry, Birla Institute of Technology, Mesra, Ranchi, Jharkhand-835215
[c] Natural Product Chemistry and Process Development division, CSIR-Institute of Himalayan Bioresource Technology, Palampur, Himachal Pradesh -176061. India



Abstract

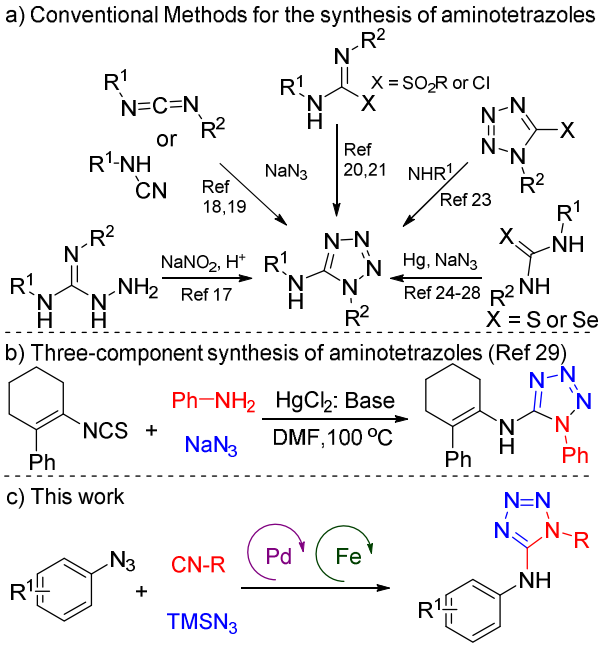
A rapid and efficient synthesis of aminotetrazole from aryl azides, isocyanides and $TMSN_3$ is developed. The reaction is promoted by sequential Pd(0)/Fe(III) catalysis. The reaction sequence utilizes the Pd-catalyzed azide-isocyanide denitrogenative coupling reaction to generate unsymmetric carbodiimide in situ, which reacts with $TMSN_3$ in the presence of $FeCl_3$ in a single pot. The methodology has distinct advantages over traditional synthetic approaches where toxic Hg and Pb salts are employed at stoichiometric scale.

Aminotetrazoles are an interesting class of five-membered nitrogen-rich aromatic heterocycles[1] with a wide range of applications such as non-classical bioisosters for the carboxylic acid,[2] cis-amide surrogate,[3] antifoggants in photographic materials,[4] plasma-polymer films in biomedical applications,[5] propellants[6] and explosives[7] in materials science, and ligand in coordination chemistry.[8] Interestingly, aminotetrazoles exhibits anti-HIV[9] and antiallergic activity,[10] and inhibits crucial protein drug targets such as glutamate receptor,[11] P_2X_7 receptors,[12] peptidyl endothelin converting enzyme (ECE),[13] fatty acid amide hydrolase (FAAH),[14] mitochondrial thymidine kinase (TK 2)[15] and hyaluronidase.[16]

Traditionally, aminotetrazoles were synthesized by diazotization of aminoguanidines,[17] azidation of cyanamides,[18] carbodiimides,[19] aminoimino-methanesulfonic acids[20] (X = SO_3R) and α–chloroformamidines[21] (X = Cl), and the reaction of amines with cyanogen azides[22] or 5-chloro- and 5-sulfonyl-tetrazoles[23] (Scheme 1a). During the last couple of decades, a two-step synthesis

of aminotetrazole is reported based on the in-situ generation of carbodiimide by either desulfurization of thiourea using mercury,[24] lead,[17a] Copper,[25] iodine[26] or IBX[27] or deselenylation of selenylurea by hypervalent iodine reagent[28] followed by azidation (Scheme 1a). Recently, Ponnuswamy and coworkers developed a three-component assembly of aminotetrazoles from isothiocyanides, amines and sodium azides in the presence of toxic mercury salts (Scheme 1b).[29] Despite their utility, these methodologies possess serious drawbacks such as use of expensive and toxic reagents (mercury, lead and iodine etc.), harsher reaction conditions, longer reaction time and sensitivity towards moisture. In addition, these synthetic strategies are either multistep linear processes or employ complex precursors[30] generated in a multistep fashion. Therefore, the development of rapid, efficient and sustainable synthetic methodologies from easily available starting materials in one-pot promoted by catalysts instead of toxic reagents at stoichiometric scale remains highly desirable.

Combining two transition metals for catalyzing new and valuable reactions has recently emerged as a powerful strategy in the field of organic synthesis. The presence of second transition metal expands the scope of synthetic transformation that wouldn't have been achieved with either of the catalysts alone. Had the combination of two metals been allowed in one-pot, additional purification of intermediates could have been avoided leading to minimization of waste. However, development of such processes is not a straightforward affair owing to redox incompatibility issues among various transition metals. In such cases, however sequential catalysis, an addition of catalysts in a stepwise manner, is employed as a strategy to exploit the synthetic potential of both metals.

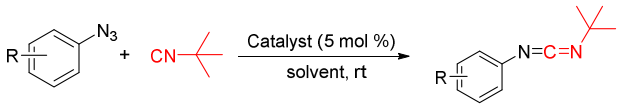


Scheme 1: Various strategies for the synthesis of aminotetrazoles

Based on our previous report on Pd-catalyzed nitrene transfer on isocyanide[31] and one pot catalyses,[32] we report herein development of three-component reaction catalyzed by sequential Pd(0)/Fe(III) catalytic system to generate aminotetrazole (Scheme 1c). Our methodology is based on Pd(0)-catalyzed azide-isocyanide denitrogenative coupling reaction to generate carbodiimide[33] *in-situ* and subsequent Fe(III)-catalyzed cyclization with TMS-N_3. The use of $FeCl_3$ allowed rapid and sustainable generation of aminotetrazoles in one-pot with excellent regioselectivity.

To achieve our goal, we embarked the investigation by optimizing the azide-isocyanide denitrogenative coupling reaction for the synthesis of carbodiimide **3** (Table 1). A mixture of arylazide **1a** and isocyanide **2a** were reacted with a catalytic amount of $Pd(PPh_3)_4$ as a catalyst in toluene at rt to furnish carbodiimide **3a** in 90 % yield (entry 6). The reaction was completed in 0.5 h. Screening with other Pd-sources and solvents for azide-isocyanide denitrogentive coupling reaction turned out to be inferior with the optimized reaction. Among various Pd-sources tried, $Pd(PPh_3)_4$ produced the best yields and the reaction failed to initiate in the absence of a catalyst.

Table 1. Optimization of reaction conditions for azide-isocyanide denitrogentive coupling reaction[a]



1a **2a** **3a**

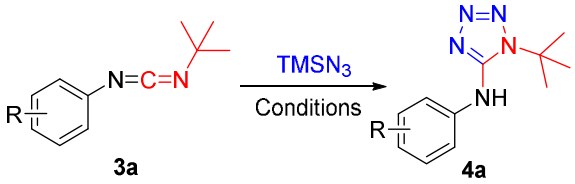
Sr. No.	Catalyst (5 mol %)	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	THF	25
2	$Pd(OAc)_2$	toluene	57
3	$Pd_2(dba)_3$	toluene	70
4	-	toluene	0
5	$Pd(PPh_3)_2Cl_2$	toluene	75
6	**$Pd(PPh_3)_4$**	**toluene**	**90**
7	$Pd(PPh_3)_4$	1,4-dioxane	45
8	$Pd(PPh_3)_4$	1,2-DCE	30

[a] Reaction conditions: all reactions (0.3 mmol scale) were performed using 1:1.2 ratio of **1a**:**2a**, 5 mol % $Pd(PPh_3)_4$, 0.5 mL of toluene, 0.5 h. [b] Isolated yield; [c] Starting material was recovered.

Then, we shifted our attention to the reaction of carbodiimide **3a** and $TMSN_3$ (Table 2). Pd-sources failed to drive this reaction. Pleasingly, screening of other metal sources such as Cu and Fe and solvents has improved the overall conversion. Of these, $FeCl_3$ furnished excellent yields of title compound **4a** in toluene at 100 ^oC. With the successes of finding a common solvent, we next directed our efforts to design a relay protocol, where both Palladium and iron catalysts

present at outset. Regrettably, we failed to develop the relay protocol and the reaction didn't initiate due to redox incompatibilities of these metals. Thus, a sequential protocol is developed, where **1a** and **2a**

Table 2: Optimization of reaction conditions for cyclization[a]



3a **4a**

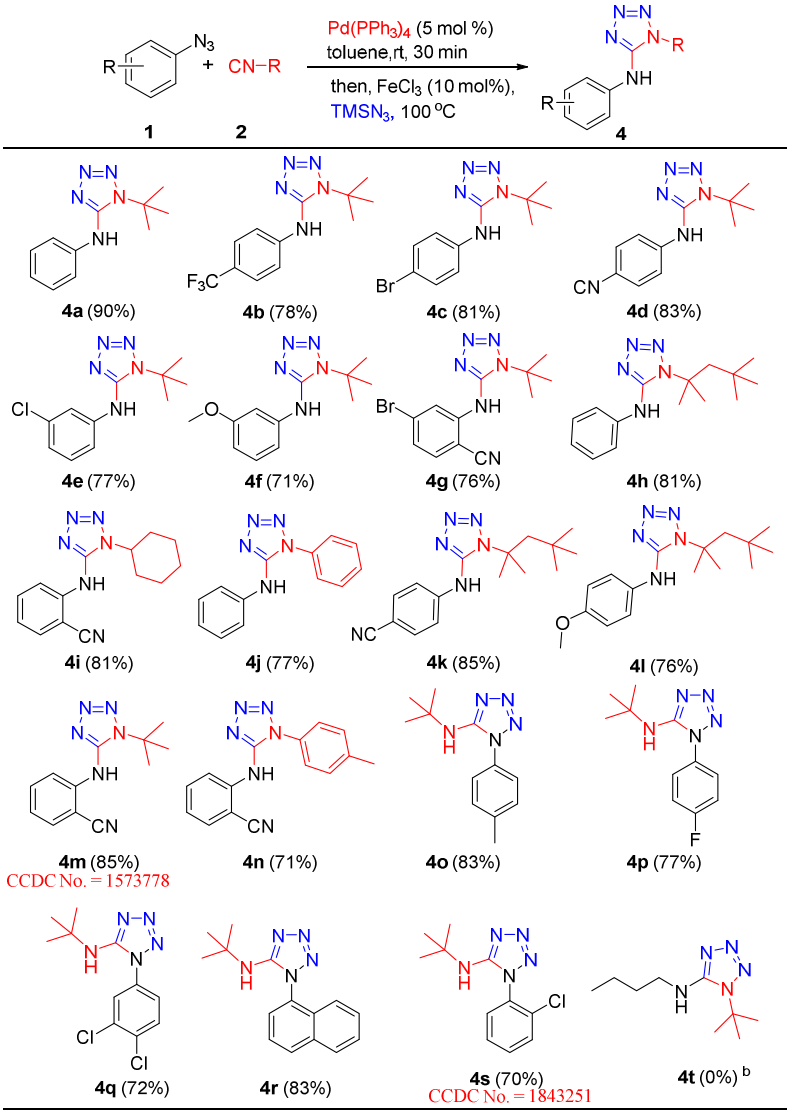
Sr. No	Catalyst (10 mol %)	Solvent	Time (h)	Temp. (^{o} C)	Yield[b] (%)
1	$Pd(PPh_3)_4$	Toluene	8	100	15
2	$ZnCl_2$	Toluene	12	100	15[c]
3	CuI	DMF	5	100	43
4	$FeCl_3$	1,4-dioxane	5	100	15
5	$FeCl_3$	Ethanol	3	85	70
6	**$FeCl_3$**	**Toluene**	**2**	**100**	**90**
7	$FeCl_3$	Toluene	8	rt	37
8	$FeCl_3$	Toluene	4	110	50
9	$FeCl_3$	Toluene	5	130	57
10	-	Toluene	8	100	Trace[c]

[a)] Reaction conditions: all reactions (0.3 mmol scale) were performed using **3a,** 1.5 equiv $TMSN_3$, 10 mol% $FeCl_3$, 100 ^{o}C, 1-2 h. followed by aqueous workup. [b] Isolated yields after chromatography; [c] Starting material was recovered.

were first reacted in presence of $Pd(PPh_3)_4$ with toluene as solvent at rt for 0.5 h, then TMS-N_3 and $FeCl_3$ were added and the reaction was refluxed to 100 ^{o}C to furnish the 5-amino tetrazole **4a** in 90% isolated yield. With optimal reaction conditions for the transformation of arylazides **1** to tetrazoles **4** in hand, we explored the generality of this reaction. As shown in scheme 2, a broad range of differently substituted aryl azides, bearing both electron donating and electron withdrawing substituents reacted efficiently with a range of isocyanides **2** and $TMSN_3$ to access the corresponding 5-amino-1*H*-tetrazoles **4** (Scheme 2). Substituents at all three positions (*ortho*-, *meta*- and *para*-) of aryl azides were well tolerated with no detrimental steric effect observed for the *ortho*-substitutions. Various alkyl-, cycloalkyl-, and aryl-substituted isocyanides reacted well under the optimized reaction conditions to generate 5-amino-1*H*-tetrazoles in good to excellent yields as shown in scheme 2. However, aryl isocyanides bearing electron-donating substituents and aliphatic azides failed to react under standard condition. Pleasingly, the bimetallic sequential reaction exhibited excellent and unique regioselectivity, which is

unambiguously confirmed by single crystal X-ray crystallographic studies. Interestingly, the regiochemical outcome was reversed for **4o-4s**.[34]

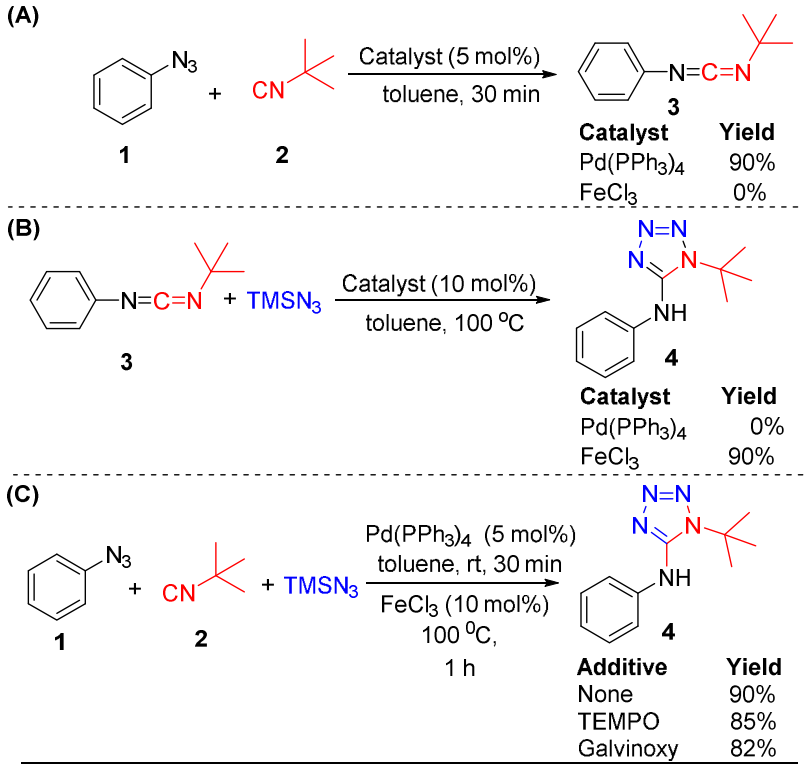
Scheme 2: Substrate scope for the synthesis of **4**[a].



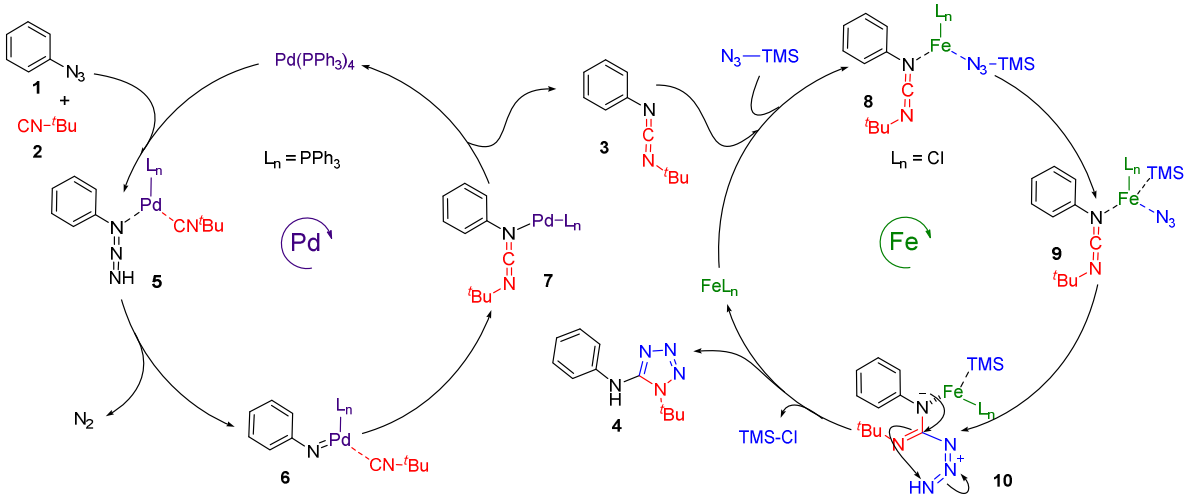
[a]Reaction conditions: All reactions (0.3 mmol scale) were performed using 1:1.2 ratio of **1a:2a**, 5 mol% $Pd(PPh_3)_4$, 0.5 mL of toluene, 0.5 h, rt; after completion of reaction, addition of 1.5 equiv $TMSN_3$, 10 mol% $FeCl_3$, 100 °C, 1-2 h followed by aqueous workup, isolated yields after chromatography. [b]Starting material recovered.

In order to gain insight into the reaction mechanism, control experiments were carried out as depicted in scheme 3. Azide-isocyanide denitrogenative coupling was a Pd-dependent process (Scheme 3A), whereas azide-carbodiimide cyclization was promoted by $FeCl_3$ (Scheme 3B). Radical scavengers did not alter the reaction pathway suggesting the involvement of a non-radical pathway (Scheme 3C).

Scheme 3: Control Experiments



On the basis of experimental findings and literature precedence,[25,31,33] the plausible mechanism was proposed as shown in scheme 4. The reaction begins with the coordination of $Pd(PPh_3)_4$ with azidobenzene **1a** and isocyanide **2** to generate **5**, which on extrusion of dinitrogen gives nitrene **6**. This is followed by intramolecular transfer of nitrene in a concerted manner[31] to furnish carbodiimide **3**. Upon entering the Fe-cycle, carbodiimide **3** first coordinates with iron metal along with azide to produce complex **9**. Azide nucleophile then attacks carbodiimide **3** to generate guanidyl intermediate **10**, which undergoes electrocyclization to furnish **4**.



Scheme 4: Plausible reaction mechanism

In conclusion, we have developed a rapid, efficient and atom-economical strategy for the synthesis of tetrazole derivatives by employing Pd and Fe as a dual catalyst system. Robust nature of each catalytic cycle of transition metals allowed development of the sequential one-pot protocol, which is evident by the failure of reaction in the absence of either of the catalyst. The reaction involves the formation of three new chemical bonds. The salient features of the methodology are shorter reaction times, broad substrate scope, milder reaction condition and use of cheaper iron salts. The method underscores applicability of Pd(0)/Fe(III) promoted sequential catalysis as an alternative for the synthesis of aminotetrazole form toxic Hg and Pb salts. The detailed study of the regiochemical outcome of bimetallic sequential catalysis is under progress.

Experimental Section

General Information: All the reactions were carried out under Ar atmosphere using standard Schlenk techniques. DMF was purchased from Spectrochem. Isocyanides were purchased from Sigma-Aldrich. All other reagents were purchased from Aldrich or Spectrochem used as such without purification. Analytical TLC was performed using 2.5 x 5cm plated coated with a 0.25mm thickness of silica gel (60F-254 Merck) and visualization was accomplished with UV light or I_2/ $KMnO_4$ staining. ^1H and ^{13}C NMR spectra were obtained from Bruker's Ascend 500MHz spectrophotometer operating at 500.3 MHz for ^1H and 125.8 MHz for ^{13}C experiments. The chemical shifts are reported in ppm scale with respect to $CDCl_3$ (7.269ppm) for ^1H and (77.00ppm) for ^{13}C NMR as an internal standard. The abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, br.s = broad singlet & br = broad signal. High-resolution mass spectra (HRMS) were taken in the ESI positive ion mode.

General Procedure for the synthesis of 1:

The compound **1** was synthesized using the procedure reported in the literature.[35] the intermediates **1** were obtained and confirmed by recording their ^1H NMR, which matched peak by peak with the reported ^1H NMR data.

CAUTION: *It is known that azides are potential explosives and must be therefore handled with care and stored at low temperature. It is also recommended to prepare azides at a maximum of 10 mmol scales to avoid risks.*

General procedure for the synthesis of 4:

A 10 mL schlenk tube equipped with a stir-bar was charged with azido benzene (0.05 g, 0.42 mmol), *tert*-butyl isocyanide (0.041 g, 0.50 mmol) in toluene (0.5 mL) as a solvent. The reaction tube was purged with argon. Then after 5-10 min. $Pd(PPh_3)_4$ (0.004 g, 0.021 mmol) was added to the reaction mixture followed by argon purging. The mixture was stirred at room temperature for 30 min. under an inert atmosphere. After completion of the reaction, $TMSN_3$ (0.05 g, 0.84 mmol) and iron chloride (0.007 g, 0.042 mmol) was added and stirred it at 100 ^oC for 1 h. After completion of the reaction, the reaction mixture was passed through celite bed and washed with EtOAc. The reaction mixture was diluted with EtOAc, which was washed with water and brine

successively, dried over anhydrous sodium sulphate, filtered, and concentrated in vacuo. Purification by silica gel (100-200 mesh) chromatography (EtOAc: Hexane) to yield the desired product 4.

Experimental procedure for the radical trap experiment:

A 10 mL schlenk tube equipped with a stir-bar was charged with azido benzene (0.05 g, 0.42 mmol), *tert*-butyl isocyanide (0.041 g, 0.50 mmol) in toluene (0.5 mL) as a solvent. The reaction tube was purged with argon. Then after 5-10 min. $Pd(PPh_3)_4$ (0.004 g, 0.021 mmol) was added to the reaction mixture followed by argon purging. The mixture was stirred at room temperature for 30 min. under an inert atmosphere. After completion of the reaction, trimethylsilylazide (0.05 g, 0.84 mmol), iron chloride (0.007 g, 0.042 mmol) and additives were added and stirred it at 100 ^oC for 1 h. After completion of the reaction, the reaction mixture was passed through celite bed and washed with EtOAc. The reaction mixture was diluted with EtOAc, which was washed with water and brine successively, dried over anhydrous sodium sulphate, filtered, and concentrated in vacuo. Purification by silica gel (100-200 mesh) chromatography (EtOAc: Hexane) to get the desired product with 82% yield.

Experimental procedure for the one pot relay process:

A 10 mL schlenk tube equipped with a stir-bar was charged with azido benzene (0.05 g, 0.42 mmol), *tert*-butyl isocyanide (0.041 g, 0.50 mmol), $TMSN_3$ in toluene (0.5 mL) as a solvent. The reaction tube was purged with argon. Then after 5-10 min. $Pd(PPh_3)_4$ (0.004 g, 0.021 mmol) and iron chloride (0.007 g, 0.042 mmol) were added and stirred it at 100 ^oC for 1-12 h. Monitored this reaction by TLC. TLC shows only 15-20% **3**, with remaining starting material as such.

4a: 1-(*tert*-butyl)-*N*-phenyl-1*H*-tetrazol-5-amine

White solid, Yield: 0.08 g (88%); m.p.: 148-150 ^oC; R_f = 0.3 (2:8 EtOAc/hexane). ^1H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.45 (d, 2H, aromatic *C-H*, *J* = 7.6 Hz), 7.36 (t, 2H, aromatic *C-H*, *J* = 7.5 Hz), 7.09 (t, 1H, aromatic *C-H, J* = 7.35 Hz), 6.13 (br s, 1H, N-*H*), 1.78 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 151.9, 139.2, 129.4, 123.2, 118.3, 59.5, 29.1. IR ν (cm^{-1}): 3313, 2962, 2925, 2854, 1733, 1601, 1564, 1499, 1455, 1372, 1261, 1098, 1024, 803, 746, 687, 498. HRMS (ESI): calcd for $C_{11}H_{16}N_5$ $[M+H]^+$ 218.1400, found 218.1388.

4b: 1-(*tert*-butyl)-*N*-(4-(trifluoromethyl)phenyl)-1*H*-tetrazol-5-amine

White solid, Yield: 0.059 g (78%); m.p.: 152-155 ^oC; R_f = 0.2 (2:8 EtOAc/hexane). ^1H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.61 (d, 2H, aromatic *C-H, J* = 8.7 Hz), 7.55 (d, 2H, aromatic *C-H*, *J* = 8.65 Hz), 6.31 (br s, 1H, N-*H*), 1.80 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 151.2, 149.5, 142.3, 126.7 (J_{CF} = 15.0 Hz), 125.0 (J_{CF} = 15.0 Hz), 123.0, 117.5, 116.2, 60.0, 29.2. ^{19}F NMR: -61.93. IR ν (cm^{-1}): 3446, 3279, 2925, 2854, 1229, 1558, 1458, 1373, 1327, 1229, 1164, 1121, 1067, 830, 801, 585. HRMS (ESI): calcd for $C_{12}H_{15}F_3N_5$ $[M+H]^+$ 286.1274, found 286.1270.

4c: *N*-(4-bromophenyl)-1-(*tert*-butyl)-1*H*-tetrazol-5-amine

White solid, Yield: 0.06 g (81%); m.p.: 137-138 ^oC; R_f = 0.3 (3:7 EtOAc/hexane). ^1H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.44 (d, 2H, aromatic *C-H*, *J* = 5.2 Hz), 7.36 (d, 2H, aromatic *C-H*, *J* = 8.5 Hz), 6.18 (br s, 1H, N-*H*), 1.77 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 151.6, 138.3, 132.3, 119.9, 115.7, 59.7, 29.2. IR ν (cm^{-1}):

3278, 3186, 3101, 2926, 2855, 1884, 1599, 1555, 1489, 1359, 1225, 1145, 1113, 1072, 819, 795, 574, 495. HRMS (ESI): calcd for $C_{11}H_{15}BrN_5$ $[M+H]^+$ 296.0506, found 296.0498.

4d: 4-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)amino)benzonitrile

Off-White solid, Yield: 0.070 g (83%); m.p.: 143-145 °C; R_f = 0.3 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$):7.62 (d, 2H, aromatic *C-H, J* = 8.5 Hz), 7.54 (d, 2H, aromatic *C-H*, *J* = 8.5 Hz), 6.58 (br s, 1H, N-*H*), 1.79 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 150.8, 143.4, 133.7, 118.9, 117.7, 105.7, 60.3, 29.3. IR ν (cm^{-1}): 3316, 3105, 2994, 2940, 2223, 1597, 1549, 1513, 1459, 1426, 1377, 1313, 1224, 1179, 1146, 1109, 1030, 835, 802, 728, 580, 544. HRMS (ESI): calcd for $C_{12}H_{15}N_6$ $[M+H]^+$ 243.1353, found 243.1355.

4e: 1-(*tert*-butyl)-*N*-(3-chlorophenyl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.063 g (77%); m.p.: 137-139 °C; R_f = 0.2 (2:8 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.43 (s, 1H, aromatic *C-H*), 7.25 (m, 1H, aromatic *C-H*), 6.98 (d, 1H, aromatic *C-H, J* = 5.1 Hz), 6.65 (s, 1H, aromatic *C-H*), 6.10 (br s, 1H, N-*H*), 1.71 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 151.4, 140.4, 135.1, 130.4, 123.2, 118.2, 116.2, 59.8, 29.2. IR ν (cm^{-1}): 3380, 3287, 2963, 2922, 2852, 1724, 1592, 1553, 1474, 1374, 1259, 1228, 1098, 1026, 906, 871, 804, 770, 680, 521. HRMS (ESI): calcd for $C_{11}H_{15}ClN_5$ $[M+H]^+$ 252.1011, found 252.1001.

4f: 1-(*tert*-butyl)-*N*-(3-methoxyphenyl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.059 g (71%); m.p.: 137-138 °C; R_f = 0.3 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.22 (t, 1H, aromatic *C-H*, *J* = 8.1 Hz), 7.14 (t, 1H, aromatic *C-H*, *J* = 2.1 Hz), 6.91 (dd, 1H, aromatic *C-H*, *J* = 1.5, 8.0 Hz), 6.61 (dd, 1H, aromatic *C-H*, *J* = 1.9, 8.2 Hz), 6.19 (br s, 1H, N-*H*), 3.82 (s, 3H, Sp^3 C-*H*), 1.77 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 160.6, 151.8, 140.6, 130.1, 110.5, 108.9, 104.1, 59.6, 55.4, 29.1. IR ν (cm^{-1}): 3356, 3071, 2979, 2923, 2851, 1733, 1609, 1562, 1506, 1458, 1349, 1215, 1171, 1036, 951, 842, 770, 684, 511, 461.

4g: 4-bromo-2-((1-(tert-butyl)-1*H*-tetrazol-5-yl)amino)benzonitrile

Yellow oil, Yield: 0.057 g (70%); R_f = 0.2 (2:8 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 8.39-8.37 (m, 1H, aromatic *C-H*), 7.74 (d, 1H, aromatic *C-H, J* = 9.0 Hz), 7.70 (s, 1H, aromatic C-*H*), 7.11 (br s, 1H, N-*H*), 1.83 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 150.2, 141.2, 137.9, 134.1, 119.9, 115.7, 114.5, 101.6, 60.3, 29.2. IR ν (cm^{-1}): 3433, 3304, 3060, 2977, 2927, 1934, 1722, 1666, 1608, 1460, 1399, 1375, 1320, 1234, 1148, 1099, 1068, 1024, 893, 816, 752, 609, 544, 428. HRMS (ESI): calcd for $C_{12}H_{14}BrN_6$ $[M+H]^+$ 321.0458, found 321.0455.

4h: *N*-phenyl-1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.093 g (81%); m.p.: 137-138 °C; R_f = 0.4 (4:6 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.49 (d, 2H, aromatic *C-H, J* = 7.9 Hz), 7.39 (t, 2H, aromatic *C-H*, *J* = 7.7 Hz), 7.12 (t, 1H, aromatic *C-H*, *J* = 7.3 Hz), 6.13 (br s, 1H, N-*H*), 2.00 (s, 2H, Sp^3 C-*H*), 1.89 (s, 6H, Sp^3 C-*H*), 0.87 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 152.3, 139.1, 129.4, 123.3, 118.5, 62.9, 52.4, 31.8, 30.7, 29.8. IR ν (cm^{-1}): 3312, 2924, 2854, 1736, 1601, 1564, 1499, 1455, 1373, 1312, 1227, 1106, 1028, 802, 746, 687, 497. HRMS (ESI): calcd for $C_{15}H_{24}N_5$ $[M+H]^+$ 274.2026, found 274.2025.

4i: 2-((1-cyclohexyl-1*H*-tetrazol-5-yl)amino)benzonitrile

Off-White solid, Yield: 0.075 g (81%); m.p.: 141-143 °C; R_f = 0.3 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 8.32 (d, 1H, aromatic *C-H, J* = 8.55 Hz), 7.65 (td, 1H, aromatic *C-H, J* = 1.2, 8.6 Hz), 7.61 (dd, 1H, aromatic C-*H, J* = 1.05, 7.8 Hz), 7.15 (t, 1H, aromatic C-*H, J* = 7.4 Hz), 6.84 (br s, 1H, N-*H*), 4.18-4.12 (m, 1H, Sp^3 C-*H*), 2.17-2.14 (m, 2H, Sp^3 C-*H*), 2.06-1.99 (m, 4H, Sp^3 C-*H*), 1.53-1.46 (m, 2H, Sp^3 C-*H*), 1.42-1.34 (m, 2H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 150.1, 141.7, 134.9, 132.3, 122.8, 118.2, 116.7, 100.1, 57.4, 32.1, 25.1, 24.8. IR ν (cm^{-1}): 3451, 3164, 2924, 2856, 2225, 1609, 1560, 1488, 1248, 1078, 852, 761. HRMS (ESI): calcd for $C_{14}H_{17}N_6$ $[M+H]^+$ 269.1509, found 269.1502.

4j: *N*,1-diphenyl-1*H*-tetrazol-5-amine[36]

Off-White solid, Yield: 0.077 g (77%); m.p.: 165-167 °C; R_f = 0.4 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.63-7.59 (m, 3H, aromatic *C-H*), 7.54 (t, 4H, aromatic *C-H, J* = 8.6 Hz), 7.34 (t, 2H, aromatic *C-H*, *J* = 7.4 Hz), 7.08 (t, 1H, aromatic *C-H*, *J* = 7.1 Hz), 6.59 (br s, 1H, N-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 151.7, 138.0, 132.7, 130.6, 130.5, 129.4, 124.8, 123.5, 118.3. IR ν (cm^{-1}): 3434, 3192, 2924, 1609, 1569, 1529, 1495, 1453, 1405, 1324, 1243, 1121, 1087, 1020, 825, 749, 690. HRMS (ESI): calcd for $C_{13}H_{12}N_5$ $[M+H]^+$ 238.1087, found 238.1080.

4k: 4-((1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)amino)benzonitrile

Off-White solid, Yield: 0.088 g (85%); m.p.: 174-176 °C; R_f = 0.2 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.63 (d, 2H, aromatic *C-H, J* = 8.5 Hz), 7.58 (d, 2H, aromatic *C-H*, *J* = 8.6 Hz), 6.55 (br s, 1H, N-*H*), 1.99 (s, 2H, Sp^3 C-*H*), 1.88 (s, 6H, Sp^3 C-*H*), 0.82 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 151.2, 143.1, 133.7, 118.9, 117.9, 105.9, 63.7, 52.6, 31.8, 30.7, 29.9. IR ν (cm^{-1}): 3341, 3183, 3110, 3055, 2951, 2907, 2224, 1599, 1550, 1515, 1474, 1365, 1228, 1179, 1093, 1027, 839, 732, 547. HRMS (ESI): calcd for $C_{16}H_{23}N_6$ $[M+H]^+$ 299.1979, found 299.1982.

4l: *N*-(4-methoxyphenyl)-1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.077 g (76%); m.p.: 137-138 °C; R_f = 0.3 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.37 (d, 2H, aromatic *C-H, J* = 7.9 Hz), 6.90 (d, 2H, aromatic *C-H*, *J* = 7.9 Hz), 6.0 (br s, 1H, N-*H*), 3.80 (s, 3H, Sp^3 C-*H*), 1.96 (s, 2H, Sp^3 C-*H*), 1.84 (s, 6H, Sp^3 C-*H*), 0.84 (s, 9H, ^{t}Bu). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 156.2, 153.1, 132.2, 121.3, 114.6, 62.6, 55.6, 52.0, 30.7, 29.8. IR ν (cm^{-1}): 3297, 2954, 2925, 2856, 1732, 1603, 1570, 1512, 1467, 1363, 1259, 1228, 1179, 1095, 1037, 823, 807, 595, 513. HRMS (ESI): calcd for $C_{16}H_{25}N_5O$ $[M+H]^+$ 304.2132, found 304.2115.

4m: 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)amino)benzonitrile

Off-White solid, Yield: 0.071 g (85%); m.p.: 137-139 °C; R_f = 0.3 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 8.44 (d, 1H, aromatic *C-H, J* = 8.6 Hz), 7.65 (t, 1H, aromatic *C-H*, *J* = 7.5 Hz), 7.60 (d, 1H, aromatic C-*H*, *J* = 7.0 Hz) 7.13 (t, 1H, aromatic C-*H*, *J* = 7.5 Hz), 7.09 (br s, 1H, N-*H*), 1.84 (s, 9H, Sp^3 C-H). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 150.5, 142.1, 134.9, 132.0, 122.6, 118.2, 116.9, 100.0, 60.1, 29.1. IR ν (cm^{-1}): 3440, 3278, 2925, 2856, 1713, 1657, 1603, 1463, 1371, 1229, 1147, 760. HRMS (ESI): calcd for $C_{12}H_{15}N_6$ $[M+H]^+$ 243.1353, found 243.1350.

4n: 2-((1-(p-tolyl)-1*H*-tetrazol-5-yl)amino)benzonitrile:

Off-White solid, Yield: 0.068 g (71%); m.p.: 178-180 °C; R_f = 0.3 (2:8 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 8.57 (d, 1H, aromatic *C-H, J* = 8.5 Hz), 7.67 (t, 1H, aromatic *C-H*, *J* = 8.4 Hz), 7.57 (d, 1H, aromatic C-*H*, *J* = 7.7 Hz), 7.47 (s, 4H, aromatic C-*H*), 7.16 (br s, 1H, N-*H*), 7.14 (d, 1H, aromatic C-*H, J* = 7.5 Hz), 2.48 (s, 3H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 150.5, 141.6, 140.9, 134.8, 132.3, 131.4, 129.5, 124.2, 123.1,

118.5, 116.2, 100.5, 21.4. IR ν (cm^{-1}): 3384, 3078, 2923, 2220, 1609, 1594, 1571, 1526, 1458, 1314, 1291, 1091, 824, 759, 720, 543, 484, 424. HRMS (ESI): calcd for $C_{15}H_{13}N_6$ $[M+H]^+$ 277.1196, found 277.1190.

4o: *N*-(*tert*-butyl)-1-(p-tolyl)-1*H*-tetrazol-5-amine

White solid, Yield: 0.071 g (83%); m.p.: 133-135 °C; R_f = 0.4 (4:6 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.38 (d, 2H, aromatic *C-H*, *J* = 8.1 Hz), 7.33 (d, 2H, aromatic *C-H*, *J* = 8.2 Hz), 4.16 (br s, 1H, N-*H*), 2.45 (s, 3H, Sp^3 *C-H*), 1.47 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 153.3, 140.3, 130.9, 130.7, 124.3, 53.1, 28.9, 21.3. IR ν (cm^{-1}): 3418, 3337, 2970, 2925, 2871, 1563, 1517, 1457, 1393, 1218, 1082, 813, 508. HRMS (ESI): calcd for $C_{12}H_{18}N_5$ $[M+H]^+$ 232.1557, found 232.1548.

4p: *N*-(*tert*-butyl)-1-(4-fluorophenyl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.066 g (77%); m.p.: 150-152 °C; R_f = 0.2 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.48-7.45 (m, 2H, aromatic *C-H*), 7.30-7.27 (m, 2H, aromatic *C-H*), 4.15 (br s, 1H, N-*H*), 1.48 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 163.0 (J_{CF} = 249.9 Hz), 153.3, 129.3, 126.7 (J_{CF} = 8.9 Hz), 117.5 (J_{CF} = 23.1 Hz), 53.3, 28.9. ^{19}F NMR: -109.5. IR ν (cm^{-1}): 3434, 3317, 3088, 2971, 2926, 2873, 1575, 1515, 1283, 1221, 1130, 1081, 841, 808, 613, 517. HRMS (ESI): calcd for $C_{11}H_{15}FN_5$ $[M+H]^+$ 236.1306, found 236.1299.

4q: *N*-(*tert*-butyl)-1-(3,4-dichlorophenyl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.054 g (72%); m.p.: 163-165 °C; R_f = 0.3 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$):7.67 (d, 1H, aromatic *C-H*, *J* = 13.5 Hz), 7.64 (d, 1H, aromatic *C-H*, *J* = 2.3 Hz), 7.36 (dd, 1H, aromatic *C-H*, *J* = 2.3, 8.5 Hz), 4.20 (br s, 1H, N-*H*), 1.49 (s, 9H, Sp^3 C-H). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 153.0, 134.7, 134.5, 132.5, 132.0, 126.4, 123.2, 53.6, 28.9. IR ν (cm^{-1}): 3400, 3107, 2991, 2929, 1595, 1555, 1473, 1414, 1342, 1221, 1131, 1098, 1025, 867, 818, 671, 584, 437. HRMS (ESI): calcd for $C_{11}H_{14}Cl_2N_5$ $[M+H]^+$ 286.0621, found 286.0614.

4r: *N*-(*tert*-butyl)-1-(naphthalen-1-yl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.065 g (83%); m.p.: 137-138 °C; R_f = 0.3 (2:8 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 8.08 (d, 1H, aromatic *C-H, J* = 8.3 Hz), 7.99 (d, 1H, aromatic *C-H, J* = 8.0 Hz), 7.64-7.60 (m, 2H, aromatic *C-H*), 7.57 (t, 1H, aromatic *C-H* , *J* = 7.4 Hz), 7.52 (d, 1H, aromatic *C-H*, *J* = 7.0 Hz), 7.37 (d, 1H, aromatic *C-H*, *J* = 8.3 Hz), 3.90 (br s, 1H, N-*H*), 1.42 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 154.5, 134.6, 131.4, 128.9, 128.8, 128.6, 128.2, 127.5, 125.5, 125.4, 122.0, 53.1, 28.9. IR ν (cm^{-1}): 3342, 3053, 2979, 2927, 2869, 1579, 1508, 1411, 1215, 1080, 990, 793, 770, 733, 659, 578, 530, 434. HRMS (ESI): calcd for $C_{15}H_{18}N_5$ $[M+H]^+$ 268.1557, found 268.1545.

4s: *N*-(*tert*-butyl)-1-(2-chlorophenyl)-1*H*-tetrazol-5-amine

Off-White solid, Yield: 0.057 g (70%); m.p.: 125-128 °C; R_f = 0.3 (3:7 EtOAc/hexane). ^{1}H NMR, (δ ppm): (500 MHz, $CDCl_3$): 7.63 (d, 1H, aromatic *C-H, J* = 7.9 Hz), 7.56 (td, 1H, aromatic *C-H, J* = 1.4, 7.5 Hz), 7.50 (td, 1H, aromatic C-*H, J* = 0.8, 7.9 Hz), 7.46 (dd, 1H, aromatic C-*H, J* = 1.4, 7.7 Hz), 3.91 (br s, 1H, N-*H*), 1.46 (s, 9H, Sp^3 C-*H*). ^{13}C NMR (δ ppm): (125 MHz, $CDCl_3$): 153.8, 132.3, 131.6, 131.2, 130.5, 129.7, 128.6, 53.3, 28.9. IR ν (cm^{-1}): 3285, 2973, 2922, 1733, 1574, 1519, 1485, 1393, 1216, 1095, 1037, 756, 718, 656, 584, 502, 456. HRMS (ESI): calcd for $C_{11}H_{15}ClN_5$ $[M+H]^+$ 252.1011, found 252.1009.

ASSOCIATED CONTENT

Supporting Information

The Supporting information is available free of charge on the ACS Publication website at DOI: 10.1021/acs.joc.XXXXXXX.

Details on mechanistic experiments, optimization studies, and the copies of ^{1}H and ^{13}C NMR spectra for all new compounds **4a-4s** (PDF)

X-ray structure and crystallographic data for compound **4m** with CCDC 1573778 and **4s** with CCDC 1843251 (CIF).

AUTHOR INFORMATION

Corresponding Authors

*Email: dms@curaj.ac.in

Notes

The authors declare no competing financial interest.

Acknowledgements

DMS and RTP are grateful to Central University of Rajasthan, DST [EMR/2016/003969 and EMR/2016/008016] and CSIR [02(0201)/14/EMR-II] for funds

References:

(1) For reviews of tetrazole chemistry see: (a) Sarvary, A.; Maleki, A. A review of syntheses of 1, 5-disubstituted tetrazole derivatives. *Mol Divers*, **2015**, *19*, 189-212. (b) Moderhack, D. Ring transformations in tetrazole chemistry. *J. Prakt. Chem*. **1998**, *340*, 687-709. (c) Wittenberger, S. J. Recent developments in tetrazole chemistry. A review. *Org. Prep. Proced. Int.* **1994**, *26*, 499-531. (d) Butler, R. N. Recent advances in tetrazole chemistry. *Adv. Heterocycl. Chem*., **1977**, *21*, 323-435

(2) (a) Herr, R. J. 5-Substituted-1*H*-tetrazoles as Carboxylic Acid Isosteres: Medicinal Chemistry and Synthetic Methods. *Bioorg. Med. Chem*., **2002**, *10*, 3379-3393. (b) Thornber, C. W. Isosterism and molecular modification in drug design. *Chem. Soc. Rev*., **1979**, *8*, 563-580. (c) Burger, A. Isosterism and bioisosterism in drug design. *Prog. Drug. Res*., **1991**, *37*, 287-371. (d) Lipinski, C. A. Chapter 27. Bioisosterlsm in Drug Design. *Annu. Rep. Med. Chem*., **1986**, *2721*, 283-291.

(3) (a) Zabrocki, J.; Smith, G. D.; Dunbar, J. B. Jr.; Iijima, H.; Marshall, G. R. Conformational Mimicry. 1. 1,5-Disubstituted Tetrazole Ring as a Surrogate for the Cis Amide Bond. *J. Am. Chem. Soc*. **1988**, *110*, 5875-5880. (b) Zabrocki, J.; Marshall, G. R. The 1,5-Disubstituted Tetrazole Ring as a *cis*-Amide Bond Surrogate. *Methods Mol. Med*. **1999**, *23*, 417-436. (c) Yu, K.-L.; Johnson, R. L. Synthesis and Chemical Properties of Tetrazole Peptide Analogues. *J. Org. Chem*. **1987**, *52*, 2051-2059.

(4) Tuites, R. C.; Whiteley, T. E.; Minsk, L. M. High molecular weight, long chain tetrazole-containing polymers for antifogging use in photographic elements. *US Patent* 1 245 614, **1971**.

(5) Marasescu, F. T.; Wertheimer, M. R. Nitrogen-Rich Plasma-Polymer Films for Biomedical Applications. *Plasma Process*. *Polym*. **2008**, *5*, 44–57.

(6) Cao, C.-Y.; Lu, S.; Zhang, D.; Gong, L.-L.; Zhang, H.-P. Effects of nitroguanidine on the thermal behavior and burning characteristics of 5-amino-1*H* tetrazole-based propellants. *RSC Adv*., **2017**, *7*, 13808-13816.

(7) (a) Fischer, N.; Klapötke, T.M.; Stierstorfer, K. J.; Wiedemann, C. 1-Nitratoethyl-5-nitriminotetrazole derivatives – Shaping future high explosives. *Polyhedron*, **2011**, *30*, 2374-2386. (b) Joo, Y. -H.; Twamley, B.; Garg, S.; Shreeve, J. M. Energetic Nitrogen-Rich Derivatives of 1,5-Diaminotetrazole. *Angew. Chem. Int. Ed*. **2008**, *47*, 6236-6239.

(8) (a) Popova, E. A.; Trifonov, R. E.; Ostrovskii, V. A. Advances in the synthesis of tetrazoles coordinated to metal ions. *ARKIVOC* **2012**, 45-65. (b) Aromí, G.; Barrios, L. A.; Roubeau, O.; Gamez, P. Triazoles and tetrazoles: Prime ligands to generate remarkable coordination materials. *Coord. Chem. Rev*. **2011**, *255*, 485-546. (c) Tappan, B. C.; Huynh, M. H.; Hiskey, M. A.; Chavez, D. E.; Luther, E. P.; Mang, J. T.; Son, S. F. Ultralow-Density Nanostructured Metal Foams: Combustion Synthesis, Morphology, and Composition. *J. Am. Chem. Soc*. **2006**, *128*, 6589-6594. (d) Rhonnstad, P.; Wensbo, D. On the relative strength of the 1*H*-tetrazol-5-yl- and the 2-(triphenylmethyl)-2*H*-tetrazol-5-yl-group in directed ortho-lithiation. *Tetrahedron Lett*., **2002**, *43*, 3137-3139.

(9) Habich, D. Synthesis of 3′-(5-Amino-1, 2, 3, 4-tetrazol-1-yl)-3′-deoxythymidines. *Synthesis*, **1992**, 358-360.

(10) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. Synthesis and Quantitative Structure-Activity Relationships of Antiallergic 2-Hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides and *N*-(2-Hydroxypheny1)- 1*H*-tetrazole-5-carboxamides. *J. Med. Chem*. **1986**, *29*, 538-549.

(11) Vieira, E.; Huwyler, J.; Jolidon, S.; Knoflach, F.; Mutel, V.; Wichmann, 9*H*-Xanthene-9-carboxylic acid [1,2,4]oxadiazol-3-yl- and (2*H*-tetrazol-5-yl)-amides as potent, orally available mGlu1 receptor enhancers. *J. Bioorg. Med. Chem. Lett*., **2005**, *15*, 4628-4631.

(12) Medrano, A. P.; Roberts, D. L. D.; Florjancic, A. S.; Nelson, D. W.; Li, T.; Namovic, M. T.; Peddi, S.; Faltynek, C. R.; Jarvis, M. F.; Carroll, W. A. Synthesis and in vitro activity of *N*-benzyl-1-(2,3-dichlorophenyl)-1*H*-tetrazol-5-amine $P2X_7$ antagonists. *Bioorg. Med. Chem. Lett*., **2011**, *21*, 3297-3300.

(13) Yamazaki, K.; Hasegawa, H.; Umekawa, K.; Ueki, Y.; Ohashi, N.; Kanaoka, M. Design, Synthesis and Biological Activity of Novel Non-Peptidyl Endothelin Converting Enzyme Inhibitors, 1-Phenyl-tetrazole-formazan Analogues. *Bioorg. Med. Chem. Lett*., **2002**, *12*, 1275-1278.

(14) Meyers, M. J.; Long, S. A.; Pelc, M. J.; Wang, J. L.; Bowen, S. J.; Schweitzer, B. A.; Wilcox, M. V.; McDonald, J.; Smith, S. E.; Foltin, S.; Rumsey, J.; Yang, Y.-S.; Walker, M. C.; Kamtekar, S.; Beidler, D.; Thorarensen, A. Discovery of novel spirocyclic inhibitors of fatty acid amide hydrolase (FAAH). Part 2. Discovery of 7-azaspiro[3.5]nonane urea PF-04862853, an orally efficacious inhibitor of fatty acid amide hydrolase (FAAH) for pain. *Bioorg. Med. Chem. Lett*., **2011**, *21*, 6545-6553.

(15) Poecke, S. V.; Negri, A.; Janssens, J.; Solaroli, N.; Karlsson, A.; Gago, F.; Balzarini, J.; Calenbergh, S. V. Synthesis, modeling and evaluation of 3′-(1-aryl-1H-tetrazol-5-ylamino)-substituted 3′-deoxythymidine derivatives as potent and selective human mitochondrial thymidine kinase inhibitors. *Org. Biomol, Chem*., **2011**, *9*, 892-901.

(16) Kato, Y.; Ninomiya, M.; Yamaguchi, Y.; Koketsu, M. Synthesis of triazole-and tetrazole-xyloside analogues as potent hyaluronidase inhibitors. *Med Chem Res*., **2015**, *24*, 1180–1188.

(17) (a) Finnegan, W. G.; Henry, R. A.; Lieber, E. Preparation and isomerization of 5-alkylaminotetrazoles. *J. Org. Chem*. **1953**, *18*, 779-791. (b) Percival, D. F.; Herbst, R. M. Alkylated 5-Aminotetrazoles, Their Preparation and Properties. *J. Org. Chem*. **1957**, *22*, 925-933. (c) Kurzer, F.; Godfrey, L. E. A. Syntheses of Heterocyclic Compounds from Aminoguanidine. *Angew. Chem., Int. Ed. Engl*. **1963**, *2*, 459-476.

(18) (a) Garbrecht, W. L.; Herbst, R. M. The synthesis of certain 5-aminotetrazole derivatives. II. The action of hydrazoic acid on monoalkylcyanamides. *J. Org. Chem*. **1953**, *18*, 1014-1021. (b) Congreve, M. S. Synthesis of 5-N-Substituted Tetrazole Derivatives of the Potent NK1 Receptor Antagonist GR203040. *Synlett*, **1996**, 359-360. (c) Henry, R. A.; Finnegan, W. G.; Lieber, E. Thermal Isomerization of Substituted 5-Aminotetrazoles. *J. Am. Chem. Soc*. **1954**, *76*, 88-93. (d) Nasrollahzadeh, M.; Habibi, D.; Shahkarami, Z.; Bayat, Y. A general synthetic method for the formation of arylaminotetrazoles using natural natrolite zeolite as a new and reusable heterogeneous catalyst. *Tetrahedron* **2009**, *65*, 10715-10719.

(19) Svetlik, J.; Hrusovsky, I.; Martvon, A. Reactions of asymmetric carbodiimides with azoimide. *Collect. Czech. Chem. Commun*.**1979**, *44*, 2982-2986.

(20) Miller, A. E.; Feenay, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E. The synthesis of aminoiminoethanenitriles, 5-aminotetrazoles, *N*-cyanoguanidines, and *N*-hydroxyguanidines from aminoiminomethanesulfonic acids. *Synth. Commun*. **1990**, *20*, 217-226.

(21) Ried, W.; Erle, H.-E. Zur Synthese und Dimroth-Umlagerung von 4-(Dialkylamino)-2H-1,3,5-oxadiazin-2-thionen. *Liebigs, Ann. Chem*. **1989**, 931-934.

(22) (a) Joo, Y.-H.; Shreeve, J. M. 1-Substituted 5-Aminotetrazoles: Syntheses from CNN3 with Primary Amines. *Org. Lett.* **2008**, *10*, 4665-4667. (b) Joo, Y.-H.; Shreeve, J. M. Energetic Mono□, Di□, and Trisubstituted Nitroiminotetrazoles. *Angew. Chem. Int. Ed.* **2009**, *48*, 564-567. (c) Katritzky, A. R.; Rogovoy, B. V.; Kovalenko, K. V. A general route to 5-aminotetrazoles. *J. Org. Chem*. **2003**, *68*, 4941-4943.

(23) (a) Barlin, G. B. The Relative Electron-releasing Power of a Singly Bound, and the Electron-attracting Power of a Doubly Bound Nitrogen Atom when present in the Same Five-membered Ring. *J. Chem. Soc. B*. **1967**, 641-647. (b) Brigas, A. F.; Clegg, W.; Dillon, C. J.; Fonseca, C. F. C.; Johnstone, R. A. W. Metal□Assisted Reactions. Part 29. Structure and Hydrogenolysis of C—N Bonds in Derivatives of Aromatic Amines. Bond Length and Electronegativity Changes from X□Ray Crystallographic Data. *J. Chem. Soc., Perkin Trans*. *2*, **2001**, 1315-1324.

(24) (a) Batey, R. A.; Powell, D. A. A general synthetic method for the formation of substituted 5-aminotetrazoles from thioureas: a strategy for diversity amplification. *Org. Lett*. **2000**, *2*, 3237-3240. (b) Yu, Y.; Ostresh, J. M.; Houghten, R. A. Solid-phase synthesis of 5-aminotetrazoles. *Tetrahedron Lett*. **2004**, *45*, 7787-7789.

(25) Guin, S.; Rout, S. K.; Gogoi, A.; Nandi, S.; Ghara, K. K.; Patel, B. K. Desulfurization strategy in the construction of azoles possessing additional nitrogen, oxygen or sulfur using a copper (I) catalyst. *Adv. Synth. Catal*. **2012**, *354*, 2757-2770.

26) Yella, R.; Khatun, N.; Rout, S. K.; Patel, B. K. Tandem regioselective synthesis of tetrazoles and related heterocycles using iodine. *Org. Biomol. Chem*., **2011**, *9*, 3235-3245.

(27) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. *o*-Iodoxybenzoic Acid Mediated Oxidative Desulfurization Initiated Domino Reactions for Synthesis of Azoles. *J. Org. Chem*. **2012**, *77*, 3716-3723.

(28) Xie, Y.; Guo, D.; Jiang, X.; Pan, H.; Wang, W.; Jin, T.; Mi, Z. An efficient method for the synthesis of substituted 5-aminotetrazoles from selenoureas using $PhI(OAc)_2$. *Tetrahedron Lett*. **2015**, *56*, 2533–2536.

(29) Murugan, S.; Poovan, S.; Sangaraiah, N.; Murugan, D.; Alagusundaram, P. Water promoted one pot three-component synthesis of tetrazoles. *New J. Chem*., **2013**, *37*, 488-493.

(30) Such as cyanamides, unsymmetrical carbodiimides and a-substituted formamide derivatives (such as aminoguanides, aminoiminomethanesulfonic acids or a-chloroformamides).

(31) Ansari, A.; Pathare, R. S.; Maurya, A.; Agnihotri, V.; Khan, S.; Roy, T. K.; Sawant, D. M.; Pardasani, R. T. Synthesis of diverse N-heterocycles via Pd-catalyzed tandem azide-isocyanide cross-coupling/cyclization: Mechanistic insight using experimental and theoretical studies. *Adv. Synth. Catal*. **2018**, *360*, 290-297.

(32) (a) Pathare, R. S.; Sharma, S.; Elagandhula, S.; Saini, V.; Sawant, D. M.; Yadav, M.; Sharon, A.; Khan, S.; Pardasani, R. T. Application of Isocyanides as Amide Surrogates in the Synthesis of Diverse Isoindolin-1-one Derivatives by a Palladium-Catalyzed Tandem Carboxamidation/Hydroamidation Reaction. *Eur. J. Org. Chem*. **2016**, 5579-5587. (b) Sharma, S.; Pathare, R. S.; Maurya, A. K.; Gopal, K.; Roy, T. K.; Sawant, D. M.; Pardasani, R. T. Ruthenium Catalyzed Intramolecular C−S Coupling Reactions: Synthetic Scope and Mechanistic Insight. *Org. Lett*. **2016**, *18*, 356-359. (c) Pathare, R. S.; Sharma, S.; Gopal, K.; Sawant, D. M.; Pardasani, R. T. Palladium-catalyzed convenient one-pot synthesis of multi-substituted 2-pyrones via transesterification and alkenylation of enynoates. *Tetrahedron Lett*. **2017**, *58*, 1387-1389. (d) Sharma, S.; Singh, S.; Kumari, A.; Sawant, D. M.; Pardasani, R. T. Ruthenium-catalyzed oxidative annulation of anilines using benzothiazole as removable directing group. *Asian J. Org. Chem*. **2017**, *6*, 728-736.

(33) (a) Zhang, Z.; Li, Z.; Fu, B.; Zhang, Z. Palladium-catalyzed cross-coupling reaction of azides with isocyanides. *Chem. Commun*. **2015**, *51*, 16312-16315. (b) Zhang, Z.; Huang, B.; Qiao, G.; Zhu, L.; Xiao, F.; Chen, F.; Fu, B.; Zhang, Z. Tandem Coupling of Azide with Isonitrile and Boronic Acid: Facile Access to Functionalized Amidines. *Angew. Chem., Int. Ed*. **2017**, *129,* 4384-4387. (c) Gu, Z.-Y.; Liu, Y.; Wang, F.; Bao, X.; Wang, S.-Y.; Ji, S.-J. Cobalt (II)-Catalyzed Synthesis of Sulfonyl Guanidines via Nitrene Radical Coupling with

Isonitriles: A Combined Experimental and Computational Study. *ACS Catal*. **2017**, *7*, 3893-3899. (d) Zhang, Z.; Xiao, F.; Huang, B.; Hu, J.; Fu, B.; Zhang, Z. Cyclization of Alkyne–Azide with Isonitrile/CO via Self-Relay Rhodium Catalysis. *Org. Lett*. **2016**, *18*, 908-911. (e) Jiang, T.; Gu, Z.-Y.; Yin, L.; Wang, S.-Y.; Ji, J. Cobalt (II)-Catalyzed Isocyanide Insertion Reaction with Sulfonyl Azides in Alcohols: Synthesis of Sulfonyl Isoureas. *J. Org. Chem*. **2017**, *82*, 7913-7919. (f) Qin, C.; Su, Y.; Shen, T.; Shi, X.; Jiao, N. Splitting a Substrate into Three Parts: Gold□Catalyzed Nitrogenation of Alkynes by C-C and C≡C Bond Cleavage. *Angew Chem. Int. Ed*. **2016**, *55*, 350-354. (g) Tsuge, O.; Urano, S.; Oe, K. Reactions of trimethylsilyl azide with heterocumulenes. *J. Org. Chem*., **1980**, 45, 5130-5136.

(34) These regioisomer shows chemical shift of N-*H* at 3.91-4.20 ppm in ^{1}H NMR spectroscopy.

(35) (a) Zilla, M. K.; Nayak, D.; Vishwakarma, R. A.; Sharma, P. R.; Goswami, A.; Ali, A. A convergent synthesis of alkyne-azide cycloaddition derivatives of 4-α, β-2-propyne podophyllotoxin depicting potent cytotoxic activity. *Eur. J. Med. Chem*., **2014**, *77*, 47-55. (b) Dai, Z.-C.; Chen, Y.-F.; Zhang, M.; Li, S.-K.; Yang, T.-T.; Shen, L.; Wang, J.-X.; Qian, S.-S.; Zhue, H. –L.; Ye, Y.-H. Synthesis and antifungal activity of 1, 2, 3-triazole phenylhydrazone derivatives. *Org. Biomol. Chem*., **2015**, *13*, 477-486. (c) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. A Metal□Free Three□Component Reaction for the Regioselective Synthesis of 1, 4, 5□Trisubstituted 1, 2, 3□Triazoles. *Angew Chem. Int Ed*., **2014**, *53*, 10155-10159. (d) Berry, M. T.; Castrejon, D.; Hein, J. E. Oxidative Esterification of Aldehydes Using Mesoionic 1, 2, 3-Triazolyl Carbene Organocatalysts. *Org. Lett*., **2014**, *16*, 3676–3679.

(36) (a) Guin, S.; Rout, S. K.; Gogoi, A.; Nandi, S.; Ghara, K. K.; Patel, B. K. Desulfurization strategy in the construction of azoles possessing additional nitrogen, oxygen or sulfur using a copper (I) catalyst. *Adv. Synth. Catal*. **2012**, *354*, 2757-2770. (b) Chaudhari, P. S.; Pathare, S. P.; Akamanchi, K. G. o-Iodoxybenzoic Acid Mediated Oxidative Desulfurization Initiated Domino Reactions for Synthesis of Azoles. *J. Org. Chem*. **2012**, *77*, 3716-3723.