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Three-Component Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide, Alkyne, with Sulfonyl Azide via a Multicatalytic Process: A Novel and Concise Approach to 2-Amino-*H*-pyrazolo[5,1-*a*]-isoquinolines

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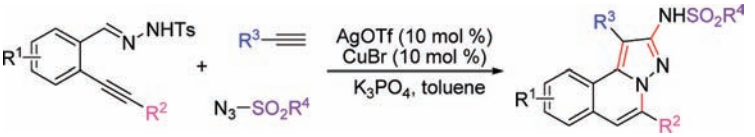
ABSTRACT



A novel and efficient route for the synthesis of 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines via a three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide, alkyne, and sulfonyl azide is described. This transformation, co-catalyzed by silver triflate and copper(I) bromide under mild conditions, proceeds efficiently to generate the 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines in good to excellent yields.

Libraries of small molecules are used in drug discovery programs to search for lead structures active in biological assays. Thus, the pursuit of practical and efficient approaches for rapid generation of natural product-like compounds is of utmost urgency and importance.[1] Recently, we have successfully prepared a small library of *H*-pyrazolo[5,1-*a*]isoquinolines[2] via tandem reactions.[3] Some of these compounds showed promising inhibitory activities versus targets such as CDC25B, TC-PTP, or PTP1B in preliminary biological assays.[2d] Consequently, synthetic methodology development for functionalized *H*-pyrazolo-[5,1-*a*]isoquinolines is highly desirable to obtain additional compounds for biological evaluation.

Ketenimine chemistry which involves a copper(I)-catalyzed azide–alkyne cycloaddition[4−6] has been used as an efficient approach for the generation of various heterocycles. Recently, *N*′-(2-alkynylbenzylidene)hydrazide has been employed as a versatile substrate for reaction development.[2] Prompted by the achievement of ketenimine chemistry, we envisioned that *N*′-(2-alkynylbenzylidene)hydrazide might be utilized in the azide–alkyne cycloaddition process. We envisioned a three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide, alkyne, and sulfonyl azide, as proposed in Scheme 1. Since a copper(I) catalyst is essential for the generation of a ketenimine intermediate and silver triflate has been

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demonstrated to be the most effective catalyst for the cyclization of *N*′-(2-alkynylbenzylidene)hydrazide,[2] a multicatalytic process is proposed. It is well-documented that multicatalytic processes[7,8] can be highly efficient in tandem reactions. For example, a one-pot Beckmann rearrangement/intramolecular cyclization/halogenation reaction of 1-(2-alkynylphenyl)ketoxime cocatalyzed by indium(III) and palladium(II) salts was developed to give the indole derivatives in good yields.[8d] As shown in Scheme 1, the presence of silver would promote the 6-*endo*-cyclization of *N*′-(2-alkynylbenzylidene)hydrazide **1** to form isoquinolinium-2-yl amide **c**. Ketenimine **b** would be formed via a copper(I)-catalyzed azide−alkyne cycloaddition. Subsequently, intermolecular [3 + 2] cycloaddition would afford compound **d**, which would then undergo aromatization to furnish 2-amino-*H*-pyrazolo[5,1-*a*]isoquinoline **4**. This strategy rapidly introduces molecular complexity and diversity.

Scheme 1. Proposed Route for a Three-Component Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **1**, Alkyne **2**, and Sulfonyl Azide **3**

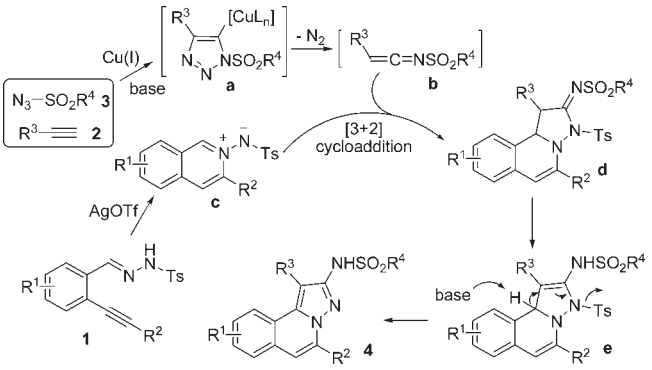
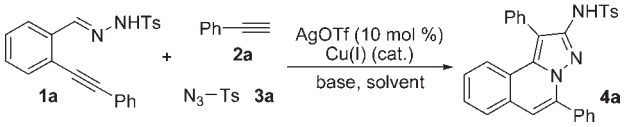


Table 1. Initial Studies for Silver(I) and Copper(I) Co-Catalyzed Three-Component Reaction of *N*′-(2-Alkynylbenzylidene)-hydrazide **1a**, Phenylacetylene **2a**, with 4-Methylbenzenesulfonyl azide **3a**



entry	[Cu]	solvent	base	yield[a] (%)
1	CuI (10 mol %)	1,4-dioxane	Et_3N	complex
2	CuI (10 mol %)	1,4-dioxane	pyridine	complex
3	CuI (10 mol %)	1,4-dioxane	Cs_2CO_3	complex
4	CuI (10 mol %)	1,4-dioxane	K_2CO_3	trace
5	CuI (10 mol %)	1,4-dioxane	K_3PO_4	34
6	CuI (10 mol %)	$ClCH_2CH_2Cl$	K_3PO_4	33
7	CuI (10 mol %)	THF	K_3PO_4	28
8	CuI (10 mol %)	*n*-hexane	K_3PO_4	nr
9	CuI (10 mol %)	cyclohexane	K_3PO_4	20
10	CuI (10 mol %)	MeCN	K_3PO_4	25
11	CuI (10 mol %)	toluene	K_3PO_4	51
12	CuI (10 mol %)	DMF	K_3PO_4	complex
13	CuBr (10 mol %)	toluene	K_3PO_4	67
14	CuCl (10 mol %)	toluene	K_3PO_4	52
15	CuOTf (10 mol %)	toluene	K_3PO_4	65
16[b]		toluene	K_3PO_4	
17	CuBr (5 mol %)	toluene	K_3PO_4	59
18[c]	CuBr (5 mol %)	toluene	K_3PO_4	57

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1a**. [b] Only isoquinolinium-2-yl amide was obtained. [c] The reaction was performed at 50 °C.

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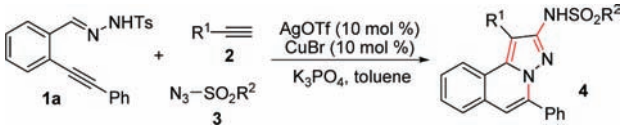
The initial studies were performed for the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a**, phenyl acetylene **2a**, and sulfonyl azide **3a** in the presence of 10 mol % of silver triflate and a copper(I) catalyst at room temperature. Different copper(I) salts, solvents, and bases were then screened. The result was a complex mixture when the reaction occurred in 1,4-dioxane with the addition of 10 mol % of copper(I) iodide and 3.0 equiv of triethylamine (Table 1, entry 1). Similar results were observed when the base was changed to pyridine or Cs_2CO_3 (Table 1, entries 2 and 3). A trace amount of product was detected when K_2CO_3 was employed as the base in the above reaction (Table 1, entry 4). Gratifyingly, the desired product **4a** was isolated in 34% yield when K_3PO_4 was added as the base (Table 1, entry 5). The structure of 2-amino-*H*-pyrazolo-[5,1-*a*]isoquinoline **4a** was unambiguously determined by X-ray crystallography analysis (see the Supporting Information). With this promising result in hand, the reaction was then explored in various solvents. The yield could not be improved in $ClCH_2CH_2Cl$, THF, *n*-hexane, cyclohexane, or MeCN (Table 1, entries 6–10). Further screening revealed that toluene was the best choice (51% yield, Table 1, entry 11). The reaction led to a complex mixture when DMF was used as the solvent (Table 1, entry 12). A comparable yield (52%) was afforded when copper-(I) chloride was employed as the catalyst (Table 1, entry 14). The yield was increased when copper(I) bromide or copper(I) triflate was utilized (Table 1, entries 13 and 15). No expected product was obtained in a blank experiment without the addition of a copper(I) salt, which indicated

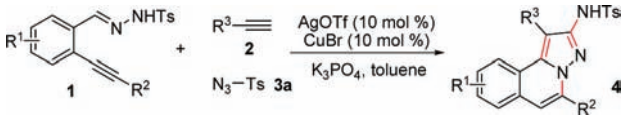
Table 2. Silver(I) and Copper(I) Co-Catalyzed Three-Component Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **1a** and Alkyne **2** with Sulfonyl Azide **3**



entry	alkyne	R^2	yield (%)[a]
1	**2a**	*p*-MeC_6H_4 (**3a**)	67 (**4a**)
2	**2b**	*p*-MeC_6H_4 (**3a**)	64 (**4b**)
3	**2c**	*p*-MeC_6H_4 (**3a**)	65 (**4c**)
4	**2d**	*p*-MeC_6H_4 (**3a**)	70 (**4d**)
5	**2e**	*p*-MeC_6H_4 (**3a**)	60 (**4e**)
6	**2f**	*p*-MeC_6H_4 (**3a**)	40 (**4f**)[b]
7	**2g**	*p*-MeC_6H_4 (**3a**)	44 (**4g**)
8	**2h**	*p*-MeC_6H_4 (**3a**)	74 (**4h**)
9	**2i**	*p*-MeC_6H_4 (**3a**)	trace
10	**2j**	*p*-MeC_6H_4 (**3a**)	trace
11	**2h**	C_6H_5 (**3b**)	67 (**4i**)
12	**2h**	*p*-BrC_6H_4 (**3c**)	55 (**4j**)
13	**2h**	*p*-$NO_2C_6H_4$ (**3d**)	37 (**4k**)

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1a**. [b] The desilyl product was afforded.

Table 3. Silver(I) and Copper(I) Co-Catalyzed Three-Component Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide **1** and Alkyne **2** with Sulfonyl Azide **3a**



entry	substrate **1**	alkyne **2**	yield (%)[a]
1	**1b**	**2a**	75 (**4l**)
2	**1b**	**2h**	66 (**4m**)
3	**1c**	**2a**	72 (**4n**)
4	**1c**	**2h**	60 (**4o**)
5	**1d**	**2a**	complex
6	**1e**	**2a**	55 (**4p**)
7	**1e**	**2h**	67 (**4q**)
8	**1f**	**2a**	65 (**4r**)
9	**1f**	**2h**	75 (**4s**)
10	**1g**	**2a**	50 (**4t**)
11	**1g**	**2h**	56 (**4u**)
12	**1h**	**2h**	67 (**4v**)
13	**1i**	**2h**	68 (**4w**)
14	**1j**	**2h**	65 (**4x**)
15	**1k**	**2a**	35 (**4y**)
16	**1k**	**2h**	45 (**4z**)

[a] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide **1**.

the essential role of copper(I) in the conversion (Table 1, entry 16). No better results were obtained when the amount of copper(I) bromide was reduced to 5 mol % or the reaction temperature was elevated to 50 °C (Table 1, entries 17 and 18). When the amount of base (K_3PO_4) was decreased to 2.5 or 2.0 equiv, a slightly lower yield was obtained. No improvement was observed when the amount of K_3PO_4 was increased to 4.0 equiv (data not shown in Table 1).

We then investigated the reaction scope of this multicatalytic system and its tolerance of functional groups in the case of *N*′-(2-alkynylbenzylidene)hydrazide **1**, alkyne **2**, and sulfonyl azide **3** under the optimized conditions [AgOTf (10 mol %), CuBr (10 mol %), K_3PO_4 (3.0 equiv), toluene, 25 °C] (Tables 2 and 3). With respect to alkynes **2a**−**h**, the expected 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines resulting from reactions of *N*′-(2-alkynylbenzylidene-)hydrazide **1a** with 4-methylbenzenesulfonyl azide **3a** were isolated in moderate to good yields (Table 2, entries 1−8). For instance, phenyl acetylenes **2b**−**d** with chloro-, methyl-, and methoxy groups attached on the aromatic ring were all good reactants in the transformation (Table 2, entries 2−4). Interestingly, trimethylsilyl acetylene **2f** was compatible with this reaction, and the desilyl product **4f** was generated (Table 2, entry 6). Reactions of *N*′-(2-alkynylbenzylidene)hydrazide **1a** and 4-methylbenzenesulfonyl azide **3a** with other alkynes such as 1-hexyne **2g** and ethynylcyclopropane **2h** were examined, which gave rise to the desired products **4g** and **4h** in 44% and 74% yield, respectively (Table 2, entries 7 and 8). However, only a trace amount of product was generated when 1-ethynyl-4-nitrobenzene **2i** or 2-ethynylpyridine **2j** was used in this three-component reaction (Table 2, entries 9 and 10). Other sulfonyl azides were then explored in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1a** with ethynylcyclopropane **2h**. Benzenesulfonyl azide **3b** worked well in the reaction, leading to the corresponding product **4i** in 67% yield (Table 2, entry 11). The product was isolated in moderate yield when 4-bromobenzenesulfonyl azide **3c** was employed in the transformation (Table 2, entry 12). However, reaction of 4-nitrobenzenesulfonyl azide **3d** afforded the desired 2-amino-*H*-pyrazolo[5,1-*a*]isoquinoline **4k** in a lower yield (37%, Table 2, entry 13).

In a second set of experiments, the scope of the process with respect to *N*′-(2-alkynylbenzylidene)hydrazide substituted with electron-rich and -poor substituents was investigated (Table 3). We rapidly noticed that most of the reactions of 4-methylbenzenesulfonyl azide **3a** with phenyl acetylene **2b** or ethynylcyclopropane **2h** proceeded smoothly to afford the expected products **4** under the standard experimental conditions. For example, fluoro-substituted *N*′-(2-alkynylbenzylidene)hydrazide **1b** reacted with phenylacetylene **2b** and 4-methylbenzenesulfonyl azide **3a** leading to the desired 2-amino-*H*-pyrazolo[5,1-*a*]-isoquinoline **4l** in 75% yield (Table 3, entry 1). The product was isolated in a slightly lower yield when ethynylcyclopropane **2h** was used as a replacement (66% yield, Table 3, entry 2). The products were isolated in similar yields when chloro-, methoxy-, and methyl-substituted *N*′-(2-alkynylbenzylidene)hydrazides were employed in the transformation (Table 3, entries 3, 4, 6−8). However, the reaction was complicated when nitro-substituted *N*′-(2-alkynylbenzylidene)hydrazide **1d** was employed in the reaction of phenylacetylene **2b** with 4-methylbenzenesulfonyl azide **3a** (Table 3, entry 5). Further investigation revealed that not only aryl groups but also alkyl groups at the R^2 position were tolerated (Table 3, entries 10−14). It is noteworthy that thiophene-yl-incorporated hydrazide **1k** was a good partner as well in this three-component reaction, although the final outcome was not as good as expected (Table 3, entries 15 and 16). Overall, most of the successful transformation of a variety of substrates indicated good functional group tolerability and generality for this multicomponent reaction.

In conclusion, we have described a novel and efficient route for the generation of 2-amino-*H*-pyrazolo[5,1-*a*]-isoquinolines via a silver(I) and copper(I) co-catalyzed three-component reaction of *N*′-(2-alkynylbenzylidene)-hydrazide, alkyne, and sulfonyl azide. The key intermediates are believed to be isoquinolinium-2-yl amide and ketenimine, which are generated in situ. This transformation proceeds with high efficiency through 6-*endo* cyclization, [3 + 2] cycloaddition, and subsequent aromatization. Currently, the related library construction is ongoing, and the evaluation of different biological activities will be reported in due course.

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Supporting Information Available. Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of compounds **4**, and X-ray data for compound **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.