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# Annulation-Induced Cascade Transformation of 5-Iodo-1,2,3-triazoles to 2-(1-Aminoalkyl)benzoxazoles

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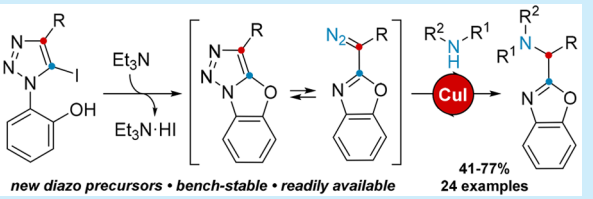
Supporting Information

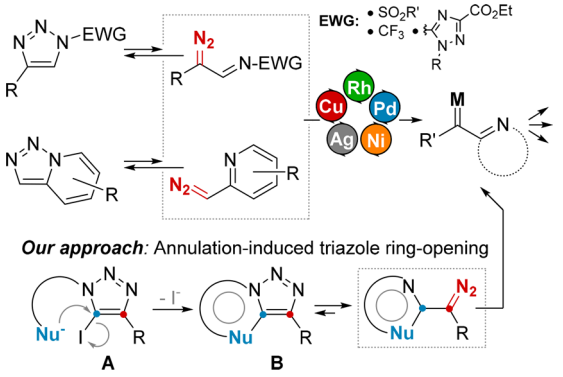
**ABSTRACT:** Base-mediated cyclization of (5-iodo-1,2,3-triazolyl)-phenols was proposed as a new synthetic strategy for the in situ generation of diazoimines via electrocyclic ring opening of the fused heterocycle. Cu-catalyzed amination of the intermediate diazo-alkanes was employed to develop an efficient cascade approach to functionalized benzoxazoles.






1,2,3-Triazoles are generally perceived as stable organic molecules. Nevertheless, one decade ago, the introduction of strong electron-withdrawing substituents at the N1 atom was used as a tool for shifting the equilibrium from the triazole toward the corresponding tautomeric diazoimine (see Scheme 1).[1] The interception of the latter by transition metals resulted

**Scheme 1. Triazoles as Precursors of Metallocarbenoids**

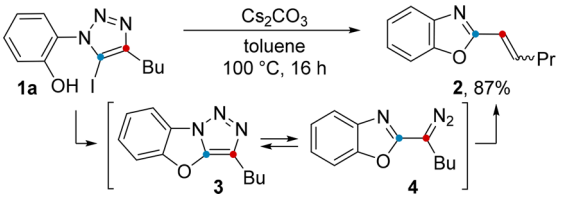



in a new methodology exploiting primarily *N*-sulfonyl-1,2,3-triazoles as precursors of metal-stabilized imino carbenes demonstrating diverse reactivity.[2,3] A similar equilibrium is known for some fused triazoles, which produce stable aromatic heterocycles with relatively non-nucleophilic nitrogen upon electrocyclic ring opening. In particular, triazolopyridines were successfully employed as convenient diazo surrogates in several useful synthetic transformations.[4] The extension of this approach to the preparation of 1,3-azole derivatives requires simple and reliable access to unstable[5] triazole-fused heterocyclic intermediates **B**. They can be perceived as products of intramolecular nucleophilic substitution in readily available[6] 5-iodotriazoles **A**. However, the modification of 5-iodotriazoles has thus far been limited to Pd-[7] or Cu-catalyzed[8] reactions. Noncatalytic nucleophilic substitution in halogenated 1,2,3-triazoles devoid of electron-withdrawing groups is a relatively rare and unexplored process. The only synthetically useful conditions were developed for fluorinated 1,2,3-triazoles.[9] Nevertheless, the intramolecular substitution reaction should still be viable for a broad range of nucleophiles.

The present study is aimed at disclosing a previously unknown reactivity of iodotriazoles acting as a new type of stable precursor of diazo compounds. Our approach is based on the intramolecular nucleophilic substitution leading to an in situ formation of the fused triazole existing in the equilibrium with the reactive diazo tautomer.

Iodotriazole **1a** chosen as a model substrate was prepared according to the standard CuIAAC protocol, although the protection of the phenol moiety by acylation was required. To evaluate the feasibility of the intramolecular nucleophilic substitution, we subjected iodotriazole **1a** to basic conditions. Thus, the heating of **1a** in toluene in the presence of $Cs_2CO_3$ afforded benzoxazole derivative **2** (see Scheme 2). The

**Scheme 2. Base-Promoted Cyclization of 1a**




transformation can be rationalized as the intramolecular substitution of the iodine by the phenolate with the formation of the fused triazole **3** existing in the equilibrium with diazo tautomer **4**. The subsequent Bamford−Stevens-type denitrogenation[10] afforded alkene **2**. Inspired by this promising result, we focused on trapping diazo tautomer **4** by transition metals,

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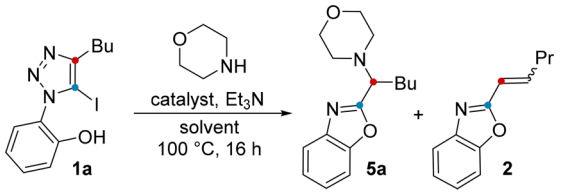
followed by insertion of the metallocarbenoid into an NH bond.

Conditions for the aminative trapping of diazo compound **4** were optimized by using iodotriazole **1a** and morpholine in the presence of $Et_3N$ as a base (see Table 1). Thus, even in the absence of catalysts, the reaction provided 17% of the desired amination product **5a**, along with 53% of alkene **2** (entry 1 in Table 1). The yield of **5a** was improved to 65% by the addition of 10 mol % CuI as a catalyst (entry 5 in Table 1). Notably, the use of $Rh_2(OAc)_4$ (entry 4 in Table 1) and $Pd(OAc)_2$ (entry 2 in Table 1) appeared much less efficient. The screening of various ligands widely employed in the Cu-catalyzed protocols (such as phenanthroline, 1,2-diamines, and $\beta$-diketones) led to diminished yields of **5a**. Only CuTC (entry 6 in Table 1) and a Cu(I)-NHC complex (entry 7 in Table 1) demonstrated efficiency comparable to that of CuI. Thus, the last one was chosen as the least expensive and the simplest variant. Further optimization revealed that dioxane is the most suitable solvent for the reaction providing sufficient selectivity and a high yield of **5a** (entry 11 in Table 1).

**Table 1. Optimization of Reaction Conditions**[a]

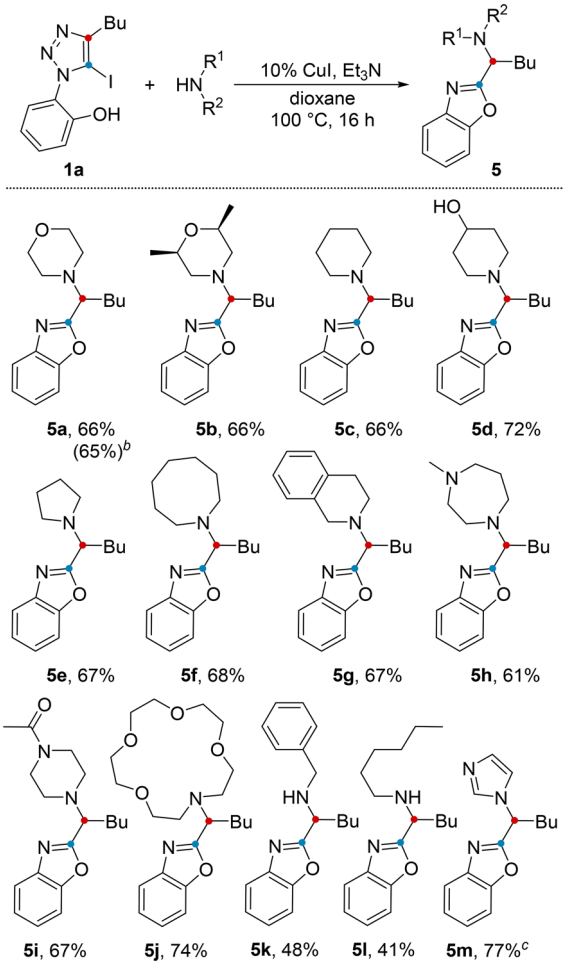



| entry | catalyst (mol %) | solvent | Yield (%)[b] 5a | 2 |
|---|---|---|---|---|
| 1 | | PhMe | 17 | 53 |
| 2 | $Pd(OAc)_2$ (10) | PhMe | 9 | 21 |
| 3 | AgCl (10) | PhMe | 17 | 66 |
| 4 | $Rh_2(OAc)_4$ (5) | PhMe | 42 | 9 |
| 5 | CuI (10) | PhMe | 65 | 5 |
| 6 | CuTC (10) | PhMe | 64 | 6 |
| 7 | Cu(IMes)Cl (10) | PhMe | 67 | 6 |
| 8 | CuI (10) | DMF | 47 | 3 |
| 9 | CuI (10) | MeCN | 65 | 7 |
| 10 | CuI (10) | THF | 72 | 5 |
| 11 | CuI (10) | dioxane | 75 | 6 |

[a]All reactions were performed with **1a** (0.1 mmol) and morpholine (0.2 mmol) in the presence of a catalyst, $Et_3N$ (0.2 mmol) in a solvent (1 mL) under an Ar atmosphere. [b]Determined by $^1H$ NMR.

With the optimized conditions in hand, we investigated the scope of the protocol utilizing various nitrogen nucleophiles (see Scheme 3). The reaction was found to be quite efficient and general, furnishing amination products **5a**–**m** in good yields (41%–77%). There was no distinct correlation between the yield of **5** and the amine basicity or the cycle size, and in the case of morpholine (**5a**, **5b**), piperidine (**5c**, **5d**), pyrrolidine (**5e**), and azocane (**5f**) the corresponding products were actually obtained in almost the same yields (66%–72%). The protocol appeared applicable to other saturated nitrogen heterocycles, including tetrahydroisoquinoline (**5g**), 1,4-diazepane (**5h**), piperazine (**5i**), and aza-crown ether (**5j**). The primary amines gave somewhat lower yields (**5k**,**5l** 41%–48%), whereas no product was observed for *p*-toluidine, *tert*-butylamine, and acetamide, probably because of their low

**Scheme 3. Scope of Nitrogen Nucleophiles**[a]




[a]Reaction conditions: **1a** (1 equiv), amine (2 equiv), $Et_3N$ (2 equiv), CuI (10 mol %), dioxane (0.1 M), 100 °C, 16 h. [b]At 1 mmol scale. [c]10 equiv of imidazole were employed.

nucleophilicity. It is noteworthy that a rather high yield of **5m** (77%) was achieved in the case of imidazole.

The scope of iodotriazoles **1** capable to serve as diazo precursors was studied in the Cu-catalyzed reaction with morpholine (see Scheme 4). Both electron-withdrawing (Cl, Br, $NO_2$, $CO_2Me$) and electron-donating groups (Me, OMe) in the aromatic ring were well-tolerated, although they substantially influence the acidity and nucleophilicity of the phenolic OH group. No aminolysis was observed for **5q**, bearing the ester group, despite the use of a 2-fold excess of morpholine. The halogen substituents (**5o**, **5p**, **5r**) were also left intact notwithstanding that Cu-catalyzed amination of aryl halides is a well-known process.[11] The developed procedure tolerates the presence of a free hydroxyl group (**5u**, **5w**) as well as a MOM-protected one (**5v**) in the alkyl side chain. Interestingly, a successful aminative trapping of a cyclopropyl diazo intermediate (**5x**) was achieved, although formation of significant amounts of rearranged byproducts was anticipated.[12]

To clarify the mechanism, several control experiments were performed (Scheme 5). The heating of iodotriazole **1a** in the presence of $Et_3N$ allowed us to isolate intramolecular cyclization product **4**. The presumed existence of **4** in diazoimine form was unambiguously confirmed by the



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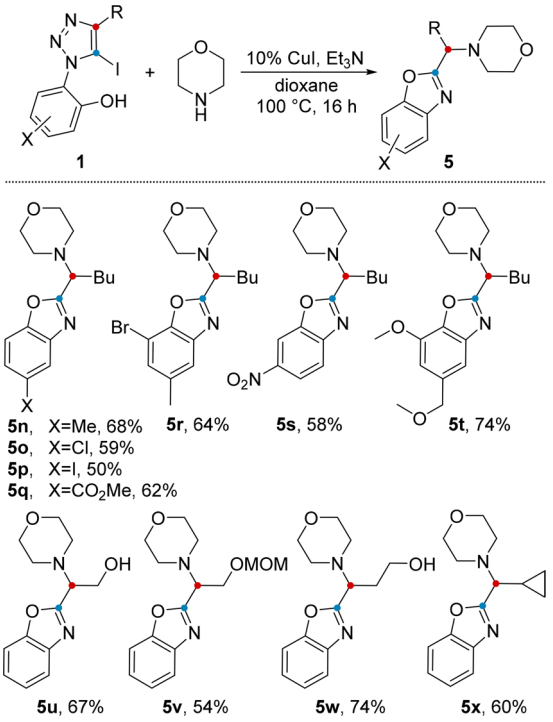
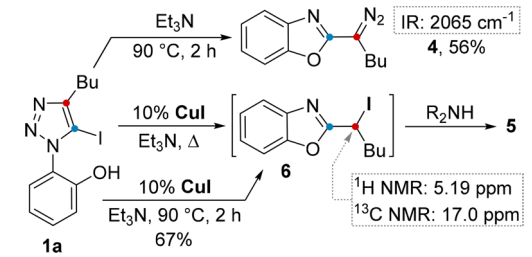
**Scheme 4. Scope of Iodotriazoles**[a]




[a]Reaction conditions: **1** (1 equiv), morpholine (2 equiv), $Et_3N$ (2 equiv), CuI (10 mol %), dioxane (0.1 M), 100 °C, 16 h.

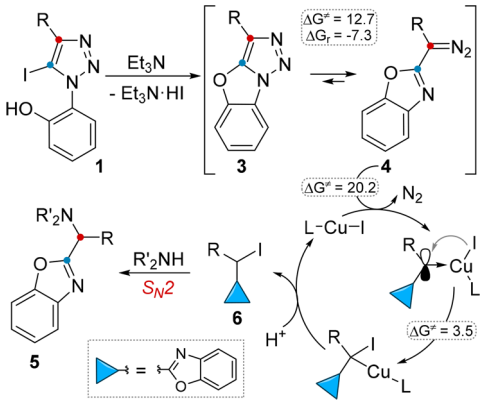
**Scheme 5. Control Experiments**




presence of a strong band with the maximum at 2065 $cm^{-1}$ in the IR spectrum. In addition, the diazo form **4** was found to be 7.3 kcal·$mol^{-1}$ more stable than the corresponding fused triazole **3**, according to DFT calculations at the B3LYP/ma-SVP level of theory.[13] However, **4** was not detected by HPLC under the optimized conditions. Instead, we observed the formation of another intermediate, which was identified as alkyl iodide **6**. It can be isolated in 67% yield in the base-mediated cyclization of **1a** in the presence of 10 mol % CuI (see Scheme 5).

Based on the foregoing observations and DFT calculations for model substrates, we propose the following mechanism for the formation of benzoxazoles **5** (see Scheme 6). The reaction is initiated by base-induced intramolecular nucleophilic substitution in **1**, followed by tautomerization of the fused heterocycle **3** and the generation of the highly reactive diazo form **4**. Denitrogenative trapping of **4** by CuI and subsequent facile ($\Delta G^{\ddagger}$ = 3.5 kcal·$mol^{-1}$) migratory insertion of iodide to the copper carbenoid, followed by protonolysis, affords alkyl iodide **6**. Finally, nucleophilic substitution of iodine by amine leads to the formation of the final compound **5**.

**Scheme 6. Plausible Mechanism**[a]




[a]DFT-calculated $\Delta G_r$ and $\Delta G^{\ddagger}$ are given in kcal·$mol^{-1}$.

In conclusion, we have utilized readily available 5-iodo-1,2,3-triazoles as convenient and stable diazo precursors. The reaction proceeds via base-promoted formation of the fused heterocycle and the subsequent ring opening of the triazole to the diazo form. An efficient protocol for the Cu-catalyzed aminative trapping of these in-situ-generated diazo intermediates has been developed, furnishing functionalized benzoxazoles in good yields. The exploration of other synthetically useful annulation-induced transformations of iodotriazoles is currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01755.

General and characterization data, $^1H$ and $^{13}C$ NMR spectra, details of DFT calculations (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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