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## Catalysis

# Copper-Catalyzed Cascade Cyclization Reaction of 2-Haloaryltriazenes and Sodium Azide: Selective Synthesis of 2*H*-Benzotriazoles in Water

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**Abstract:** A new approach to the synthesis of 2*H*-benzotriazoles is described. This strategy is based on the copper-catalyzed C–N coupling of 2-haloaryltriazenes or 2-haloazo compounds with sodium azide and the intramolecular addition of nitrene to N=N bonds. This approach allows the synthesis of various *N*-amino- and *N*-aryl-2*H*-benzotriazoles in water, in good to excellent yields. The procedure is simple and the starting materials and catalyst are easily available, offering a practical and convenient synthetic route to 2-substituted benzotriazoles.

Benzo[1,2,3]triazole derivatives are important nitrogen-containing heterocyclic compounds. They have been widely used in material science,[1] synthetic organic chemistry,[2] pharmaceutical chemistry, and agricultural chemistry[3] owing to high reactivity, interesting structures, and anticancer properties. Benzo[1,2,3]triazole exists as $N_1$-, $N_2$-, and $N_3$-substituted isomers; the 1*H* isomer is predominant because of its stability.

Aryl-1*H*-benzo[*d*][1,2,3]triazole can be reliably and conveniently prepared from the [3+2] annulation reactions of arynes with organic azides,[4] the reaction of (*Z*)-1-aryl-3-hexen-1,5-diynes with sodium azide,[5] the intramolecular cyclization of 2-haloaryltriazenes through copper-catalyzed C–N coupling,[6] and 1,7-palladium migration by means of C–H activation followed by intramolecular amination.[7] However, to the best of our knowledge, there are few reports on the direct and regioselective preparation of 2*H*-benzotriazole derivatives. The direct N-arylation of unsubstituted benzotriazole with benzyne proceeded well, but afforded a 1:3.5 mixture of $N_2$- and $N_1$-arylation products.[8] Recently, regioselective alkynylation at the 2-position of benzotriazole, giving 2-silylethynyl-2*H*-1,2,3-benzotriazoles as the major products, was achieved by using silylethynyliodonium triflates as the alkynylating agents.[9]

The azido group can function as a nitrene precursor and participate in intramolecular annulation reactions. Examples include rhodium-catalyzed intramolecular cyclization reactions of 2-azidoarylalkenes,[10] gold-catalyzed intramolecular nucleophilic addition of *ortho*-azidophenylalkyne,[11] and CuI-mediated cascade-cyclization of a range of substituted 1-(2-azidophenyl)-3-alkenylallenes, leading to various substituted indoles and cyclopentannelated indoles.[12] The synthesis of 2-azidoarylimines, generated from *N*-(2-bromobenzylidene)anilines and sodium azide in the presence of a copper catalyst, has been applied to the synthesis of indazoles.[13] An iron(II)-catalyzed transformation of aryl and vinyl azides, with ketone or methyl oxime, into 2,1-benzisoxazoles, indazoles, or pyrazoles through the formation of an N–O or N–N bond has also been reported.[14]

Aryl azides can be prepared through CuI-catalyzed C–N coupling of aryl halides and sodium azide.[15] We envisioned that the intramolecular annulation of 2-azidoaryltriazene or 2-azidoarylazo compounds, generated from the C–N cross-coupling reaction of 2-halotriazene or 2-haloazo compounds with sodium azide, could occur by means of a reaction between the nitrene species and the N=N bond, after releasing one molecule of $N_2$. Thus, benzotriazoles could be produced with the retention of the substituents at the 2-position. Herein, we describe a cascade reaction between 2-haloaryltriazene and sodium azide to form substituted 2*H*-benzotriazoles in water.

Initially, the reaction between 2-iodoaryltriazene and sodium azide was carried out, in DMSO at 130 °C, by using CuI (0.1 equivalents) and L-proline (0.2 equivalents) as the catalyst and ligand, respectively. To our delight, the desired product, 5-methyl-2-(pyrrolidin-1-yl)-2*H*-benzo[*d*][1,2,3]triazole (**2a**), was successfully obtained in 56% yield (Table 1, entry 1). The structure of **2a** was unambiguously determined by single-crystal analysis (Figure 1). Other N donors, such as 1,2-cyclohexanediamine and 1,10-phenanthroline, are also efficient ligands, providing benzotriazole in 51% and 59% yields, respectively (Table 1, entries 2 and 3). The combination of 2,2′-bipyridyl and CuI was found to be completely inactive (Table 1, entry 4). When TMEDA was used as the ligand, the yield can be increased to 86%. Next, various copper sources, such as CuCl, CuBr, $Cu_2O$, and $Cu(OAc)_2$ were screened as catalysts. Both copper(I) and copper(II) species were found to be active catalysts, showing little difference with respect to their activities. We also examined the influence of solvents. Polar solvents were found to be more appropriate for the reaction. For example,

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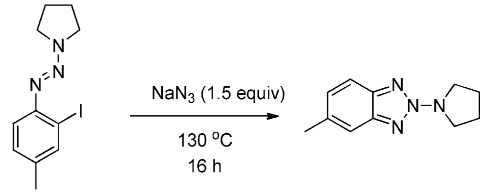
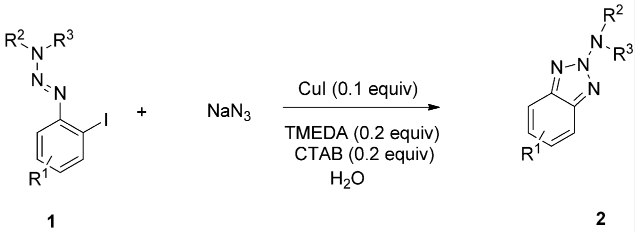
**Table 1.** Optimization of the reaction conditions.



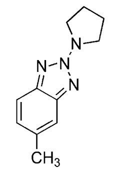
| | Catalyst (0.1 equiv) | Ligand (0.2 equiv) | Additive (0.2 equiv) | Solvent | Yield [%] |
|---|---|---|---|---|---|
| 1 | CuI | L-proline | – | DMSO | 56 |
| 2 | CuI | 1,2-cyclohexanediamine | – | DMSO | 51 |
| 3 | CuI | 1,10-phenanthroline | – | DMSO | 59 |
| 4 | CuI | 2,2′-bipyridyl | – | DMSO | N.R.[d] |
| 5 | CuI | TMEDA | – | DMSO | 86 |
| 6 | CuBr | TMEDA | – | DMSO | 56 |
| 7 | CuCl | TMEDA | – | DMSO | 62 |
| 8 | $Cu_2O$ | TMEDA | – | DMSO | 60 |
| 9 | $Cu(OAc)_2$ | TMEDA | – | DMSO | 55 |
| 10 | CuI | TMEDA | – | dioxane | 15 |
| 11 | CuI | TMEDA | – | *p*-xylene | 18 |
| 12 | CuI | TMEDA | – | DMF | 71 |
| 13 | CuI | TMEDA | – | $H_2O$ | 76 |
| 14 | CuI | TMEDA | Macrogol 400[a] | $H_2O$ | 62 |
| 15 | CuI | TMEDA | SDS[b] | $H_2O$ | 73 |
| 16 | CuI | TMEDA | CTAB[c] | $H_2O$ | 81 |
| 17 | CuI | – | CTAB[c] | $H_2O$ | 64 |

[a] Polyethylene glycol. [b] Sodium *n*-dodecyl sulfate. [c] Hexadecyltrimethylammonium bromide. [d] N.R. = no reaction.

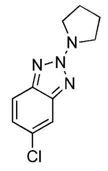
**Table 2.** Reactions of 2-iodoaryltriazenes with sodium azide.[a]



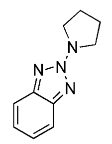
**1** **2**



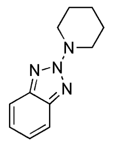
**2a**, 81%



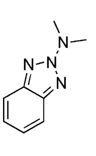
**2b**, 82%



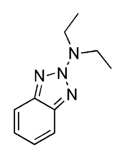
**2c**, 81 %



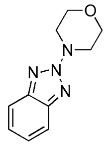
**2d**, 91 %



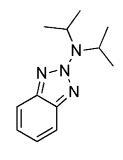
**2e**, 76%



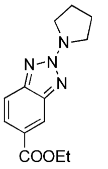
**2f**, 72 %



**2g**, 89%



**2h**, 58 %



**2i**, 51%

[a] All reactions were carried out with 2-iodoaryltriazene (1.0 mmol), NaN$_3$ (1.5 mmol) CuI, TMEDA, and CTAB in water (2.0 mL) at 130 °C, under nitrogen in a sealed tube, for 16 h.

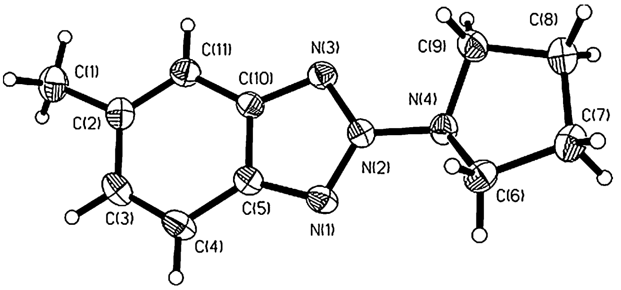


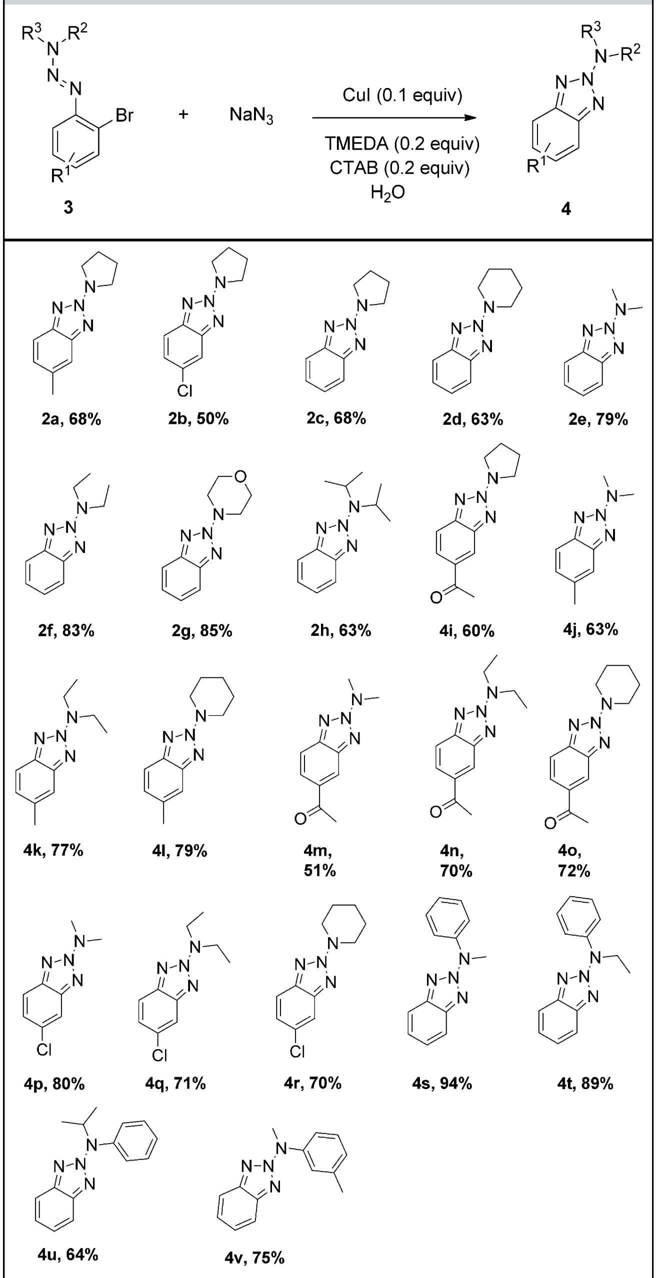
**Figure 1.** X-ray crystal structure of compound **2a**.

the reaction of 2-iodoaryltriazene and sodium azide in dioxane and in *p*-xylene gave the desired benzotriazole in low yields (15 and 18%, respectively), whereas when DMF and water were used as the solvents the yields of the reaction were increased to 71 and 76%, respectively, (Table 1, entries 12 and 13). The addition of a non-ionic surfactant, macrogol 400, or an anionic surfactant, sodium *n*-dodecyl sulfate (SDS), did not improve the reaction in water (Table 1, entries 14 and 15). However, the yield increased to 81% in the presence of the cationic surfactant, hexadecyltrimethylammonium bromide (CTAB, Table 1, entry 16). Although the yield of the reaction in water is slightly lower than that of the reaction in DMSO, we chose the green solvent, water, as the final solvent for the following investigations. In addition, we found that the reaction could proceed in the absence of N-donating ligands, giving a moderate yield (Table 1, entry 17).

Under the optimized conditions, the reactions of various 2-iodoaryltriazenes with sodium azide were screened and the results are summarized in Table 2. 2-Iodoaryltriazenes with either electron-donating groups or electron-withdrawing groups reacted smoothly, affording the corresponding benzotriazoles in moderate to excellent yields. The effect of the amino group was also studied and it was revealed that cyclic amino groups, such as piperidyl and morpholinyl moieties, react favorably. For example, the reaction of 1-(2-iodophenyl)-2-(piperidin-1-yl)diazene (**1d**) and sodium azide afforded the corresponding product in 91% yield. In contrast, when a triazene bearing a diisopropylamino group (**1h**) was used, only 58% of the corresponding product (**2h**) was obtained; probably owing to the effects of steric hindrance. 2-Bromoaryltriazene derivatives could also be converted to benzotriazoles in moderate to excellent yields. Both electron-donating and electron-withdrawing substituents at the phenyl ring can be tolerated in this reaction.

The reactions of 2-bromotriazenes with sodium azide were also investigated by using a CuI/TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) catalyst. The copper-catalyzed C–N coupling of aryl bromides is expected to show lower activity than that of the corresponding aryl iodides. The reactions of pyrrolidin-1-yl and piperidin-1-yl derivatives **3a–d** with sodium azide gave the corresponding annulation products, **2a–d**, in reduced yields at 130 °C, in comparison with the iodo analogues (Table 3). However, the annulation reactions of *N*,*N*-dimethyl and *N*,*N*-diethyl derivatives provided the 2*H*-triazoles

**Table 3.** Reactions of 2-bromoaryltriazenes with sodium azide.[a]



**2a**, 68%; **2b**, 50%; **2c**, 68%; **2d**, 63%; **2e**, 79%

**2f**, 83%; **2g**, 85%; **2h**, 63%; **4i**, 60%; **4j**, 63%

**4k**, 77%; **4l**, 79%; **4m**, 51%; **4n**, 70%; **4o**, 72%

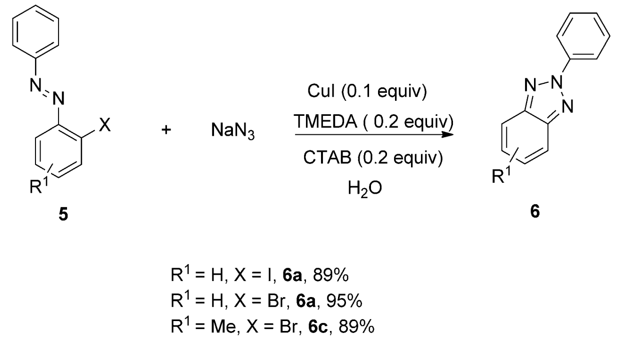
**4p**, 80%; **4q**, 71%; **4r**, 70%; **4s**, 94%; **4t**, 89%

**4u**, 64%; **4v**, 75%

[a] All reactions were carried out with 2-bromoaryltriazene (1.0 mmol), $NaN_3$ (1.5 mmol), CuI, TMEDA, and CTAB in water (2.0 mL) at 130 °C, under nitrogen in a sealed tube, for 16 h.

(**4j**, **4k**, **4n**, **4p**, and **4q**) in yields comparable to those obtained from the corresponding 2-iodotriazenes. The cascade C–N coupling and cyclization reaction was also applied to *N*-aryltriazenes. The *N*-aryl-substituted triazenes, **3s**–**3v**, could easily be transformed into 2-(*N*-alkyl-*N*-phenylamino)-2*H*-benzo[d][1,2,3]triazole (**4s**–**4v**) in moderate to excellent yield.

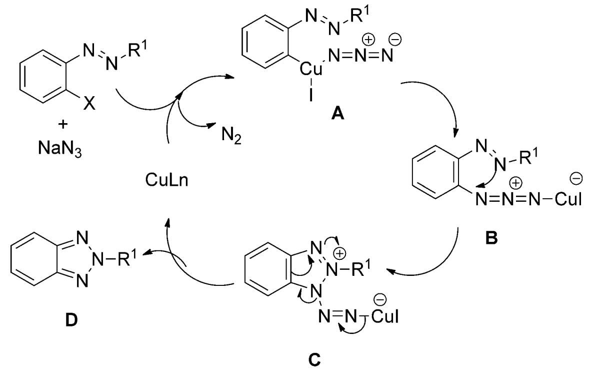
In the presence of a CuI/TMEDA catalyst, the 2-haloazo compounds also reacted with sodium azide in water, providing 2-arylbenzotriazoles in excellent yields. As shown in Scheme 1, 1-(2-bromophenyl)-2-phenyldiazene and 1-(2-iodophenyl)-2-phenyldiazene could be converted into their corresponding 2-phenyltriazoles, in up to 95% yield, in the presence of 10 mol% of CuI.



$R^1$ = H, X = I, **6a**, 89%
$R^1$ = H, X = Br, **6a**, 95%
$R^1$ = Me, X = Br, **6c**, 89%

**Scheme 1.** Reactions of 2-haloazo compounds. All reactions were carried out with 2-haloazo compound (1.0 mmol), $NaN_3$ (1.5 mmol), CuI, TMEDA, and CTAB in water (2.0 mL) at 130 °C, under nitrogen in a sealed tube, for 16 h.

Based on a previous report,[13] a possible mechanism is described in Scheme 2. The copper-catalyzed C–N coupling reaction between 2-haloaryltriazene and sodium azide yields 2-azidoaryltriazene. Thermal decomposition of 2-azidoarytriazene could generate the active nitrene intermediate by releasing one molecule of $N_2$. The terminal N atom of the activated azide is then attacked by the nucleophilic nitrogen atom of the aryltriazene, resulting in the formation of a N–N bond. The loss of one molecule of $N_2$, followed by dissociation of the copper ion from intermediate **C**, generates the final product.



**Scheme 2.** A proposed mechanism.

In summary, we have described a copper-catalyzed cascade reaction between 2-haloaryltriazenes and sodium azide in water. The reaction is highly regioselective and a number of 2-aryl- and 2-aminobenzotriazoles have been obtained in moderate to excellent yield. The procedure is simple and the starting materials and catalyst are easily available. This reaction offers a practical and convenient synthetic route to 2-substituted benzotriazoles from aryltriazenes and azo compounds.

## Experimental Section

Sodium azide (1.5 equivalents), copper iodide (0.1 equivalents), TMEDA (0.2 equivalents) and CTAB (0.2 equivalents) were added to a solution of 2-haloaryltriazene or 2-haloazo compound (1 mmol) in water (2 mL). The mixture was stirred at 130 °C, in a sealed tube under nitrogen, for 16 h. After completion, monitored by thin-layer chromatography (TLC), the reaction mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure and purified by silica-gel chromatography.

## *Acknowledgements*

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**Keywords:** benzotriazoles · cascade cyclizations · sodium azide · water

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