Copper(I) Iodide Catalyzed Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from *anti*-3-Aryl-2,3-dibromopropanoic Acids and Organic Azides

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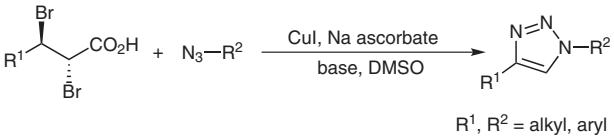
Abstract: A series of 1,4-disubstituted 1,2,3-triazoles were synthesized in a one-pot process from *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides in dimethyl sulfoxide with inexpensive copper (I) iodide as the catalyst.

Key words: cyclizations, heterocycles, azides, triazoles

Click chemistry was developed at the beginning of the 21st century from the Huisgen 1,3-dipolar cycloaddition of azides to alkynes.[1] Since then, the synthesis of 1,2,3-triazoles has become important in medical,[2] materials,[3] and biological[4] research. Further interest in this reaction stems from the interesting biological activities of 1,2,3-triazoles, including their antibacterial,[5] herbicidal, fungicidal,[6] anti-allergic,[7] and anti-HIV[8] properties. Recently, the use of 1,2,3-triazoles as catalysts and ligands in transition-metal catalysis systems has also been reported.[9] The rapidly increasing number of requirements for the synthesis of these heterocycles has led to a need to develop effective methods for the preparation of diverse 1,2,3-triazole derivatives.

Although there are numerous methods for the preparation of 1,4-disubstituted 1,2,3-triazoles,[10] the starting materials are mainly terminal alkynes that need to be prepared and isolated separately.[11] Hence, a method that eliminates the need to isolate the terminal alkynes is desirable.[12] The generation of terminal alkynes in situ from suitable precursors, followed by the reaction with azides in a one-pot process to form the corresponding 1,2,3-triazoles would avoid the difficulties associated with the volatile nature of terminal alkynes.

Our group recently reported[13] an interesting one-pot synthesis of 4-aryl-1*H*-1,2,3-triazoles from easily available *anti*-3-aryl-2,3-dibromopropanoic acids and sodium azide by using a catalyst system consisting of tris(benzylideneacetone)dipalladium and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (Xantphos).[13] Later, the reaction conditions were simplified by using inexpensive copper(I) iodide as the catalyst, and the reaction times were reduced to four hours.[14] Inspired by these results, we attempted to expand the scope of the reaction by using a series of substituted *anti*-3-aryl-2,3-dibromopropanoic acids and organic azides. In the current study, we examined the synthesis of 1,4-disubstituted 1,2,3-triazoles from easily available *anti*-3-aryl-2,3-dibromopropanoic acids with copper(I) iodide as the catalyst (Scheme 1). In this reaction, the *anti*-3-aryl-2,3-dibromopropanoic acids served as precursors of terminal alkynes and underwent direct reaction with organic azides in a one-pot process.



Scheme 1 One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles

To determine the optimal reaction conditions, we used *anti*-2,3-dibromo-3-(4-tolyl)propanoic acid (**1a**) and 4-tolyl azide (**2a**) as model substrates. We initially chose the inorganic compounds potassium carbonate and cesium carbonate as bases, and dimethyl sulfoxide and *N*,*N*-dimethylformamide as solvents. When the reaction was performed at 110 °C for twelve hours, the products were isolated in moderate yields (Table 1, entries 1–3). We also examined several organic bases. No product was obtained when triethylamine was used (entry 4) but, interestingly, an excellent yield of 85% was obtained when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used at 80 °C for three hours (entry 5). When the solvent used was changed to *N*,*N*-dimethylformamide instead of dimethyl sulfoxide, the yield fell markedly to 70% (entry 6). At room temperature, a surprisingly moderate yield of product **3a** (70%) was obtained (entry 7).The reaction proceeded most efficiently and was completed within three hours when it was promoted by copper(I) iodide (20 mol%) and sodium ascorbate (40 mol%) and when DBU (3 equivalents) was used as the base, and dimethyl sulfoxide was used as the solvent at 80 °C (entry 5).

Having identified the optimal conditions, we examined the substrate scope of the copper(I) catalyzed-catalyzed synthesis of 1,4-disubstituted-1,2,3-triazoles (Table 2). The necessary *anti*-3-aryl-2,3-dibromopropanoic acids were easily prepared by bromination of the corresponding *trans*-α,β-unsaturated carboxylic acids,[15] and the organic azides were obtained from the corresponding organic amine or organic halide.[16] The results summarized in Table 2 show that the method can be used for the synthe-

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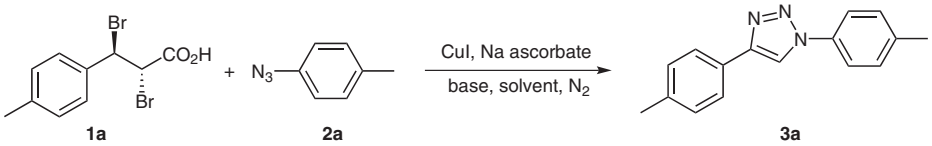
Table 1 Screening for Optimal Reaction Conditions



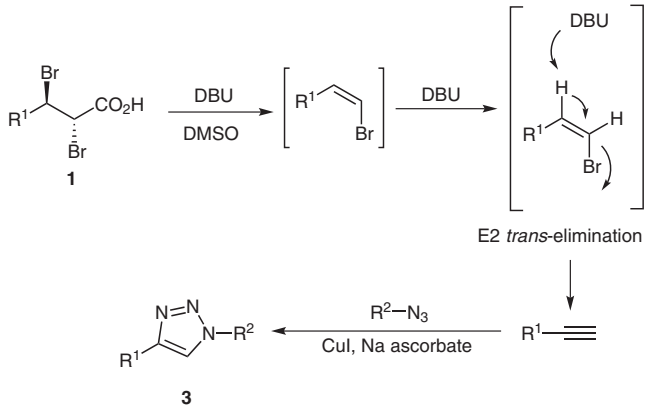
1a 2a 3a

Entry[a]	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	K_2CO_3	DMSO	110	12	54
2	Cs_2CO_3	DMSO	110	12	60
3	Cs_2CO_3	DMF	110	12	56
4	Et_3N	DMSO	80	3	0
5	**DBU**	**DMSO**	**80**	**3**	**85**
6	DBU	DMF	80	3	70
7	DBU	DMSO	25	3	70

[a] **1a** (0.5 mmol), **2a** (1.5 equiv), base (3 equiv), CuI (20 mol%), Na ascorbate (40 mol%), solvent (4 mL), under N_2.
[b] Isolated yield based on **1a**.

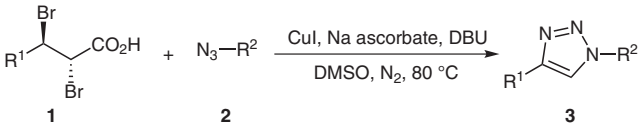
sis of 1,4-disubstituted 1,2,3-triazoles carrying either an electron-donating substituent (such as methyl, isopropyl, *tert*-butyl, or methoxy; entries 1–3 and 9) or an electron-withdrawing group (entries 4–8) as the R^1 or R^2 group. Notably, pyridyl- and alkyl-substituted products were also smoothly obtained in moderate-to-excellent yields (entries 10–12). Moreover, the yield was not significantly decreased by steric congestion. Substrates bearing an electron-donating or an electron-withdrawing group at the *para*-, *meta*-, or *ortho*- position all gave the corresponding 1,4-disubstituted 1,2,3-triazoles in good-to-excellent yields (entries 1–9).

To study the mechanism of the reaction, we carried out a control experiment with **1a** in the absence of the azide partner and we obtained the corresponding terminal alkyne in 93% yield. This suggests that an aralkyne is generated in situ in the one-pot reaction. The proposed reaction pathway is shown in Scheme 2. The reaction probably proceeds by the initial *trans*-elimination reaction of the *anti*-3-aryl-2,3-dibromopropanoic acid **1**, involving a simultaneous loss of carbon dioxide and bromide ions, to generate the intermediate (*Z*)-β-arylvinyl bromide. A subsequent E2 *trans*-elimination gives the terminal alkyne. A copper-catalyzed [3+2] cycloaddition of the aralkyne with azide **2** then gives the 1,4-disubstituted 1,2,3-triazole **3**.



Scheme 2 Mechanism of the one-pot reaction

Table 2 Copper(I) Iodide Catalyzed Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from *anti*-3-Aryl-2,3-dibromopropanoic Acids and Organic Azides



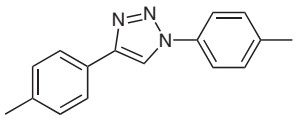
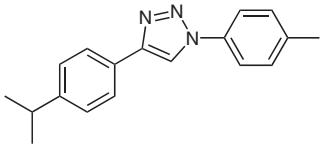
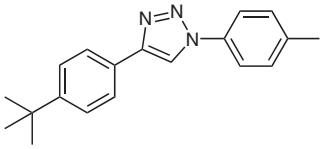
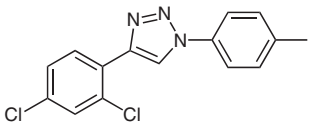
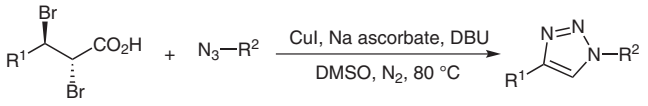
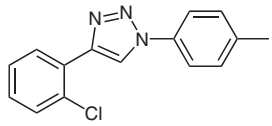
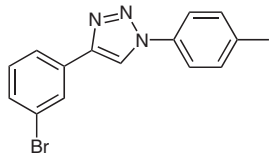
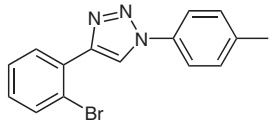
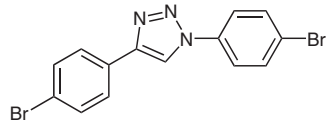
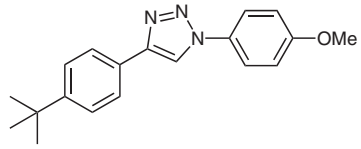
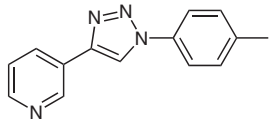
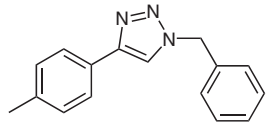
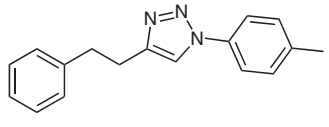
Entry[a]	Product	Yield (%)[b]
1	 **3a**	85
2	 **3b**	85
3	 **3c**	86
4	 **3d**	73

Table 2 Copper(I) Iodide Catalyzed Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from *anti*-3-Aryl-2,3-dibromopropanoic Acids and Organic Azides (continued)



1 2 3

Entry[a]	Product	Yield (%)[b]
5	 **3e**	76
6	 **3f**	80
7	 **3g**	75
8	 **3h**	71
9	 **3i**	70
10	 **3j**	72
11	 **3k**	90
12	 **3l**	62

[a] **1** (0.5 mmol), **2** (0.75 mmol), DBU (1.5 mmol), CuI (0.1 mmol), Na ascorbate (0.2 mmol), DMSO (4 mL), under N_2, 80 °C, 3 h.
[b] Isolated yield based on substrate **1**.

In conclusion, we have demonstrated a simple and efficient one-pot method for the preparation of 1,4-disubstituted 1,2,3-triazoles **3** from *anti*-3-aryl-2,3-dibromopropanoic acids **1** and organic azides **2**. The catalyst is inexpensive copper(I) iodide and moderate-to-excellent yields are obtained. The process has considerable advantages in terms of its use of easily available substrates, its product diversity, and its mild reaction conditions. The simplicity of the reaction procedure and the moderate-to-excellent yields are also advantageous. The method provides access to various 1,4-disubstituted 1,2,3-triazoles, important in medical, materials, and biological research.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer in $CDCl_3$ with TMS as the internal standard. Melting points were recorded on a WRS-2A micro melting-point apparatus and are uncorrected. A Nicolet AVATAR 360 FT-IR spectrophotometer was used to record the IR spectra. Commercially sourced reagents were used without additional purification. All reactions were conducted under N_2 and were monitored by TLC on HuanghaiGF 254 silica gel coated plates. Column chromatography was carried out by using 300–400 mesh silica gel at medium pressure. The *anti*-3-aryl-2,3-dibromopropanic acids **1** and organic azides **2** were synthesized by the procedures reported in the literature.[15,16] (**CAUTION!** Aryl azides are poisonous and potentially explosive if subjected to heat, light, or pressure. Any azides synthesized should be stored in darkness at below 0 °C.)

1,4-Disubstituted 1,2,3-Triazoles (3a–3l); General Procedure

A soln of acid **1** (0.5 mmol), azide **2** (0.75 mmol), DBU (228 mg, 1.5 mmol), CuI (19 mg, 0.1 mmol), and Na ascorbate (39.6 mg, 0.2 mmol) in DMSO (4 mL) was placed in a sealed tube and stirred under N_2 for 5 min, then heated to 80 °C for 3 h. The mixture then was allowed to cool to r.t. and the reaction was quenched with H_2O (25 mL). The mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine (3 × 10 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude product that was purified by column chromatography (silica gel; EtOAc–PE).

1,4-Bis(4-tolyl)-1*H*-1,2,3-triazole (3a)[17]

Yield: 105 mg (85%); yellow solid; mp 197.5–198.5 °C (Lit.[17] 196–199 °C).

IR (KBr): 3108, 3023, 2917, 2858, 1520, 1497, 1226, 1040, 815 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.80 (d, *J* = 8.1 Hz, 2 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 2.44 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.3, 138.8, 138.3, 134.9, 130.3, 129.6, 127.5, 125.8, 120.4, 117.3, 21.3, 21.1.

ESI-MS: *m/z* (%) = 249 [M^+].

4-(4-Isopropylphenyl)-1-(4-tolyl)-1*H*-1,2,3-triazole (3b)

Yield: 118 mg (85%); yellow solid; mp 174.6–175.6 °C.

IR (KBr): 3124, 3108, 2962, 2924, 2871, 1517, 1493,1226, 1040, 841, 818 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 7.67 (d, *J* = 8.4Hz, 2 H), 7.35–7.31 (m, 4 H), 2.99–2.92 (m, 1 H), 2.44 (s, 3 H), 1.29 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.3, 148.3, 138.9, 134.9, 130.3, 127.8, 127.0, 125.9, 120.4, 117.3, 34.0, 23.9, 21.1.

ESI-MS: *m/z* (%) = 277 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3$: 278.1657; found: 278.1658.

4-(4-*tert*-Butylphenyl)-1-(4-tolyl)-1*H*-1,2,3-triazole (3c)
Yield: 125 mg (86%); yellow solid; mp 187.7–188.4 °C.

IR (KBr): 3127, 2965, 2865, 1517, 1495, 1226, 1037, 840, 817 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 2.44 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.5, 148.3, 138.8, 134.9, 130.3, 127.5, 125.8, 125.6, 120.4, 117.3, 34.7, 31.3, 21.1.

ESI-MS: *m/z* (%) = 291 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{22}N_3$: 292.1814; found: 292.1813.

4-(2,4-Dichlorophenyl)-1-(4-tolyl)-1*H*-1,2,3-triazole (3d)
Yield: 110 mg (73%); white solid; mp 140.7–141.7 °C.

IR (KBr): 3182, 3093, 2921, 2854, 1548, 1518, 1467, 1375, 1221, 1103, 1043, 819, 803 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.57 (s, 1 H), 8.29 (d, *J* = 8.5 Hz, 1 H), 7.68 (d, *J* = 8.3 Hz, 2 H), 7.51 (d, *J* = 2.0 Hz, 1 H), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.35 (d, *J* = 8.3 Hz, 2 H), 2.45 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.6, 139.2, 134.6, 134.4, 131.7, 130.7, 130.3, 130.0, 127.7, 121.2, 120.6, 21.2.

ESI-MS: *m/z* (%) = 303 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}{}^{35}Cl_2N_3$: 304.0410; found: 304.0409.

4-(2-Chlorophenyl)-1-(4-tolyl)-1*H*-1,2,3-triazole (3e)
Yield: 102 mg (76%); white solid; mp 104.5–105.2 °C.

IR (KBr): 3187, 2924, 1548, 1518, 1470, 1403, 1218, 1120, 1041, 811, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.59 (s, 1 H), 8.32 (d, *J* = 7.4 Hz, 1 H), 7.69 (d, *J* = 7.2 Hz, 2 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.43–7.29 (m, 4 H), 2.45 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.5, 139.0, 134.8, 131.3, 130.3, 130.0, 129.2, 129.0, 127.2, 121.3, 120.6, 21.1.

ESI-MS: *m/z* (%) = 269 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}{}^{35}ClN_3$: 270.0799; found: 270.0798.

4-(3-Bromophenyl)-1-(4-tolyl)-1*H*-1,2,3-triazole (3f)
Yield: 125 mg (80%); yellow solid; mp 153.9–154.8 °C.

IR (KBr): 3122, 2917, 1602, 1565, 1518, 1472, 1399, 1225, 1072, 1043, 816, 790, 685 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 8.06 (s, 1 H), 7.85 (d, *J* = 7.7 Hz, 1 H), 7.66 (d, *J* = 8.3 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.36–7.31 (m, 3 H), 2.45(s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 139.1, 134.6, 132.4, 131.3, 130.5, 130.3, 128.8, 124.4, 123.0, 120.5, 118.0, 21.1.

ESI-MS: *m/z* (%) = 315 [M + 2]$^+$, 313 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}{}^{79}BrN_3$: 314.0294; found: 314.0292.

4-(2-Bromophenyl)-1-(4-tolyl)-1*H*-1,2,3-triazole (3g)
Yield: 117 mg (75%); yellow solid; mp 95.9–96.8 °C.

IR (KBr): 3157, 3061, 2919, 1517, 1465, 1403, 1222, 1048, 1022, 814, 764 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1 H), 8.19 (d, *J* = 7.9 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 3 H), 7.47–7.43 (m, 1 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.24–7.22 (m, 1 H), 2.45(s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.8, 139.1, 134.7, 133.6, 131.0, 130.7, 130.3, 129.6, 127.8, 121.2, 121.1, 120.6, 21.2.

ESI-MS: *m/z* (%) = 315 [M + 2]$^+$, 313 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{13}{}^{79}BrN_3$: 314.0294; found: 314.0292.

1,4-Bis(4-bromophenyl)-1*H*-1,2,3-triazole (3h)
Yield: 135 mg (71%); yellow solid; mp 164.7–164.5 °C.

IR (KBr): 3121, 2922, 2851, 1592, 1471, 1224, 1074, 1040, 1012, 815 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.98 (s, 1 H), 7.80–7.75 (m, 3 H), 7.61–7.59 (m, 3 H), 7.45–7.41 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9, 132.2, 131.9, 131.2, 128.9, 127.4, 123.6, 123.4, 122.6, 119.0, 117.6.

ESI-MS: *m/z* (%) = 379 [M + 2]$^+$, 377 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{10}{}^{79}Br_2N_3$: 377.9242; found: 377.9241.

4-(4-*tert*-Butylphenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (3i)
Yield: 107 mg (70%); yellow solid; mp 183.6–184.5 °C.

IR (KBr): 3140, 2959, 2863, 1523, 1493, 1452, 1260, 1233, 1047, 1034, 836 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.83 (d, *J* = 7.5 Hz, 2 H), 7.69 (d, *J* = 7.8 Hz, 2 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 7.04 (d, *J* = 7.9 Hz, 2 H), 3.88 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.8, 151.5, 148.2, 130.6, 127.6, 125.8, 125.6, 122.2, 117.5, 114.8, 55.7, 34.7, 31.3.

ESI-MS: *m/z* (%) = 307 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{22}N_3O$: 308.1763; found: 308.1764.

3-[1-(4-Tolyl)-1*H*-1,2,3-triazol-4-yl]pyridine (3j)
Yield: 85 mg (72%); white solid; mp 175.9–176.2 °C.

IR (KBr): 3140, 3051, 2959, 1523, 1493, 1260, 1233, 1047, 1034, 836 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.08 (s, 1 H), 8.62 (s, 1 H), 8.31–8.25 (m, 2 H), 7.68 (d, *J* = 7.5 Hz, 2 H), 7.42–7.35 (m, 3 H), 2.45(s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9, 147.1, 145.2, 139.3, 134.6, 133.2, 130.4, 126.6, 123.9, 120.5, 118.0, 21.1.

ESI-MS: *m/z* (%) = 236 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}N_4$: 237.1140; found: 237.1141.

1-Benzyl-4-(4-tolyl)-1,2,3-1*H*-triazole (3k)[18]
Yield: 112 mg (90%); white solid; mp 154.2–155.0 °C.

IR (KBr): 3143, 3018, 2975, 1496, 1457, 1348, 1223, 1047, 828 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.5 Hz, 2 H), 7.62 (s, 1 H), 7.38–7.32 (m, 5 H), 7.21 (d, *J* = 7.1 Hz, 2 H), 5.57 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.3, 138.0, 134.8, 129.5, 129.2, 128.8, 128.1, 127.7, 125.6, 119.2, 54.2, 21.3.

ESI-MS: *m/z* (%) = 249 [M^+].

1-(4-Methoxyphenyl)-4-(2-phenylethyl)-1*H*-1,2,3-triazole (3l)
Yield: 82 mg (62%); yellow solid; mp 112.8–113.7 °C.

IR (KBr): 3116, 3073, 3031, 2922, 2856, 1518, 1496, 1453, 1384, 1222, 1049, 821, 725, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 3 H), 7.25–7.13 (m, 7 H), 3.09 (t, *J* = 7.1 Hz, 2 H), 2.99 (t, *J* = 7.1 Hz, 2 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.7, 141.0, 138.7, 134.9, 130.2, 128.5, 128.4, 126.2, 120.4, 119.3, 35.5, 27.4, 21.1.

ESI-MS: *m/z* (%) = 263 [M^+].

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3$: 264.1500; found: 264.1501.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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