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ORIGINAL ARTICLE

A synthesis of functionalized 3-amino-1,2,4-triazoles from nitrile imines and guanidine derivatives

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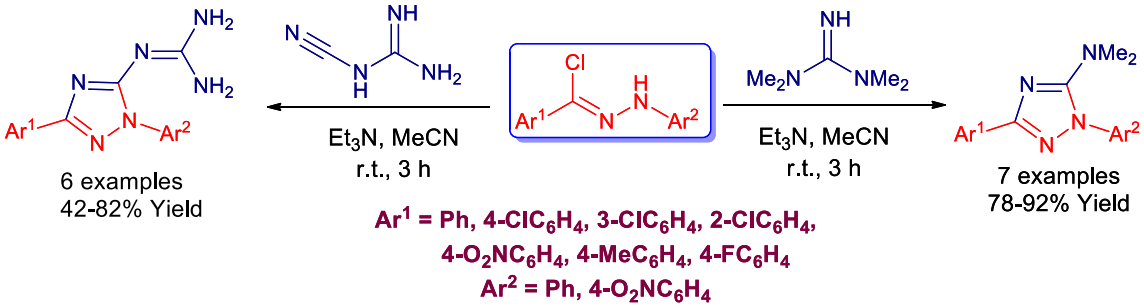
Abstract

A regioselective synthesis of trisubstituted 1,2,4-triazoles through reaction of nitrile imines with guanidine derivatives is described. These 1,3-dipolar cycloaddition reactions proceeded smoothly in moderate to good yields and excellent regioselectivity under ambient conditions. This method provides fast access to a range of functionalized 3-amino-1,2,4-triazoles.

Graphical abstract



Keywords Cyanoguanidine · Huisgen reaction · Nitrile imine · Tetramethylguanidine · Aminotriazole

Introduction

Triazoles, in particular 1,2,4-triazoles, are privileged structural constituents of many pharmaceutical agents as well as natural products [1, 2]. Amino-1,2,4-triazoles, a subclass of 1,2,4-triazoles, are widely used in materials chemistry, medicinal chemistry [3], and synthetic chemistry as synthons [4]. Selected 1,2,4-triazoles with biological activities are depicted in Fig. 1 [5]. Since all triazoles are of synthetic origin and there is no triazole ring system detected as yet in nature, the development of new methodologies for the synthesis of functionalized triazoles continues to be an active area of research in fine chemistry. Among the conventional approaches developed over the past decades for the construction of the triazole skeleton [6–8], the most commonly used include the reaction of acyl hydrazides with isothioureas [9], oxidative coupling of *N,N*-dimethylguanidine with benzonitrile [10], and [3 + 2]-cycloaddition reaction of nitrile ylides with diazonium salts [11].

Guanidines can be categorized as organic super bases due to the resonance stability of their conjugated acids [12]. Thus, they are expected to catalyze base-mediated organic reactions and can be widely and easily modified into a variety of chiral bases [13]. Guanidine derivatives serve as building blocks in various drugs, natural products, and agrochemicals [14–16]. Finally, neutral guanidines have found themselves as good supporting ligands in organometallic and coordination chemistry [17]. In continuation of our work on the developments of new routes to construct azole system via nitrile imines [18–20], we now report a [3 + 2] dipolar cycloaddition/elimination process for the synthesis of 1,2,4-triazoles.

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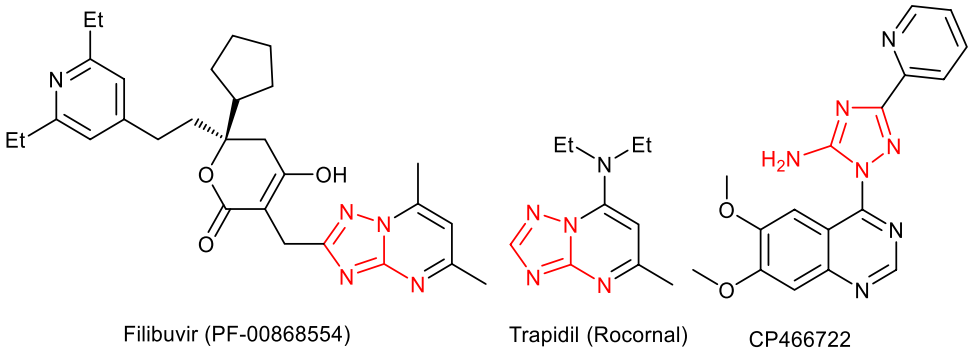


Fig. 1 Selected 1,2,4-triazoles with biological activities

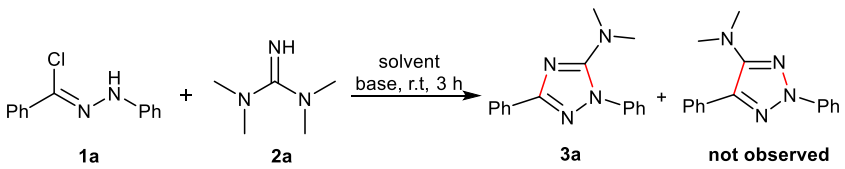
Results and discussion

Our initial studies focused on searching for an optimal reaction condition to generate *N,N*-dimethyl-1,3-diphenyl-1*H*-1,2,4-triazol-5-amine (**3a**) using *N*-phenylbenzohydrazonoyl chloride (**1a**) [21] and tetramethylguanidine (**2a**, TMG) as reaction substrates (Table 1). Initially, the reaction between **1a** and TMG was conducted in the presence of Et_3N in MeCN at room temperature. After 3 h, the product **3a** was isolated in 90% yield. The regioselective formation of **3a** was confirmed on the basis of its ^{13}C NMR spectrum, which exhibited two signals at 159.2 and 159.3 ppm for the N–C=N moieties. Thus, the isomeric 1,2,3-triazol derivative (see Table 1) is ruled out because it is expected to show only one carbon signal for its N–C=N carbon atom above 150 ppm. In order to optimize the reaction conditions for the formation of **3a**, the effects of solvent and base were studied. Thus, a survey of different solvents such as THF, DMSO, DMF, and CH_2Cl_2 was made. As shown in Table 1, the best yield was obtained in MeCN. Then, different bases such as K_2CO_3, DABCO, DBU, and Cs_2CO_3 were examined. None of these bases were superior compared to Et_3N. Thus, the optimum reaction condition for preparation of **3a** is equimolar amounts of **1a** and **2a** in MeCN at 25 °C.

The scope of the present method was further explored by the utilization of a range of hydrazonoyl chlorides. As shown in Table 2, the reactivity of substrates **3** with different substituents on the nitrogen and carbon atoms was almost the same and the reactions proceeded smoothly, giving the desired products with satisfactory yields.

The structures of products **3a–g** were deduced from their IR, ^1H NMR, and ^{13}C NMR spectral data. For example, the ^1H NMR spectrum of **3a** exhibited a sharp singlet for the two methyl groups at about 2.87 ppm and aromatic protons appeared at $\delta = 7.35–8.15$ ppm. The ^{13}C NMR spectrum of **3a** exhibited 11 signals in agreement with the proposed

Table 1 Optimization of the reaction conditions for synthesis of 1,2,4-triazole **3a**

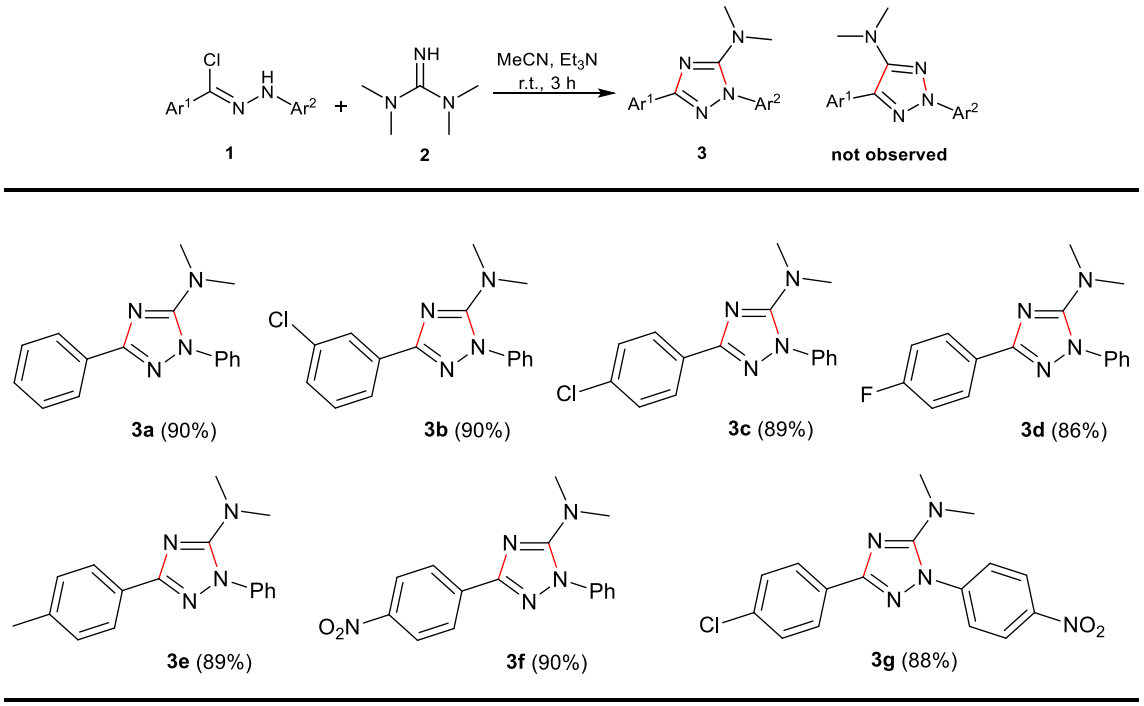


Entry	Base	Solvent	Yield (%)[a]
1	Et_3N	MeCN	90
2	Et_3N	THF	80
3	Et_3N	DMSO	88
4	Et_3N	DMF	87
5	Et_3N	CH_2Cl_2	86
6	K_2CO_3	MeCN	85
7	DABCO	MeCN	84
8	DBU	MeCN	83
9	Cs_2CO_3	MeCN	82

Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), base (1 mmol), in solvent (5 mL) at r.t.

[a]Isolated yield

Table 2 Synthesis of highly substituted 1,2,4-triazoles **3**



Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), base (1 mmol), in solvent (5 mL) at r.t.

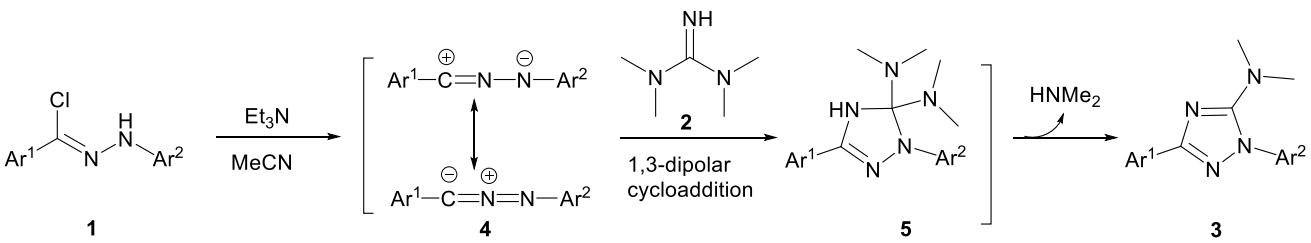
[a]Isolated yield

structure. The mass spectrum of **3a** displayed the molecular ion peak at $m/z = 264$. The NMR spectra of compounds **3b–g** are similar to those of **3a**, except for the substituents, which showed characteristic signals in the appropriate regions of the spectra.

The regioselective formation of substituted triazole derivatives **3** can be explained by a plausible mechanism depicted in Scheme 1. Presumably, the initial event is elimination of HCl by Et_3N, which leads to the formation of nitrile imine intermediate **4**. This 1,3-dipolar intermediate is ceased by TMG to yield adduct **5**, which undergoes subsequent loss of dimethylamine to generate product **3**.

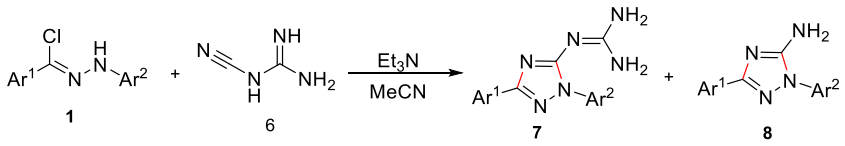
To extend the scope of this reaction, we used cyanoguanidine (**6**) as the guanidine derivatives. As shown in Table 3 (entries 1–4), the reaction of **6** with **1** gave a mixture of 2-(1,3-diaryl-1*H*-1,2,4-triazol-5-yl)guanidine (**7**) and 1,3-diaryl-1*H*-1,2,4-triazol-5-amine (**8**). However, when a nitro group existed in the substrate, only a single product (namely **7e** or **7f**) was obtained (Table 3, entries 5 and 6). Products **8e** and **8f** were not observed in the proton NMR spectra of the reaction mixtures. The absence of these products in the reaction mixture can be explained by reduction of reactivity of the nitrile imine intermediate as a result of the presence of a nitro group. These less reactive nitrile imines are more selective toward the nitrile group of **6** and lead to the formation of **7** via the more stable "aromatic" transition state **I** compared to **II** (see Fig. 2).

The formation of 3-amino-1,2,4-triazoles **7** and **8** can be explained by a plausible mechanism depicted in Scheme 1. The initial event may be generation of nitrile imine intermediate **4** by elimination of HCl from **1**. Intermediate **4** can be ceased by the cyano group of **6** to generate intermediate



Scheme 1 A plausible mechanism for the regioselective formation of 1,2,4-triazoles derivatives **3**

Table 3 Synthesis of highly substituted 1,2,4-triazoles **7** and **8**



Entry	Ar^1	Ar^2	Products	Ratio **7**:**8**	Yield (%)
1	*m*-Cl-C_6H_4	Ph	**7a, 8a**	1:1	84
2	*p*-Cl-C_6H_4	Ph	**7b, 8b**	1:1	88
3	*p*-F-C_6H_4	Ph	**7c, 8c**	1:1	92
4	*p*-Me-C_6H_4	Ph	**7d, 8d**	5:2	91
5	*p*-O_2N-C_6H_4	Ph	**7e**	≥19:1	82
6	*p*-Cl-C_6H_4	*p*-O_2N-C_6H_4	**7f**	≥19:1	78

Reaction conditions: **1** (1 mmol), **2** (0.084 g, 1 mmol), Et_3N (0.101 g, 1 mmol), in MeCN (5 mL) at r.t.

[a]Isolated yield

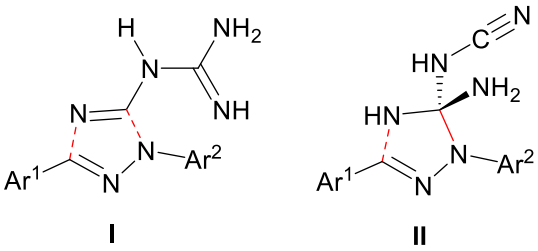
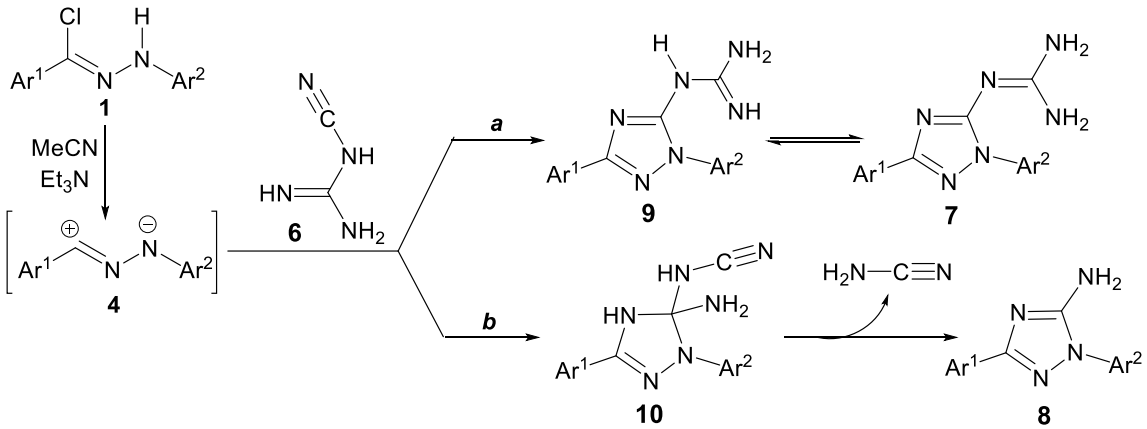


Fig. 2 Transition states **I** and **II** for the formation of products **7** and **8**, respectively

9, which is in equilibrium with its tautomer **7** (route ***a***). As shown in Scheme 1, in route ***b***, 1,3-dipolar cycloaddition reaction involves the imino double bond of **6** to give intermediate **10**, which is converted to product **8** by elimination of cyanamide (Scheme 2).

In summary, we have developed an operational approach for the synthesis of functionalized 3-amino-1,2,4-triazoles in MeCN at 25 °C. Thus, the nitrile imines generated in situ from hydrazonoyl chlorides were seized by guanidine derivatives featuring the synthesis of triazoles in good yields and excellent regioselectivity. The reaction proceeds through a cascade [3 + 2] cycloaddition and elimination sequence. This methodology offers a simple and efficient strategy to construct structurally diverse 1,2,4-triazos from readily available starting materials in a one-step fashion under mild condition.



Scheme 2 Plausible mechanism for the formation of 1,2,4-triazoles derivatives **7** and **8**

Experimental section

General remarks

All purchased solvents and chemicals had analytical grade and were used without further purification. Melting points: Electrothermal-9100 apparatus. IR (KBr) spectra: Shimadzu-IR-460 spectrometer; ν in cm^{-1}. ^1H NMR (500 MHz, 300 MHz) and ^{13}C NMR (125 MHz, 75 MHz) spectra were obtained using Bruker DRX-500 Avance and Bruker DRX-300 Avance spectrometers. All NMR spectra were recorded at room temperature in $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Coupling constants are reported in hertz (Hz), and standard abbreviations were used to indicate spin multiplicities. Mass spectra were recorded on a Finnigan-MAT-8430EI-MS mass spectrometer, at an ionization potential 70 eV, in *m/z* (rel. %). Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer.

Typical procedure for the synthesis of products 3

A mixture of hydrazonoyl chloride derivative **1** (1 mmol) and Et_3N (0.101 g, 1 mmol) in MeCN (3 mL) was stirred at r.t. for 15 min. Then guanidine derivatives **2** (1 mmol) were added to the above mixture, and the reaction was stirred at r.t. for 3 h. After completion of the reaction (the progress of the reaction was followed by TLC), the solvent was removed under reduced pressure. The crude residue was purified by column chromatography [silica gel (230–400 mesh; Merck, *n*-hexane/AcOEt 3:1] to give the products **3a–3g**

N,N-Dimethyl-1,3-diphenyl-1*H*-1,2,4-triazol-5-amine (3a)

Colorless powder, m.p.: 56–58 °C; Yield: 0.24 g (90%). IR (KBr) (ν_{max}, cm^{-1}): 3058, 2878, 2804, 1588, 1555, 1494, 1408, 1365. ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 2.87$ (6 H, *s*, 2 Me), 7.37 (1 H, *t*, $^3J = 7.5$ Hz, Ar), 7.39 (1 H, *t*, $^3J = 7.3$ Hz, Ar), 7.44 (2 H, *t*, $^3J = 7.3$ Hz, Ar), 7.49 (2 H, *t*, $^3J = 7.8$ Hz, Ar), 7.68 (2 H, *d*, $^3J = 8.1$ Hz, Ar), 8.14 (2 H, *d*, $^3J = 8.2$ Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta_C = 41.3$ (2 Me), 123.9 (2 CH), 126.3 (2 CH), 127.7 (CH), 128.4 (2 CH), 128.9 (CH), 129.3 (2 CH), 131.3 (C), 138.9 (C), 159.2 (C=N), 159.3 (C=N). MS: *m/z* (%) = 264 (M^+, 1), 249 (8), 194 (10), 118 (22), 103 (30), 91 (100), 77 (80). Anal. Calcd for $C_{16}H_{16}N_4$ (264.33): C, 72.70; H, 6.10; N, 21.20%. Found: C, 73.08; H, 6.14; N, 21.55%.

3-(3-Chlorophenyl)-*N,N*-dimethyl-1-phenyl-1*H*-1,2,4-triazol-5-amine (3b)

Colorless powder, m.p.: 73–75 °C; Yield: 0.27 g (90%). IR (KBr) (ν_{max}, cm^{-1}): 3208, 2878, 1574, 1485, 1404, 1368. ^1H NMR (300 MHz, $CDCl_3$): $\delta_H = 2.86$ (6 H, *s*, 2 Me), 7.33–7.35 (2 H, *m,* Ar), 7.37 (1 H, *t*, $^3J = 7.4$ Hz, Ar), 7.48 (2 H, *t*, $^3J = 7.6$ Hz, Ar), 7.64 (2 H, *d*, $^3J = 8.2$ Hz, Ar), 7.99 (1 H, *t*, $^3J = 8.1$ Hz, Ar), 8.13 (1 H, *s*, Ar). ^{13}C NMR (75.0 MHz, $CDCl_3$): $\delta_C = 41.2$ (2 Me), 123.9 (2 CH), 124.3 (CH), 126.3 (CH), 127.8 (CH), 128.9 (CH), 129.3 (2 CH), 129.6 (CH), 133.1 (C), 134.4 (C), 138.7 (C), 158.0 (C=N), 159.3 (C=N). MS: *m/z* (%) = 298 (M^+, 1), 283 (40), 269 (50), 228 (8), 207 (70), 118 (10), 91 (100), 77 (10), 64 (4). Anal. Calcd for $C_{16}H_{15}ClN_4$ (298.77): C, 64.32; H, 5.06; N, 18.75%. Found: C, 64.75; H, 5.10; N, 19.19%.

3-(4-Chlorophenyl)-*N,N*-dimethyl-1-phenyl-1*H*-1,2,4-triazol-5-amine (3c)

Colorless powder, m.p.: 79–81 °C; Yield: 0.27 g (89%). IR (KBr) (ν_{max}, cm^{-1}): 3058, 2922, 1594, 1487, 1348, 764. ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 2.86$ (6 H, *s*, 2 Me), 7.36–7.39 (3 H, *m,* Ar), 7.48 (2 H, *t*, $^3J = 7.5$ Hz, Ar), 7.64 (2 H, *d*, $^3J = 8.1$ Hz, Ar), 8.04 (2 H, *d*, $^3J = 8.5$ Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta_C = 41.3$ (2 Me), 123.9 (2 CH), 127.6 (2 CH), 127.8 (CH), 128.6 (2 CH), 129.3 (2 CH), 129.8 (C), 134.8 (C), 138.7 (C), 158.3 (C=N), 159.3 (C=N). MS: *m/z* (%) = 298 (M^+, 1), 283 (35), 269 (50), 228 (12), 207 (70), 118 (15), 91 (100), 77 (10), 64 (15). Anal. Calcd for $C_{16}H_{15}ClN_4$ (298.77): C, 64.32; H, 5.06; N, 18.75%. Found: C, 64.79; H, 5.09; N, 19.17%.

3-(4-Fluorophenyl)-*N,N*-dimethyl-1-phenyl-1*H*-1,2,4-triazol-5-amine (3d)

Colorless powder, m.p.: 43–45 °C; Yield: 0.24 g (86%). IR (KBr) (ν_{max}, cm^{-1}): 3054, 2924, 1580, 1497, 1410, 1365. ^1H NMR (500 MHz, $CDCl_3$): $\delta_H = 2.86$ (6 H, *s*, 2 Me), 7.11 (2 H, *dd*, $^3J = 8.78$, 8.78 Hz, Ar), 7.37 (1 H, *t*, $^3J = 7.5$ Hz, Ar), 7.48 (2 H, *t*, $^3J = 7.9$ Hz, Ar), 7.65 (2 H, *t*, $^3J = 7.4$ Hz, Ar), 8.11 (2 H, *dd*, $^3J = 8.9$, 5.5 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta_C = 41.3$ (2 Me), 115.3 (*d*, $^2J_{C\text{-}F} = 21.5$ Hz), 123.9 (2 CH), 127.5 (*d*, $^4J_{C\text{-}F} = 3.2$ Hz), 127.7 (CH), 128.2 (*d*, $^3J_{C\text{-}F} = 8.3$ Hz), 129.3 (2 CH), 138.8 (C), 158.4 (C=N), 159.3 (C=N), 163.4 (*d*, $^1J_{C\text{-}F} = 250$ Hz). MS: *m/z* (%) = 282 (M^+, 1), 267 (33), 253 (10), 212 (22), 121 (13), 91 (100), 77 (15). Anal. Calcd for $C_{16}H_{15}FN_4$ (282.13): C, 68.07; H, 5.36; N, 19.85%. Found: C, 68.46; H, 5.39; N, 20.26%.

N,N-Dimethyl-1-phenyl-3-(*p*-tolyl)-1*H*-1,2,4-triazol-5-amine (3e)

Colorless powder, m.p.: 65–68 °C; Yield: 0.25 g (89%). IR (KBr) (ν_{max}, cm^{-1}): 3058, 2913, 2804, 1566, 1496, 1411, 1365. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 2.40 (3 H, *s*, Me), 2.87 (6 H, *s*, 2 Me), 7.24 (2 H, *d*, ^3J = 7.9 Hz, Ar), 7.36 (1 H, *t*, ^3J = 7.5 Hz, Ar), 7.48 (2 H, *t*, ^3J = 7.9 Hz, Ar), 7.68 (2 H, *d*, ^3J = 7.4 Hz, Ar), 8.03 (2 H, *d*, ^3J = 8.1 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 21.4 (Me), 41.3 (2 Me), 123.9 (2 CH), 126.2 (2 CH), 127.6 (CH), 128.5 (C), 128.1 (2 CH), 129.2 (2 CH), 138.8 (C), 138.9 (C), 159.2 (C=N), 159.3 (C=N). MS: *m/z* (%) = 279 (M^+, 1), 263 (23), 249 (10), 208 (22), 118 (22), 91 (100), 77 (26). Anal. Calcd for $C_{17}H_{18}N_4$ (279.15): C, 73.35; H, 6.52; N, 20.13%. Found: C, 73.81; H, 6.55; N, 20.45%.

N,N-Dimethyl-3-(4-nitrophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-amine (3f)

Colorless powder, m.p.: 122–125 °C; Yield: 0.28 g (90%). IR (KBr) (ν_{max}, cm^{-1}): 3058, 2927, 2804, 1593, 1508, 1413, 1336. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 2.89 (6 H, *s*, 2 Me), 7.41 (1 H, *t*, ^3J = 7.5 Hz, Ar), 7.51 (2 H, *t*, ^3J = 8.1 Hz, Ar), 7.64 (2 H, *d*, ^3J = 7.5 Hz, Ar), 8.23–8.31 (4 H, *m*, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 41.3 (2 Me), 123.8 (2 CH), 124.1 (2 CH), 126.9 (2 CH), 128.2 (CH), 129.4 (2 CH), 137.3 (C), 138.5 (C), 148.0 (C), 157.1 (C=N), 159.4 (C=N). MS: *m/z* (%) = 309 (M^+, 1), 294 (33), 280 (10), 262 (8), 160 (8), 118 (15), 91 (100), 77 (10). Anal. Calcd for $C_{16}H_{15}N_5O_2$ (309.12): C, 62.13; H, 4.89; N, 22.64%. Found: C, 62.53; H, 4.91; N, 22.96%.

3-(4-Chlorophenyl)-*N,N*-dimethyl-1-(4-nitrophenyl)-1*H*-1,2,4-triazol-5-amine (3g)

Colorless powder, m.p.: 132–135 °C; Yield: 0.30 g (88%). IR (KBr) (ν_{max}, cm^{-1}): 3115, 2875, 2804, 1597, 1584, 1511, 1405, 1333. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 2.93 (6 H, *s*, 2 Me), 7.42 (2 H, *d*, ^3J = 8.5 Hz, Ar), 7.97 (2 H, *d*, ^3J = 9.0 Hz, Ar), 8.06 (2 H, *d*, ^3J = 8.5 Hz, Ar), 8.37 (2 H, *d*, ^3J = 9.0 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C = 41.8 (2 Me), 122.7 (2 CH), 124.9 (2 CH), 127.7 (2 CH), 128.7 (2 CH), 129.2 (C), 135.4 (C), 143.5 (C), 145.8(C), 159.3 (C=N), 160.1 (C=N). MS: *m/z* (%) = 343 (M^+, 1), 328 (48), 314 (15), 273 (22), 207 (15), 192 (10), 149 (8), 139 (51), 91 (100). Anal. Calcd for $C_{16}H_{14}ClN_5O_2$ (343.08): C, 55.90; H, 4.10; N, 20.37%. Found: C, 56.23; H, 4.14; N, 20%.

Typical procedure for the synthesis of products 7 and 8

A mixture of hydrazonoyl chloride **1** (1 mmol) and Et_3N (0.101 g, 1 mmol) in MeCN (3 mL) was stirred at r.t. for 15 min. Then guanidine **6** (1 mmol) was added to the above mixture, and the reaction was stirred at r.t. for 3 h. After completion of the reaction (the progress of the reaction was followed by TLC), the solvent was removed under reduced pressure. The crude residue was purified by column chromatography [silica gel (230–400 mesh); Merck, *n*-hexane/AcOEt 3:1] to give the products **7a–7f** and **8a–8d**.

Formation of products 7a and 8a in 1:1 ratio

Colorless powder; mp: 134–142 °C; IR (KBr) (ν_{max}, cm^{-1}): 3423, 3298, 3115, 1637, 1544, 1503, 1417, 1366, 752. MS: *m/z* (%) = 312 (M^+, 1), 270 (M^+, 1), 295 (15), 228 (20), 133 (15), 91 (100), 77 (18).

2-[3-(3-Chlorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]guanidine (7a)

Yield: 0.12 g (40%); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 6.95 (4 H, br, 2 NH_2), 7.26 (1 H, *t*, ^3J = 7.4 Hz, Ar), 7.37–7.48 (4 H, *m*, Ar), 8.00 (1 H, *dd*, ^3J = 6.6, 1.9 Hz, Ar), 8.04 (1 H, *s,* Ar), 8.13 (2 H, *d*, ^3J = 7.7 Hz, Ar).^{13}C NMR (75 MHz, DMSO-d_6): 121.9 (2 CH), 124.1 (CH), 125.2 (CH), 125.5 (CH), 128.5 (2 CH), 128.6 (CH), 130.5 (CH), 133.4 (C), 133.5 (C), 138.6 (C), 155.2 (C=N), 156.9 (C=N), 158.7 (C=N). Anal. Calc. for $C_{15}H_{13}ClN_6$: (312.09): C, 57.60; H, 4.19; N, 26.87%.

3-(3-Chlorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-amine (8a)

Yield: 0.12 g (44%); ^{1}H NMR (300 MHz, DMSO-d_6): δ_H = 6.62 (2 H, br, NH_2), 7.37–7.48 (3 H, *m*, Ar), 7.54 (2 H, *t*, ^3J = 7.7 Hz, Ar), 7.62 (2 H, *d*, ^3J = 7.5 Hz, Ar), 7.89 (1 H, *dd,* ^3J = 6.6, 1.9 Hz, Ar), 7.91 (1 H, *s*, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): 122.9 (2 CH), 124.0 (CH), 125.1 (CH), 127.3 (CH), 128.6 (CH), 129.4 (2 CH), 130.6 (CH), 133.3 (C), 133.4 (C), 137.1 (C), 155.5 (C=N), 158.4 (C=N). Anal. Calc. for $C_{14}H_{11}ClN_4$: (270.07): C, 62.11; H, 4.10; N, 20.70%.

Formation of products 7b and 8b in 1:1 ratio

Colorless powder; mp: 130–138 °C; IR (KBr) (ν_{max}, cm^{-1}): 3427, 3296, 3101, 1635, 1548, 1500, 1411, 1366, 754. MS: *m/z* (%) = 312 (M^+, 1), 270 (M^+, 1), 295 (5), 228 (33), 133 (18), 91 (100), 77 (18).

2-[3-(4-Chlorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]guanidine (7b)

Yield: 0.13 g (42%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 6.66$ (4 H, br, 2 NH_2), 7.26 (1 H, *t*, $^{3}J = 8.0$ Hz, Ar), 7.40–7.44 (4 H, *m*, Ar), 7.92 (2 H, *d*, $^{3}J = 8.0$ Hz, Ar), 8.05 (2 H, *d,* $^{3}J = 8.5$ Hz, Ar).^{13}C NMR (125 MHz, $CDCl_3$): 123.4 (2 CH), 127.4 (2 CH), 128.3 (CH), 128.6 (2 CH), 129.9 (2 CH), 130.0 (C), 134.7 (C), 138.2 (C), 156.8 (C=N), 157.3 (C=N), 157.8 (C=N). Anal. Calc. for $C_{15}H_{13}ClN_6$: (312.09): C, 57.60; H, 4.19; N, 26.87%.

3-(4-Chlorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-amine (8b)

Yield: 0.13 g (46%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 5.02$ (2 H, br, NH_2), 7.40–7.44 (3 H, *m*, Ar), 7.53 (2 H, *t*, $^{3}J = 8.3$ Hz, Ar), 7.56 (2 H, *d*, $^{3}J = 7.3$ Hz, Ar), 7.98 (2 H, *d,* $^{3}J = 8.4$ Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 123.7 (2 CH), 126.7 (CH), 127.4 (2 CH), 128.6 (2 CH), 128.8 (2 CH), 129.4 (C), 135.1 (C), 136.7 (C), 154.3 (C=N), 158.4 (C=N). Anal. Calc. for $C_{14}H_{11}ClN_4$: (270.07): C, 62.11; H, 4.10; N, 20.70%.

Formation of products 7c and 8c in 1:1 ratio

Colorless powder; mp: 179–185 °C; IR (KBr) (ν_{max}, cm^{-1}): 3447, 3183, 1608, 1540, 1500, 1417, 758. MS: *m/z* (%) = 296 (M^+, 1), 253 (M^+, 1), 279 (20), 212 (15), 121 (10), 91 (100), 77 (15).

2-[3-(4-Fluorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl]guanidine (7c)

Yield: 0.13 g (43%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 6.59$ (4 H, br, 2 NH_2), 7.12 (2 H, *d*, $^{3}J = 8.6$ Hz, Ar), 7.25 (1 H, *t*, $^{3}J = 7.4$ Hz, Ar), 7.42 (2 H, *t*, $^{3}J = 7.7$ Hz, Ar), 7.93 (2 H, *d,* $^{3}J = 8.0$ Hz, Ar), 8.10 (2 H, *dd,* $^{3}J = 8.6$, 5.6 Hz, Ar).^{13}C NMR (125 MHz, $CDCl_3$): 115.5 (*d*, $^{2}J_{C\text{-}F} = 21.9$ Hz), 123.4 (2 CH), 127.8 (*d*, $^{4}J_{C\text{-}F} = 3.2$ Hz), 128.1 (*d*, $^{3}J_{C\text{-}F} = 8.3$ Hz), 128.2 (CH), 128.6 (2 CH), 138.3 (C), 156.9 (C=N), 157.4 (C=N), 157.8 (C=N), 163.5 (*d*, $^{1}J_{C\text{-}F} = 250$ Hz). Anal. Calc. for $C_{15}H_{13}FN_6$: (296.12): C, 60.80; H, 4.42; N, 28.36%.

3-(4-Fluorophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-amine (8c)

Yield: 0.13 g (49%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 5.02$ (2 H, br, NH_2), 7.11 (2 H, *d*, $^{3}J = 8.6$ Hz, Ar), 7.42 (1 H, *t*, $^{3}J = 7.7$ Hz, Ar), 7.53 (2 H, *t*, $^{3}J = 7.7$ Hz, Ar), 7.58 (2 H, *d,* $^{3}J = 7.7$ Hz, Ar), 8.04 (2 H, *dd,* $^{3}J = 8.4$, 5.5 Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta_C = 115.3$ (*d*, $^{2}J_{C\text{-}F} = 21.9$ Hz), 123.6 (2 CH), 126.5 (CH), 127.2 (*d*, $^{4}J_{C\text{-}F} = 3.2$ Hz), 127.9 (*d*, $^{3}J_{C\text{-}F} = 8.3$ Hz), 129.8 (2 CH), 136.8 (C), 154.2 (C=N), 158.6 (C=N), 163.3 (*d*, $^{1}J_{C\text{-}F} = 250$ Hz). Anal. Calc. for $C_{14}H_{11}FN_4$: (254.10): C, 66.13; H, 4.36; N, 22.04%.

Formation of products 7d and 8d in 5:2 ratio

Colorless powder; mp: 197–205 °C; IR (KBr) (ν_{max}, cm^{-1}): 3430, 3304, 3201, 2921, 1610, 1590, 1552, 1381, 755. MS: *m/z* (%) = 292 (M^+, 1), 250 (M^+, 1), 275 (5), 208 (20), 174 (50), 105 (20), 91 (100), 77 (40).

2-[1-Phenyl-3-(*p*-tolyl)-1*H*-1,2,4-triazol-5-yl]guanidine (7d)

Yield: 0.172 g (59%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 2.41$ (3 H, *s,* Me), 6.90 (4 H, br, 2 NH_2), 7.25–7.29 (3 H, *m*, Ar), 7.44 (2 H, *t*, $^{3}J = 7.9$ Hz, Ar), 7.96 (2 H, *d*, $^{3}J = 8.0$ Hz, Ar), 8.02 (2 H, *d,* $^{3}J = 8.0$ Hz, Ar).^{13}C NMR (125 MHz, $CDCl_3$): 21.4 (Me), 123.5 (2 CH), 126.0 (2 CH), 126.4 (CH), 128.6 (2 CH), 128.7 (C), 129.1 (2 CH), 134.5 (C), 138.7 (C), 157.1 (C=N), 157.6 (C=N), 157.8 (C=N). Anal. Calc. for $C_{16}H_{16}N_6$: (292.14): C, 65.74; H, 5.52; N, 28.75%.

1-Phenyl-3-(*p*-tolyl)-1*H*-1,2,4-triazol-5-amine (8d)

Yield: 0.069 g (32%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta_H = 2.41$ (3 H, *s,* Me), 5.82 (2 H, br, NH_2), 7.28 (2 H, *t*, $^{3}J = 7.5$ Hz, Ar), 7.42 (1 H, *t*, $^{3}J = 7.3$ Hz, Ar), 7.53 (2 H, *t*, $^{3}J = 8.0$ Hz, Ar), 7.59 (2 H, *d,* $^{3}J = 7.9$ Hz, Ar), 7.96 (2 H, *d,* $^{3}J = 8.0$ Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 21.4 (Me), 123.4 (2 CH), 126.1 (2 CH), 128.1 (CH), 129.0 (C), 129.2 (2 CH), 129.8 (2 CH), 135.1 (C), 138.4 (C), 154.0 (C=N), 159.5 (C=N). Anal. Calc. for $C_{15}H_{14}N_4$: (250.12): C, 71.98; H, 5.64; N, 22.38%.

2-[3-(4-Nitrophenyl)-1-phenyl-1*H*-1,2,4-triazol-5-yl] guanidine (7e)

Yellow powder, m.p.: 189–192 °C; Yield: 0.26 g (82%). IR (KBr) (ν_{max}, cm^{-1}): 3320, 3251, 1629, 1597, 1504, 1337, 1256, 1102, 501. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta_H = 7.00$ (4 H, br, 2 NH_2), 7.28 (1 H, *t*, $^{3}J = 7.4$ Hz, Ar), 7.46 (2 H, *t*, $^{3}J = 8.0$ Hz, Ar), 8.13 (2 H, *d,* $^{3}J = 7.9$ Hz, Ar), 8.25–7.32 (4 H, *m*, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta_C = 122.0$ (2 CH), 124.0 (2 CH), 125.9 (CH), 126.5 (2 CH), 128.6 (2 CH), 137.4 (C), 138.5 (C), 147.3 (C), 154.8 (C=N), 158.5 (C=N), 158.9 (C=N). MS: *m/z* (%) = 323 (M^+, 1), 306 (15), 281 (12), 231 (11), 91 (100), 77 (5). Anal. Calcd for $C_{15}H_{13}N_7O_2$ (323.11): C, 55.72; H, 4.05; N, 30.33%.

2-[3-(4-Chlorophenyl)-1-(4-nitrophenyl)-1*H*-1,2,4 -triazol-5-yl]guanidine (7f)

Yellow powder, m.p.: 227–230 °C; Yield: 0.28 g (78%). IR (KBr) (ν_{max}, cm^{-1}): 3318, 3241, 1633, 1597, 1503, 1333, 1258, 1102, 842. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta_H = 7.15$ (4 H, br, 2 NH_2), 7.53 (2 H, *d*, $^3J = 8.5$ Hz, Ar), 8.07 (2 H, *t*, $^3J = 8.5$ Hz, Ar), 8.28 (2 H, *d*, $^3J = 9.3$ Hz, Ar), 8.65 (2 H, *d*, $^3J = 9.3$ Hz, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta_C = 120.6$ (2 CH), 124.4 (2 CH), 127.7 (2 CH), 128.7 (2 CH), 129.6 (C), 134.0 (C), 143.5 (C), 143.8 (C), 156.7 (C=N), 158.8 (C=N), 159.7 (C=N). MS: *m/z* (%) = 357 (M^+, 1), 294 (33), 281 (10), 262 (8), 91 (100), 77 (10). Anal. Calcd for $C_{15}H_{12}ClN_7O_2$ (357.07): C, 50.36; H, 3.38; N, 27.41%.

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