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Synthesis of [1,2,3]Triazolo-[1,5-*a*]quinoxalin-4(5*H*)-ones through Copper-Catalyzed Tandem Reactions of *N*-(2-Haloaryl)propiolamides with Sodium Azide

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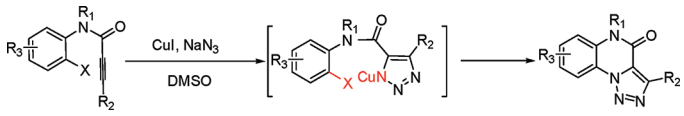
ABSTRACT



A simple and efficient approach for the synthesis of [1,2,3]triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones is described. The methodology is based on a tandem reaction of 1-(2-haloaryl)propiolamides with sodium azide through a [3 + 2] azide−alkyne cycloaddition and intramolecular Ullmann-type C−N coupling process.

Structurally novel and diverse heterocycles are very useful in drug discovery and related fields. However, modern drug discoveries have also stimulated the rapid development of innovative synthetic strategies for the synthesis of such compounds.[1] The [1,2,3]triazolo[1,5-*a*]-quinoxalin-4(5*H*)-one and its analogue tricyclic systems have been found to possess important biological activities such as agonists for the G-protein-coupled Niacin receptor 109A[2] and inhibitors for the benzodiazepine receptor and adenosine receptors.[3] The broad potential biological activities for these kinds of compounds, however, have not yet been fully explored, which is perhaps due to the lack of general methods for the synthesis of the unique tricyclic core. The reported methods for synthesizing such compounds often involve multiple reaction steps, with low efficiency, and difficulties in introducing different functional groups.[2−4]

Our continued efforts to develop efficient and practical methodologies for the synthesis of novel *N*-containing heterocyclic compounds have led to the development of tandem copper-catalzyed [3 + 2] cycloaddition−coupling reactions for the synthesis of 4-oxo-indeno[1,2-*b*]-pyrroles and pyrrolo[3,2-*c*]quinoline-4-ones.[5] The [3 + 2]

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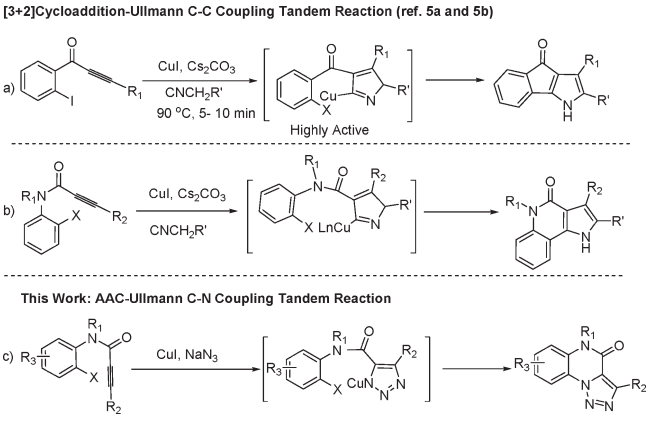
cycloaddition of ethyl isocyanoacetate with carbon–carbon triple bonds produced highly reactive organocopper intermediates, which were then trapped intramolecularly by aryl halides and formed aryl C–C bonds. Based on these results, we envisoned that the intermediate produced in the [3 + 2] azide–alkyne cycloaddition (AAC)[6,7] may also be trapped intramolecularly with aryl halides under copper-catalyzed conditions, which may lead to the formation of aryl C–N bonds[8,9] (Scheme 1).

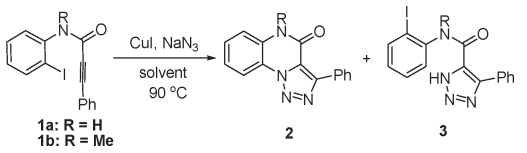
In this paper, we would like to disclose our discoveries on the copper-catalyzed tandem reaction of *N*-(2-haloaryl)-propiolamides with sodium azide for the synthesis of [1,2,3]triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones.

Scheme 1. Design of Copper-Catalyzed Tandem Reaction of *N*-(2-Haloaryl)propiolamides with Sodium Azide for the Synthesis of [1,2,3]Triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones



The investigation was initiated by exploring the copper-catalyzed reaction of *N*-(2-iodophenyl)-3-phenylpropiolamide **1a** with sodium azide. As shown in Table 1, with CuI as the catalyst and DMSO as the solvent, no desired tandem reaction product **2a** or aryl azide product[10] was detected at 90 °C. The only isolated product was **3a**, which was formed through the [3 + 2] cycloaddition reaction of sodium azide to **1a** (Table 1, entry 1). The same result was observed upon reaction in different solvents, such as DMF, MeCN, and 1,4-dioxane. We speculated that it was caused by the hydrogen of the amide group, which may transfer to the nitrogen atom of triazole and make the N–Cu intermediate hard to form, impeding proceeding to the coupling reaction.[11] When *N*-methylated substrate **1b** was tested, the desired product **2b** was isolated in 10% yield even without a copper catalyst (Table 1, entry 2). A much better result was obtained when 10 mol % CuI was used as the catalyst and the desired tandem reaction product **2b** was isolated in 88% yield, accompanied with a small amount of byproduct **3b**. Compared to other screened solvents such as DMF, 1,4-dioxane, and toluene, DMSO appeared to be the best solvent for our tandem reaction (Table 1, entries 3–6). The product yield decreased upon lowering the reaction temperature to 70 °C or ambient, with most of the starting material **1b** remaining unreacted (Table 1, entries 7 and 8). Furthermore, when **3b** was subjected to the copper-catalzyed conditions with K_2CO_3 as the base,[12] the desired product **2b** was obtained in 60% yield in 24 h at 90 °C. However, **3a** was not converted into **2a** under the same reaction conditions.

Table 1. Condition Screening[a]



entry	substrate	solvent	temp (°C)	yield of **2**(%)[b]
1	**1a**	DMSO	90	n.d.[c,d]
2	**1b**	DMSO	90	10[e,f]
3	**1b**	**DMSO**	**90**	**88**
4	**1b**	DMF	90	72
5	**1b**	dioxane	90	n.d.[c]
6	**1b**	toluene	90	n.d.[c]
7	**1b**	DMSO	70	60[g]
8	**1b**	DMSO	rt	<10[g]

[a] Reagents and reaction conditions: **1** (0.5 mmol, 1.0 equiv), CuI (10 mol %), solvent (1 mL), 24 h. [b] Isolated yields. [c] No desired product was detected. [d] The [3 + 2] product **3a** was isolated in >90% yield. [e] No copper catalyst was added. [f] The [3 + 2] product **3b** was isolated in >80% yield. [g] With recovery of **1b**.

With the optimized conditions in hand, we then explored the scope of the new methodology. As displayed in Table 2, in most cases, the desired tandem reaction products were obtained in good to excellent yields. Both the alkyl and aryl substituents on the alkyne moieties were well tolerated, and

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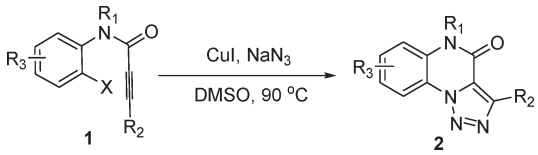
(10) Aryl azides could be synthesized through amino acid promoted copper-catalzyed coupling reactions of aryl halides with sodium azide. See: Zhu, W.; Ma, D. *Chem. Commun.* **2004**, *7*, 888.

(11) A similar result was observed in the copper-catalyzed tandem reaction of *N*-(2-haloaryl)propiolamides with ethyl isocyanoacetate; see ref 5b.

(12) No **2b** was detected without the necessary base.

Table 2. Synthesis of [1,2,3]Triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones through Copper-Catalyzed Tandem Reaction[a]



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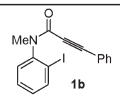
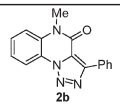
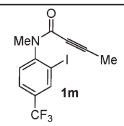
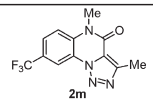
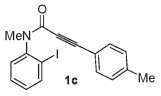
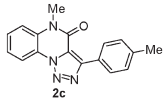
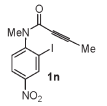
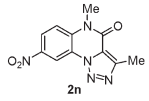
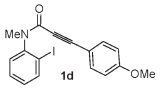
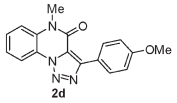
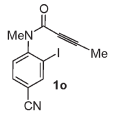
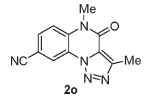
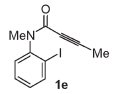
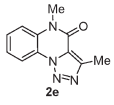
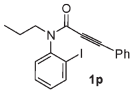
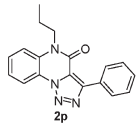
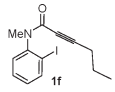
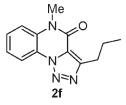
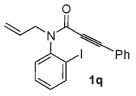
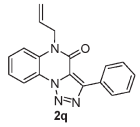
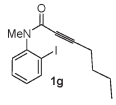
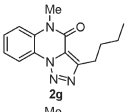
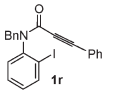
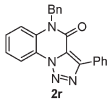
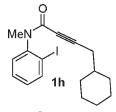
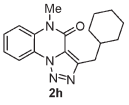
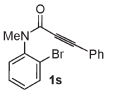
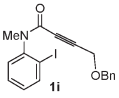
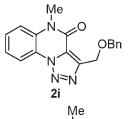
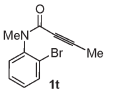
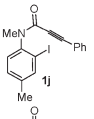
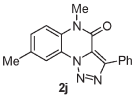
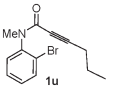
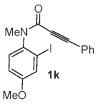
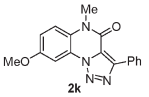
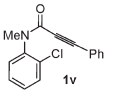
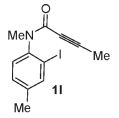
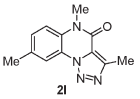
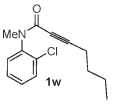
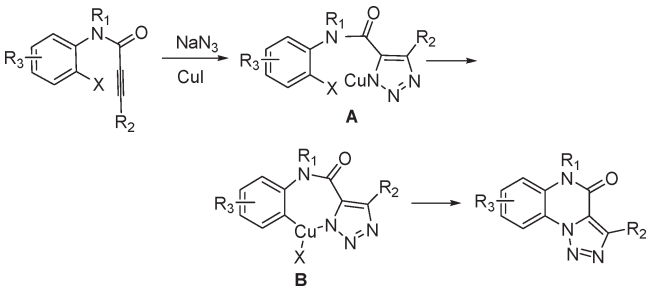
1			88	12			80
2			88	13			83
3			86	14			81
4			87	15			87
5			88	16			94
6			92	17			93
7			67	18		**2b**	81
8			73	19		**2e**	88
9			77	20		**2f**	87
10			75	21		**2b**	58[c]
11			63	22		**2g**	61[c]

[a] Reagents and reaction conditions: aryl halides **1** (0.5 mmol), sodium azide (0.6 mmol), CuI (0.05 mmol), DMSO, 90 °C, 24 h. [b] iIsolated yields. [c] 120 °C.

the corresponding tandem reaction products were delivered in high yields. Furthermore, both the electron-donating and -withdrawing substituents on the 1-(2-iodoaryl) ring were well tolerated and the corresponding reaction products were obtained in high yields (Table 2, entries 9−14). Excellent yields of the desired products were also achieved for other *N*-substituted-(2-haloaryl)propiolamides (Table 2, entries 15−17). In addition, aryl bromides were explored under the same reaction conditions and exhibited similar reactivity to aryl iodides, with generally high reaction yields (Table 2, entries 18−20). As for less reactive aryl chlorides, the desired products were obtained in rather moderate yields even at an elevated temperature of 120 °C (Table 2, entries 21 and 22).

Based on the literature reports and our experimental observations, a plausible reaction process is proposed as shown in Scheme 2. First, the N−Cu species **A** was formed through an azide−alkyne [3 + 2] cycloaddition in the presence of CuI, which was then quickly inserted into the aryl C-halo bond and eventually led to the Ullmann C−N coupling product.

Scheme 2. A Plausible Reaction Process



In summary, we have successfully developed a novel, simple, and efficient method for the synthesis of [1,2,3]-triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones. The method is based on the copper-promoted reaction of 1-(2-haloaryl)-propamides with sodium azide through a tandem azide−alkyne cycloaddition/Ullmann C−N coupling process, which is applicable to a variety of 1-(2-haloaryl) propiolamides. Further, the reaction displayed wide functional group compatibility. It should find further application in organic synthesis and medicinal chemistry.

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Supporting Information Available. Full experimental procedures, characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.