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Synthesis of H-Pyrazolo[5,1-a]isoquinolines via Copper(II)-Catalyzed Oxidation of an Aliphatic C−H Bond of Tertiary Amine in Air

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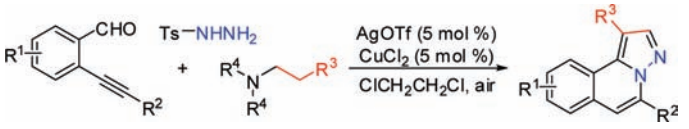
ABSTRACT



A multicomponent reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and tertiary amine is discovered, which generates the unexpected H-pyrazolo[5,1-a]isoquinolines in good yields under mild conditions. In the reaction process, silver(I)-catalyzed intramolecular cyclization and copper(II)-catalyzed oxidation of an aliphatic C−H bond of tertiary amine in air are involved.

Recently, studies of copper−dioxygen interactions mimicked for the biological pathway involving the activation of dioxygen by copper enzymes have been explored.[1] Many applications of dioxygen−copper systems in organic synthesis have been discovered, and most of them focus on the oxidation reactions of aliphatic C−H bonds.[2−4] For instance, Loh and co-workers reported the synthesis of α-amino acetals via a rearrangement of tertiary amine through the oxidation of an aliphatic C−H bond with a dioxygen−copper catalytic system.[4n] Shi described the

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pyrroles formation via dehygronative deamination process.[2e] Compared with the commonly used methods which employed expensive metal catalysts and stoichiometric metal oxidants,[3] dioxygen−copper systems are more attractive for C−H bond activation.[4] Herein, we report an interesting and unprecedented result for a three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and tertiary amine, which generates *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. In the reaction process, the tertiary amine is activated via oxidation of an aliphatic C−H bond catalyzed by a dioxygen−copper system.

The development of new strategies with a high efficiency has been an important goal as well as a great challenge in synthetic chemistry.[5] The multicomponent reaction is an attractive device since it can serve as a powerful tool for the assembly of complex structures.[6] Currently, much attention has been paid to this exciting research area, especially for construction of natural product-like compounds. It is well recognized that the isoquinoline nucleus is one of the most abundant structural motifs found in natural products and biologically active molecules.[7] Additionally, many compounds possessing this subunit exhibit a broad range of pharmacological activity, including antifungal, antimalarial, antihypertensive, antitumor, and antihistaminic activity.[8−11] For instance, the opium alkaloid papaverine is discovered to be useful as a vasodilator.[10] Decumbenine B is efficient for inhibition of spontaneous contraction of the intestine.[11] Therefore, extensive studies have been performed toward the design and synthesis of this ring system.[12,13] For example, Larock, Takemoto, and Yamamoto reported isoquinoline generation via transition-metal catalyzed cyclization of *ortho*-alkynylaryl aldimines, respectively.[13] We also developed methods for formation of diverse isoquinolines starting from 2-alkynylbenzaldehyde and related compounds.[14] Among the compounds synthesized, it was found that *H*-pyrazolo[5,1-*a*]isoquinoline was effective for inhibition of PTP1B (protein tyrosine phosphatase 1 B, IC_{50} 1.75 μg/mL).[14a] With an expectation to find better hits, it is highly desirable to generate functionalized fused isoquniolines using diversity-oriented synthesis.

In our previous reports,[14,15] we demonstrated that *N*′-(2-alkynylbenzylidene)hydrazide was the key species in tandem reactions for construction of *N*-heterocycles. During our studies, we recognized that *N*′-(2-alkynylbenzylidene)-hydrazide could be easily cyclized to isoquinolinium-2-ylamide via 6-*endo*-cyclization catalyzed by silver salts or promoted by electrophiles.[14,15] Thus, further cycloadditions might occur under suitable conditions. Indeed, a series of substrates including dimethyl acetylenedicarboxylate,[15a] phenylacetylene,[15b,c] and methyl acrylate[14c] have been

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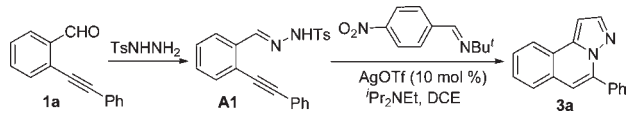
Scheme 1. Initial Studies for the Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **A1** with 4-Nitrophenylaldimine in the Presence of *N,N*-Diisopropylethylamine (DIPEA)



successfully employed as partners in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide, since 1,3-dipolar cycloaddition of ylidic species is a powerful method for the construction of complex *N*-heterocycles.[16] As mentioned above, we would like to develop efficient methods to produce novel structures of isoquniolines. Initially, we conceived that imine might be a good substrate as well in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide. Thus, 4-nitrophenylaldimine was treated with *N*′-(2-alkynylbenzylidene)hydrazide **A1** in the presence of silver(I) triflate (10 mol %) and *N,N*-diisopropylethylamine (DIPEA) in dichloroethane (DCE) at room temperature (Scheme 1). To our surprise, we found that 4-nitrophenylaldimine was not involved in the reaction. An unexpected product was isolated in low yield (8%), which was identified as compound **3a**. The structure was confirmed by ^{1}H and ^{13}C NMR, mass spectrum, and X-ray diffraction analysis (see the Supporting Information).

With this unexpected result in hand, we recognized that *N,N*-diisopropylethylamine might be the reactant in this transformation. Therefore, we commenced to optimize the reaction conditions (Table 1). We found that the reaction occurred under an air atmosphere and no reaction took place under an argon or a nitrogen atmosphere (Table 1, entry 2). From this result, it seemed that oxygen was indispensable which played the key role in the process. Thus, we considered that the reaction route might proceed through the oxidation of an aliphatic C−H bond of *N,N*-diisopropylethylamine. As mentioned above, dioxygen−copper systems have been demonstrated efficiently for C−H bond activation.[4] Thus, copper(II) bromide was added to the reaction system. To our delight, the desired product **3a** was isolated with 75% yield when 10 mol % of $CuBr_2$ was utilized (Table 1, entry 3). Further screening of solvents demonstrated that DCE was the best choice for this transformation and reactions performed in other solvents led to inferior yields (Table 1, entries 4−9). Different metal salts were examined as a catalyst subsequently. It was found that copper salts were superior to other metal reagents. The reaction time was shortened to 2 h with a 78% yield when copper chloride was utilized as a catalyst in the reaction (Table 1, entry 14). The amount of catalyst was examined as well. A similar result was observed when the amounts of $CuCl_2$ and AgOTf were all lowered to

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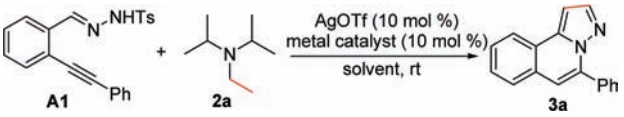
Table 1. Initial Studies for the Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **A1** with *N,N*-Diisopropylethylamine **2a**



entry	metal catalyst	solvent	time (h)	yield (%)[a]
1	–	DCE	15	8
2[b]	–	DCE	24	NR
3	$CuBr_2$	DCE	10	75
4	$CuBr_2$	EtOH	40	65
5	$CuBr_2$	toluene	45	50
6	$CuBr_2$	DCM	24	63
7	$CuBr_2$	1,4-dioxane	24	62
8	$CuBr_2$	MeCN	10	69
9	$CuBr_2$	DMF	10	54
10	$FeCl_3$	DCE	30	12
11	$BiCl_3$	DCE	30	13
12	$ZnCl_2$	DCE	30	12
13	$Cu(OTf)_2$	DCE	4	65
14	$CuCl_2$	DCE	2	78
15	$Cu(OAc)_2$	DCE	14	60
16[c]	CuBr	DCE	4	73
17[d]	$CuCl_2$	DCE	2	77
18[e]	$CuCl_2$	DCE	48	50
19	$CuCl_2$	DCE	48	76

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **A1**. [b] The reaction occurred under argon or nitrogen atmosphere. [c] In the presence of AgOTf (5 mol %) and $CuCl_2$ (5 mol %). [d] In the presence of AgOTf (10 mol %) and $CuCl_2$ (2 mol %). [e] In the presence of AgOTf (10 mol %) and $CuCl_2$ (20 mol %).

5 mol % (77% yield, Table 1, entry 17). However, no better yield was obtained when the catalytic amount of $CuCl_2$ was changed to 2 mol % or 20 mol % (Table 1, entries 18 and 19). Since selectivity has been attributed to both steric and kinetic acidity effects on the deprotonation step as mentioned by Lewis,[17] it is reasonable that the ethyl group in the diisopropylethylamine selectively incorporated into the final product rather than the isopropyl group in this transformation.

Since (2-alkynylbenzylidene)hydrazide **A** could be traced back to 2-alkynylbenzaldehyde **1** with sulfonohydrazide, thus under the optimized reaction conditions (AgOTf 5 mol %, $CuCl_2$ 5 mol %, DCE, air), we next explored the three-component reaction of 2-alkynylbenzaldehyde **1**, sulfonohydrazide, and tertiary amine **2**. The results are summarized in Table 2. It was found that most of the reactions provided good yields under the standard conditions. For example, the reaction of 2-alkynylbenzaldehyde **1a**, 4-methylbenzenesulfono-hydrazide, and triethylamine **2b** gave rise to the corresponding product **3a** in 71% yield (Table 2, entry 2). A similar result was obtained when tri(*n*-propyl)amine **2c** or tri(*n*-butyl)amine **2d** was employed in the above reaction (Table 2, entries 3 and 4). The reaction

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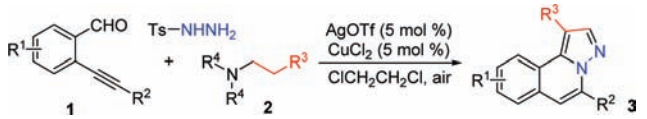
Table 2. Three-Component Reaction of 2-Alkynylbenzaldehyde **1**, Sulfonohydrazide, and Tertiary Amine **2**

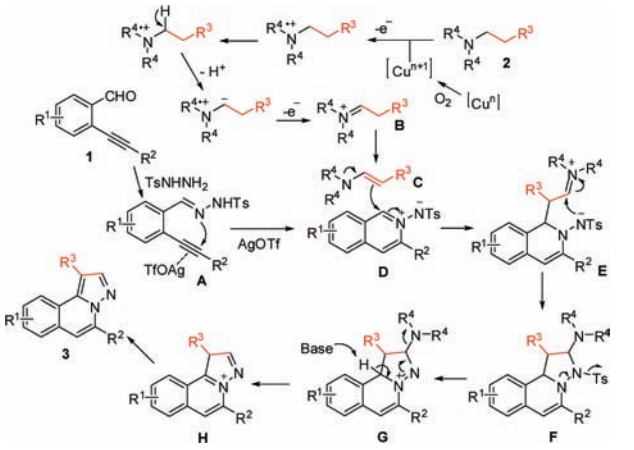


entry	R^1, R^2	R^3, R^4	T (°C)	time (h)	yield (%)[a]
1	H, C_6H_5 (**1a**)	H, ^{i}Pr (**2a**)	30	2	77 (**3a**)
2	H, C_6H_5 (**1a**)	H, Et (**2b**)	30	2	71 (**3a**)
3	H, C_6H_5 (**1a**)	Me, ^{n}Pr (**2c**)	30	2	75 (**3b**)
4	H, C_6H_5 (**1a**)	Et, ^{n}Bu (**2d**)	30	2	78 (**3c**)
5	H, cyclopropyl (**1b**)	Et, ^{n}Bu (**2d**)	30	4	98 (**3d**)
6	H, ^{n}Bu (**1c**)	Et, ^{n}Bu (**2d**)	30	5	84 (**3e**)
7	5-Cl, C_6H_5 (**1d**)	H, ^{i}Pr (**2a**)	30	3	77 (**3f**)
8	5-Cl, C_6H_5 (**1d**)	Et, ^{n}Bu (**2d**)	30	4	92 (**3g**)
9	5-Cl, cyclopropyl (**1e**)	H, ^{i}Pr (**2a**)	30	5	99 (**3h**)
10	5-Cl, cyclopropyl (**1e**)	Et, ^{n}Bu (**2d**)	30	4	98 (**3i**)
11	5-Cl, ^{n}Bu (**1f**)	H, ^{i}Pr (**2a**)	30	6	95 (**3j**)
12	5-Cl, ^{n}Bu (**1f**)	Et, ^{n}Bu (**2d**)	30	6	96 (**3k**)
13	4-F, C_6H_5 (**1g**)	H, ^{i}Pr (**2a**)	30	5	60 (**3l**)
14	4-F, C_6H_5 (**1g**)	Et, ^{n}Bu (**2d**)	30	5	72 (**3m**)
15	4-F, cyclopropyl (**1h**)	Et, ^{n}Bu (**2d**)	30	5	86 (**3n**)
16	4-F, ^{n}Bu (**1i**)	Et, ^{n}Bu (**2d**)	30	5	87 (**3o**)
17	5-Me, C_6H_5 (**1j**)	H, ^{i}Pr (**2a**)	30	8	56 (**3p**)
18	5-Me, C_6H_5 (**1j**)	Et, ^{n}Bu (**2d**)	30	8	64 (**3q**)
19	5-Me, cyclopropyl (**1k**)	Et, ^{n}Bu (**2d**)	50	12	78 (**3r**)
20	5-Me, ^{n}Bu (**1l**)	Et, ^{n}Bu (**2d**)	50	18	75 (**3s**)
21	4,5-$(OMe)_2$, C_6H_5 (**1m**)	H, ^{i}Pr (**2a**)	60	12	38 (**3t**)
22	4,5-$(OMe)_2$, C_6H_5 (**1m**)	Et, ^{n}Bu (**2d**)	60	40	trace
23	H, *p*-ClC_6H_4 (**1n**)	Et, ^{n}Bu (**2d**)	30	5	63 (**3u**)
24	H, *p*-MeC_6H_4 (**1o**)	Et, ^{n}Bu (**2d**)	30	5	67 (**3v**)

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

proceeded smoothly when 2- alkynylbenzaldehyde **1b** or **1c** was used in the reaction of 4-methylbenzene-sulfonohydrazide with tri(*n*-butyl)amine **2d** (Table 2, entries 5 and 6). 5-Chloro- or 4-fluoro substituted 2-alkynylbenzaldehydes **1d**−**1i** were suitable substrates as well in this three-component reaction. For instance, an almost quantitative yield was generated for the reaction of 2-alkynylbenzaldehyde **1e**, 4-methylbenzenesulfonohydrazide, and *N,N*-diisopropylethylamine **2a** (Table 2, entry 9). The structure of compound **3g** was confirmed by X-ray diffraction analysis meanwhile (see the Supporting Information). However, inferior results were observed for the 2-alkynylbenzaldehydes with electron-donating group R^1 attached on the aromatic ring. The reaction of 4,5-dimethoxy 2-alkynylbenzaldehyde **1m**, 4-methylbenzenesulfonohydrazide, and *N,N*-diisopropylethylamine **2a** led to the desired product **3t** in 38% yield (Table 2, entry 21). Only a trace amount of product was detected when

Scheme 2. Proposed Synthetic Route for the Reaction of 2-Alkynylbenzaldehyde **1**, Sulfonohydrazide, and Tertiary Amine **2**



tri(*n*-butyl)amine **2d** was utilized as a replacement in the reaction (Table 2, entry 22). The reaction of 4-methylbenzene-sulfonohydrazide, tri(*n*-butyl)amine **2d**, and 2-alkynylbenzaldehyde **1n** or **1o** was examined meanwhile. As expected, the reactions worked well to afford the desired product in good yields (Table 2, entries 23 and 24). Prompted by the advancement of an oxygen−copper catalytic system applied in the oxidation of aliphatic C−H bonds,[4] we reasoned that, in the presence of a copper catalyst in air, the tertiary amine **2** would be transferred to an enamine **C** through oxidation of an aliphatic C−H bond. Meanwhile, isoquinolinium-2-ylamide **D** would be formed via silver-catalyzed cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **A**. Therefore, the intermolecular nucleophilic attack would occur to generate the intermediate **E**, which then underwent tosyl group release and subsequent aromatization to afford the *H*-pyrazolo[5,1-*a*]-isoquinoline **3** (Scheme 2).

In conclusion, we have described an unprecedented silver and copper cocatalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and tertiary amine, which provides a novel and efficient route for the generation of *H*-pyrazolo[5,1-*a*]isoquinolines. In this reaction process, the tertiary amine is activated via oxidation of an aliphatic C−H bond catalyzed by a dioxygen−copper system. Application of rearrangement of tertiary amine in other transformations is under investigation, and the results will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**, X-ray crystal data of compounds **3a** and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.