Copper(I) Iodide-Catalyzed Synthesis of 4-Aryl-1*H*-1,2,3-triazoles from *anti*-3-Aryl-2,3-dibromopropanoic Acids and Sodium Azide

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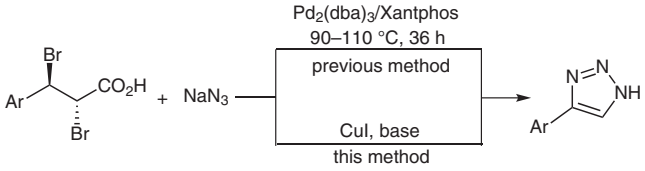
Abstract: 4-Aryl-1*H*-1,2,3-triazoles were synthesized from *anti*-3-aryl-2,3-dibromopropanoic acids and sodium azide by using inexpensive copper(I) iodide as the catalyst in dimethyl sulfoxide.

Key words: cyclizations, catalysis, heterocycles, azides, triazoles

Since the development of 'click chemistry' from the Huisgen 1,3-dipolar cycloaddition of azides and alkynes in the early 2000s,[1] the synthesis of 1,2,3-triazoles has grown in importance in medicinal,[2] materials,[3] and biological[4] research. Furthermore, a number of these compounds show a broad spectrum of biological activities, displaying, for example, antibacterial,[5] herbicidal, fungicidal,[6] antiallergic,[7] or anti-HIV[8] properties. Recently, 1,2,3-triazoles have also been used as catalysts and ligands in transition metal-based catalyst systems.[9] The rapidly growing demand for these heterocycles necessitates the development of effective methods for the preparation of a range of 1,2,3-triazole derivatives.

Although the vigorous 'click chemistry' of copper(I)-catalyzed [3+2]-cycloaddition reactions of organic azides and terminal alkynes is capable of producing 1,4-disubstituted 1,2,3-triazoles regioselectively under mild conditions,[10] it has a limitation in that it has a reduced efficiency in the case of inorganic azides. As a result, 4-monosubstituted 1*H*-1,2,3-triazoles cannot be prepared directly by means of a click-chemistry strategy, and their preparation requires a sequence involving deprotection steps and the use of more elaborate azides.[11] Other routes to 1*H*-1,2,3-triazoles include dipolar cycloadditions between sodium azide and alkynes bearing electron-withdrawing substituents,[12] the reactions of sodium azide with nitroalkenes,[13] and the rearrangement of propargyl azides.[14]

In 2006, Barluenga and co-workers[15] reported a new method for the synthesis of 1*H*-triazoles from (*E*)-β-arylvinyl bromides and sodium azide catalyzed by a tris(dibenzylideneacetone)dipalladium/Xantphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] catalyst system. This efficient transformation affords 4-aryl-1*H*-1,2,3-triazoles in near-quantitative yields. Recently, we reported an interesting one-pot synthesis of 4-aryl-1*H*-1,2,3-triazoles from readily available *anti*-3-aryl-2,3-dibromopropanoic acids and sodium azide using the same catalyst system.[16] Both these methods require expensive catalysts and suffer from long reaction times. We now report our recent studies on the synthesis of 4-aryl-1*H*-1,2,3-triazoles from readily available *anti*-3-aryl-2,3-dibromopropanoic acids by using inexpensive copper(I) iodide as a catalyst to give reaction times of as little as four hours (Scheme 1).



Scheme 1

To identify suitable reaction conditions, we used *anti*-2,3-dibromo-3-phenylpropanoic acid (**1a**) as a model substrate with sodium azide. Initially, toluene and dioxane were chosen as solvents and the reaction was performed at 110 °C for 24 hours with potassium carbonate as the base. Products were isolated, albeit in somewhat low yields, when a catalyst system consisting of 10% copper(I) iodide and 20% of sodium ascorbate was used (Table 1, entries 1–2). We obtained moderate yields in shorter reaction times of six to eight hours when *N*,*N*-dimethylformamide was used as the solvent (Table 1, entries 3–4). To our delight, the yield increased to 65% when the reaction was conducted in dimethyl sulfoxide with potassium carbonate as the base (Table 1, entry 5). Inspired by this result, we examined other bases such as cesium carbonate, tripotassium phosphate, and potassium bicarbonate in dimethyl sulfoxide. Cesium carbonate was identified as the best base (Table 1, entries 6–8). The necessity of the using copper(I) iodide was obvious, as no product was obtained in its absence (Table 1, entry 10). On the other hand, sodium ascorbate also appeared to play an important role in the reaction, as the yield decreased in its absence (Table 1, entry 9). This may be because the copper(I) species is stabilized by sodium ascorbate in the system. As expected, only a trace of product was obtained when the temperature was reduced to 90 °C, even after twenty-four hours (Table 1, entry 11). In addition, adding more equivalents of copper(I) iodide and sodium ascorbate appeared to be unnecessary, whereas reducing the quantities of copper(I) iodide and sodium ascorbate lowered the yield (Table 1,

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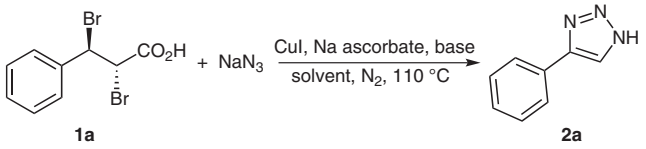
entries 12–13). The reaction proceeded most efficiently and was complete in four hours when it was promoted by copper(I) iodide (10%) and sodium ascorbate (20%) in the presence of 2.5 equivalents of cesium carbonate as the base in dimethyl sulfoxide at 110 °C (Table 1, entry 8).

Table 1 Optimization of the Conditions for the Conversion of Acid **1a** into Triazole **2a**



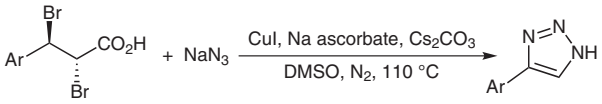
1a **2a**

Entry[a]	Solvent	Base	Time (h)	Yield (%)[b]
1	toluene	K_2CO_3	24	18
2	dioxane	K_2CO_3	12	32
3	DMF	K_2CO_3	8	56
4	DMF	Cs_2CO_3	6	60
5	DMSO	K_2CO_3	6	65
6	DMSO	K_3PO_4	8	40
7	DMSO	$KHCO_3$	10	38
8	DMSO	Cs_2CO_3	4	76
9[c]	DMSO	Cs_2CO_3	4	68
10[d]	DMSO	Cs_2CO_3	4	0
11[e]	DMSO	Cs_2CO_3	24	trace
12[f]	DMSO	Cs_2CO_3	4	70
13[g]	DMSO	Cs_2CO_3	10	55

[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.5 mmol), NaN_3 (1.3 equiv), base (2.5 equiv), CuI (10%), Na ascorbate (20%), solvent (3 mL), 110 °C, N_2 atmosphere.
[b] Isolated yields based on **1a**.
[c] The reaction was conducted in the absence of Na ascorbate.
[d] The reaction was conducted in the absence of both CuI and Na ascorbate.
[e] The reaction was conducted at 90 °C.
[f] 20% CuI and 40% Na ascorbate were used.
[g] 5% CuI and 10% Na ascorbate were used.

Having identified the optimal conditions, we examined the substrate scope of this copper(I) iodide catalyzed synthesis of 4-aryl-1*H*-1,2,3-triazoles, and we found that these conditions appeared to be general for a broad spectrum of *anti*-3-aryl-2,3-dibromopropanoic acids (Table 2). The starting *anti*-3-aryl-2,3-dibromopropanoic acids were readily prepared by bromination of the corresponding *trans*-α,β-unsaturated carboxylic acids.[17] The results summarized in Table 2 show that the present method can be used for the synthesis of 4-aryl-1*H*-1,2,3-triazoles carrying either an electron-donating substituent, such as methyl or isopropyl (Table 2, entries 2–3), or an electron-withdrawing group, such as bromo, chloro, fluoro, trifluoromethyl, or methoxycarbonyl (Table 2, entries 4–13). Moreover, the reaction of the pyridyl-substituted substrate also proceeded smoothly, giving an excellent yield of 95% (Table 2, entry 14). Substrates bearing an electron-donating or an electron-withdrawing group at either the *para*- or the *meta*-position gave the corresponding 4-aryl-1*H*-1,2,3-triazoles in good-to-excellent yields (Table 2, entries 2–11). Although the *anti*-3-aryl-2,3-dibromopropanoic acids bearing *ortho*-substituents gave lower yields, the reactions also proceeded to completion within four hours (Table 2, entries 11–13). It is obvious that electron-withdrawing groups at either the *para*- or the *meta*- position of the substrates are favored for this method, and higher yields were achieved in these cases (Table 2, entries 4–10).

Table 2 Copper(I) Iodide Catalyzed Synthesis of 4-Aryl-1*H*-1,2,3-triazoles from *anti*-3-Aryl-2,3-dibromopropanoic Acids and Sodium Azide



1 **2**

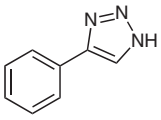
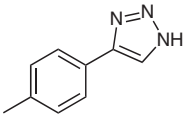
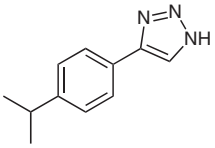
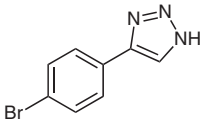
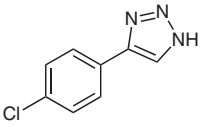
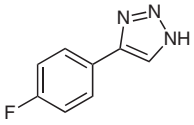
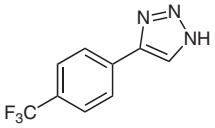
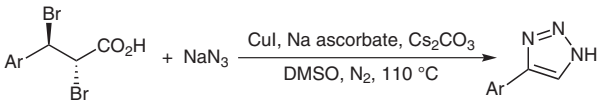
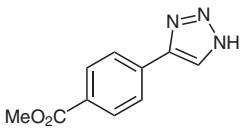
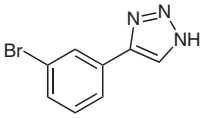
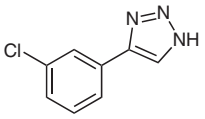
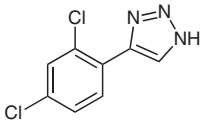
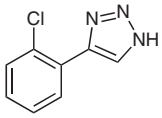
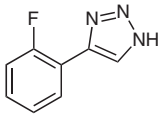
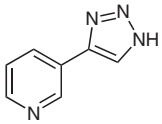
Entry[a]	Product		Yield (%)[b]
1	**2a**		76
2	**2b**		68
3	**2c**		62
4	**2d**		76
5	**2e**		83
6	**2f**		86
7	**2g**		88

Table 2 Copper(I) Iodide Catalyzed Synthesis of 4-Aryl-1*H*-1,2,3-triazoles from *anti*-3-Aryl-2,3-dibromopropanoic Acids and Sodium Azide (continued)



Entry[a]	Product		Yield (%)[b]
8	**2h**		78
9	**2i**		74
10	**2j**		82
11	**2k**		66
12	**2l**		52
13	**2m**		60
14	**2n**		95

[a] The reaction conditions were as follows: substrate **1** (0.5 mmol), NaN_3 (0.65 mmol), Cs_2CO_3 (1.25 mmol), CuI (0.05 mmol), Na ascorbate (0.1 mmol), DMSO (3 mL), 110 °C, 4 h, N_2 atmosphere.
[b] Isolated yield based on substrate **1**.

To study the mechanism, we examined the reactions of 1-ethynyl-4-methylbenzene, 1-[(*Z*)-(2-bromovinyl]-4-methylbenzene, and 1-[(*E*)-(2-bromovinyl]-4-methylbenzene under the optimized conditions. 1-Ethynyl-4-methylbenzene and 1-[(*Z*)-(2-bromovinyl]-4-methylbenzene gave isolated yields of 76% and 70%, respectively, whereas no product was observed in the case of 1-[(*E*)-(2-bromovinyl]-4-methylbenzene. This suggests that an aralkyne is generated in situ by debrominative decarboxylation of the *anti*-3-aryl-2,3-dibromopropanoic acid **1** with subsequently elimination of hydrogen bromide. The aralkyne then undergoes copper-catalyzed [3+2] cycloaddition with the azide to give the corresponding 4-aryl-1*H*-1,2,3-triazole **2**.

In summary, we have developed a simple and efficient method for the preparation of 4-aryl-1*H*-1,2,3-triazoles **2** from *anti*-3-aryl-2,3-dibromopropanoic acids **1** and sodium azide that is catalyzed by inexpensive copper(I) iodide. The products are obtained in moderate-to-excellent yields, and the reaction provides a novel access to compounds that are important in medicinal, materials, and biological research.

^{1}H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ with TMS as the internal standard by using a Bruker AM-500 spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ by using a Bruker AM-500 spectrometer. Mass spectra were recorded on a Varian-310 mass spectrometer. Commercially obtained reagents were used without further purification. All reactions were conducted under N_2 and monitored by TLC on HuanghaiGF 254 silica gel coated plates. Column chromatography was carried out on 300–400 mesh silica gel at medium pressure. The *anti*-3-aryl-2,3-dibromopropanic acids **1** were synthesized according to literature procedures.[17]

4-Aryl-1*H*-1,2,3-triazoles 2: General Procedure

A soln of *anti*-3-aryl-2,3-dibromopropanic acid **1** (0.5 mmol), NaN_3 (42 mg, 0.65 mmol), Cs_2CO_3 (408 mg, 1.25 mmol), CuI (10 mg, 0.05 mmol), and Na ascorbate (20 mg, 0.1 mmol) in DMSO (3 mL) was stirred in a sealed tube under N_2 for 5 min and then heated at 110 °C for 4 h. The mixture was allowed to cool to r.t. and then 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), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, EtOAc–hexane (1:10 to 1:2)].

4-Phenyl-1*H*-1,2,3-triazole (2a)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.83 (d, *J* = 7.1 Hz, 2 H), 7.48–7.45 (m, 2 H), 7.40–7.37 (m, 1 H).[16]

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (s, 1 H), 7.71 (d, *J* = 7.6 Hz, 2 H), 7.27 (d, *J* = 7.6 Hz, 2 H), 2.40 (s, 3 H).[16]

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 2.98–2.93 (m, 1 H), 1.29 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.7, 146.9, 129.2, 127.1, 126.2, 126.1, 34.0, 23.8.

ESI-MS: *m*/*z* (%) = 187 (100) [M^+].

HRMS (ESI): *m*/*z* [$M]^+$ calcd for $C_{11}H_{13}N_3$: 187.1111; found: 187.1110.

4-(4-Bromophenyl)-1*H*-1,2,3-triazole (2d)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.70 (d, *J* = 8.6 Hz, 2 H), 7.59 (d, *J* = 8.6 Hz, 2 H).[16]

4-(4-Chlorophenyl)-1*H*-1,2,3-triazole (2e)

^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6): δ = 7.89 (s, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 2 H).[16]

4-(4-Fluorophenyl)-1*H*-1,2,3-triazole (2f)

^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6): δ = 7.86 (s, 1 H), 7.82–7.79 (m, 2 H), 7.14–7.10 (m, 2 H).[16]

4-[4-(Trifluoromethyl)phenyl]-1*H*-1,2,3-triazole (2g)
^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6): δ = 8.01–7.94 (m, 3 H), 7.69 (d, *J* = 8.2 Hz, 2 H).[18]

Methyl 4-(1*H*-1,2,3-triazol-4-yl)benzoate (2h)
^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6): δ = 8.08 (d, *J* = 8.3 Hz, 2 H), 7.93 (s, 1 H), 7.87 (d, *J* = 8.3 Hz, 2 H), 3.93 (s, 3 H).[16]

4-(3-Bromophenyl)-1*H*-1,2,3-triazole (2i)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.99 (s, 1 H), 7.76 (d, *J* = 7.7 Hz, 1 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 7.34–7.31 (m, 1 H).[19]

4-(3-Chlorophenyl)-1*H*-1,2,3-triazole (2j)
^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6): δ = 7.87 (s, 1 H), 7.77 (s, 1 H), 7.64 (s, 1 H), 7.32–7.29 (m, 1 H), 7.23 (d, *J* = 7.2 Hz, 1 H).[20]

4-(2,4-Dichlorophenyl)-1*H*-1,2,3-triazole (2k)
^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6): δ = 8.19 (s, 1 H), 7.92 (br s, 1 H), 7.48 (s, 1 H), 7.34 (d, *J* = 8.3 Hz, 1 H).[18]

4-(2-Chlorophenyl)-1*H*-1,2,3-triazole (2l)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 7.93 (dd, *J* = 1.3, 7.7 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.38–7.31 (m, 2 H).[16]

4-(2-Fluorophenyl)-1*H*-1,2,3-triazole (2m)
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 3.5 Hz, 1 H), 8.10–8.07 (m, 1 H), 7.38–7.34 m, 1 H), 7.27–7.24 (m, 1 H), 7.21–7.17 (m, 1 H).[18]

3-(1*H*-1,2,3-Triazol-4-yl)pyridine (2n)
^{1}H NMR (500 MHz, $CDCl_3$–DMSO-d_6) δ = 9.06 (s, 1 H), 8.57 (s, 1 H), 8.15–8.14 (d, *J* = 2.0 Hz, 1 H), 7.99 (d, *J* = 1.8 Hz, 1 H), 7.41–7.38 (m, 1 H).[16]

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