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Efficient Generation of Biologically Active *H*-Pyrazolo[5,1-*a*]isoquinolines via Multicomponent Reaction

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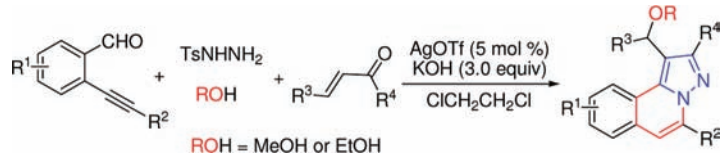
ABSTRACT



A highly efficient multicomponent reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, alcohol, and α,β-unsaturated aldehyde or ketone is disclosed, which generates the diverse *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. This reaction proceeds with good functional group tolerance under mild conditions with high efficiency and excellent selectivity. Preliminary biological assays show that some of these compounds display promising activities as CDC25B inhibitor, TC-PTP inhibitor, and PTP1B inhibitor.

Drug discovery programs use large collections of small molecules to look for lead structures from biological assays. Thus, availability of practical and efficient devices for generation of natural product-like compounds is of utmost urgency and importance. Currently, diversity-oriented synthesis has been successfully applied for the synthesis of structurally diverse and complex collections of natural product-like compounds.[1] Among the strategies utilized, multicomponent reactions (MCRs) are of increasing importance due to their high efficiency for delivering molecular diversity.[2] As part of an ongoing program in our laboratory for generation of small molecules used in different biological assays,[3,4] we are interested in the methodology development of multicomponent reactions for accessing privileged scaffolds.

Recently, we reported a metal and *N*-heterocyclic carbene cocatalyzed three-component reaction of *N*′-(2-alkynylbenzylidene)hydrazide, methanol, and α,β-unsaturated aldehyde

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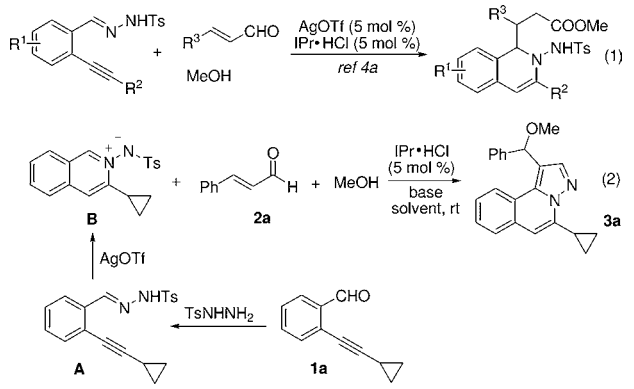
Scheme 1. Preliminary Result for *H*-Pyrazolo[5,1-*a*]isoquinoline Generation



(Scheme 1, eq 1).[4a] This reaction proceeded with high efficiency to afford 2-amino-1,2-dihydroisoquinolines in good yields. However, it was found that the R^2 group attached to the triple bond of *N*′-(2-alkynylbenzylidene)hydrazide was crucial for successful conversion. Only the aryl group was effective and no reactions occurred when the group was replaced by the *n*-butyl or the cyclopropyl group. With an expectation to broaden the scope of this transformation, we reinvestigated the reaction of *N*′-(2-alkynylbenzylidene)hydrazide **A**. To avoid competitive reactions, the key intermediate isoquinolinium **B** was directly employed in the reaction of cinnamaldehyde **2a** with methanol at room temperature (Scheme 1, eq 2). At the outset, the reaction occurred in THF in the presence of different bases (2.0 equiv) and IPr•HCl (5 mol %). No product was detected when DBU, DABCO, NaOAc, or Et_3N was employed in the reaction. A trace amount of product was observed when *t*-BuOK was used as a replacement. A product was generated when patassium hydroxide was utilized as the base. However, surprisingly structural identification by X-ray diffraction analysis (see the Supporting Information) showed that this product was the unexpected 5-cyclopropyl-1-(methoxy(phenyl)methyl)*H*-pyrazolo[5,1-*a*]isoquinoline **3a** instead of the desired 2-amino-1,2-dihydroisoquinoline. From this result, we doubted the role of *N*-heterocyclic carbene in the reaction. Thus, a blank experiment without the addition of IPr•HCl was examined, which gave rise to compound **3a** as well in 60% yield. Further screening of solvents identified that 1,2-dichloroethane (DCE) was the best choice (73% yield). The reaction performed in other solvents afforded inferior yields.

With this promising result in hand, we were interested in the scaffold of compound **3a**, which incorporated both isoquinoline and pyrazolo[1,5-*a*]pyridine skeletons. It is well-known that isoquinolines and their derivatives stand out as privileged frameworks in naturally occurring alkaloids and biologically active molecules.[5] Therefore, there has been considerable interest concerning the synthesis of these compounds.[6] As a member of this family, the fused isoquinoline has attracted much attention recently due to the remarkable biological activities.[7] For example, Lamellarin D is found as a potent inhibitor of human topoisomerase I[7b] and lamellarin α-20-sulfate shows selective inhibition against HIV-1 integrase in vitro (Figure 1).[7c,d] The scaffold could

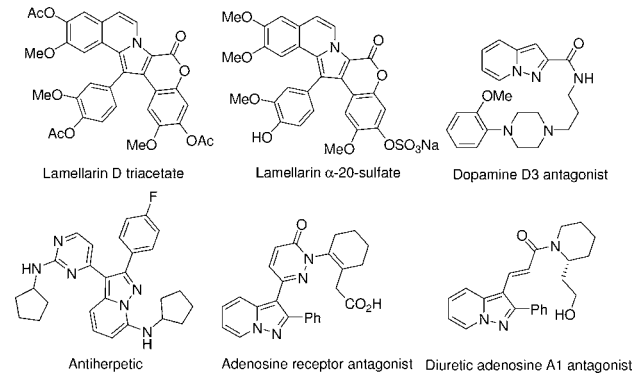


Figure 1. Examples of fused isoquinolines and pyrazolo[1,5-*a*]pyridines.

be efficiently synthesized via tandem cyclization/1,3-dipolar cycloaddition reaction.[8] On the other hand, pyrazolo[1,5-*a*]pyridines represent an important class of heterocycls in drug discovery as they display numerous biological activities (Figure 1).[9−11] For instance, several of these compounds as effective D3 and D4 agonists and antagonists are used in

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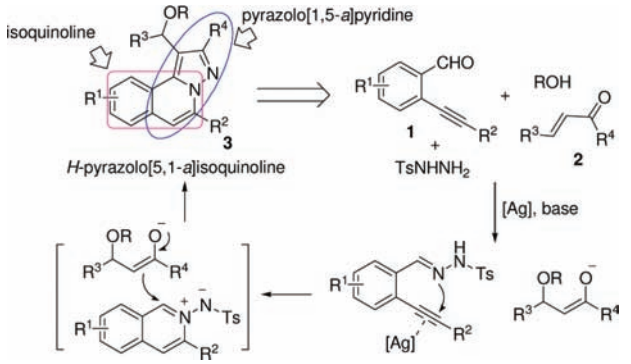
the treatment of neurological disorders including schizophrenia, attentiondeficit disorder, and Parkinson's disease.[9] Additionally, some derivatives show potent antiherpetic and diuretic activity due to their ability to act as adenosine agonists and antagonists.[10] Inspired by these results, we envisioned that we could construct a focused library of *H*-pyrazolo[5,1-*a*]isoquinolines (Scheme 2), which incorporated both isoquinoline and pyrazolo[1,5-*a*]pyridine skeletons. We expected the compounds with the scaffold in Scheme 2 would display interesting biological activities as well, and hopefully some hits would be generated from these compounds in our specific biological assays.

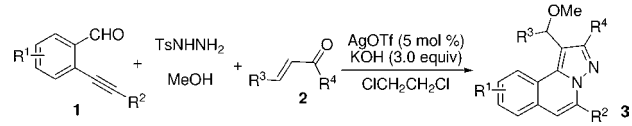
Scheme 2. Proposed Synthetic Route for Generation of Diverse *H*-Pyrazolo[5,1-*a*]isoquinolines



As mentioned above, reaction of isoquinolinium **B** with cinnamaldehyde **2a** and methanol gave rise to compound **3a** in 73% yield in the presence of KOH in DCE at room temperature. The result in Scheme 1 and our continued interest in tandem reactions prompted us to search a more efficient way for generation of diverse *H*-pyrazolo[5,1-*a*]isoquinolines. Encouraged by the above results and our previous efforts in the tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide, we conceived that the starting materials of this transformation could be traced back to 2-alkynylbenzaldehyde **1**, sulfonohydrazide, alcohol, and α,*β*-unsaturated aldehyde or ketone **2** (Scheme 2). For this multicomponent reaction, we anticipated that treatment of 2-alkynylbenzaldehyde **1** with sulfonohydrazide would lead to *N*′-(2-alkynylbenzylidene)hydrazide, which then underwent cyclization to furnish isoquinolinium intermediate in the presence of suitable metal catalyst. Meanwhile, the enolate would be produced in situ via nucleophilic attack of alcohol to α,*β*-unsaturated aldehyde or ketone **2**. Thus, after subsequent transformation (including intermolecular nucleophilic addition, intramolecular condensation, and aromatization),[3k] the desired *H*-pyrazolo[5,1-*a*]isoquinoline **3** would be afforded. With these considerations in mind, we started to explore the possibility of this multicomponent reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, alcohol, and α,*β*-unsaturated aldehyde or ketone.

In our previous reports,[3] we have demonstrated that silver triflate is an efficient catalyst for isoquinolinium **B** formation via 6-*endo* cyclization of *N*′-(2-alkynylbenzylidene)hydrazide. Thus, the multicomponent reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide, cinnamaldehyde **2a**, and methanol was initially catalyzed by 5 mol % of silver triflate in the presence of KOH (3.0 equiv) in DCE at room temperature. Gratifyingly, this reaction worked well leading to the desired product **3a** in 51% yield (Table 1, entry 1). No improvement was observed by changing other metal

Table 1. Generation of Diverse *H*-Pyrazolo[5,1-*a*]isoquinolines via Multicomponent Reaction of 2-Alkynylbenzaldehyde, Sulfonohydrazide, Methanol, and α,*β*-Unsaturated Aldehyde or Ketone



entry	R^1, R^2	R^3, R^4	yield (%)[a]
1	H, cyclopropyl (**1a**)	C_6H_5, H (**2a**)	51 (**3a**)
2	H, cyclopropyl (**1a**)	4-BrC_6H_4, H (**2b**)	76 (**3b**)
3	H, cyclopropyl (**1a**)	4-MeOC_6H_4, H (**2c**)	78 (**3c**)
4	H, cyclopropyl (**1a**)	$-(CH_2)_3-$ (**2d**)	72 (**3d**)
5	H, Ph (**1b**)	C_6H_5, H (**2a**)	77 (**3e**)
6	H, Ph (**1b**)	4-BrC_6H_4, H (**2b**)	78 (**3f**)
7	H, Ph (**1b**)	4-MeOC_6H_4, H (**2c**)	84 (**3g**)
8	H, Ph (**1b**)	4-MeC_6H_4, H (**2e**)	76 (**3h**)
9	H, Ph (**1b**)	Et, H (**2f**)	92 (**3i**)
10	H, Ph (**1b**)	3-pyridinyl, H (**2g**)	67 (**3j**)
11	H, Ph (**1b**)	2-furanyl, H (**2h**)	54 (**3k**)
12	H, 4-MeC_6H_4 (**1c**)	4-BrC_6H_4, H (**2b**)	88 (**3*l***)
13	H, 4-MeC_6H_4 (**1c**)	$-(CH_2)_3-$ (**2d**)	91 (**3m**)
14	H, 4-ClC_6H_4 (**1d**)	4-BrC_6H_4, H (**2b**)	76 (**3n**)
15	H, 4-ClC_6H_4 (**1d**)	$-(CH_2)_3-$ (**2d**)	68 (**3o**)
16	H, ^{n}Bu (**1e**)	4-BrC_6H_4, H (**2b**)	93 (**3p**)
17	5-Cl, Ph (**1f**)	4-BrC_6H_4, H (**2b**)	80 (**3q**)
18	5-Cl, Ph (**1f**)	4-MeOC_6H_4, H (**2c**)	62 (**3r**)
19	5-Cl, Ph (**1f**)	$-(CH_2)_3-$ (**2d**)	62 (**3s**)
20	5-Cl, Ph (**1f**)	4-MeC_6H_4, H (**2e**)	66 (**3t**)
21	5-Cl, cyclopropyl (**1g**)	4-BrC_6H_4, H (**2b**)	77 (**3u**)
22	5-F, ^{n}Bu (**1h**)	4-BrC_6H_4, H (**2b**)	66 (**3v**)
23	4-F, Ph (**1i**)	4-BrC_6H_4, H (**2b**)	55 (**3w**)
24	4-OMe, Ph (**1j**)	4-BrC_6H_4, H (**2b**)	70 (**3x**)

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

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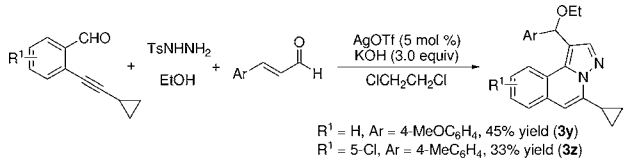
catalysts or reducing the amount of base. Thus, under the preliminary optimized conditions, we started to explore the scope of this multicomponent reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, methanol, and α,β-unsaturated aldehyde or ketone. The results are presented in Table 1. From Table 1, we found that all reactions proceeded smoothly to afford the expected *H*-pyrazolo[5,1-*a*]isoquinolines in moderate to good yields. For instance, reaction of 2-(2-cyclopropylethynyl)benzaldehyde **1a**, 4-methylbenzenesulfonohydrazide, methanol, and (*E*)-3-(4-bromophenyl)-acrylaldehyde **2b** gave rise to the corresponding *H*-pyrazolo[5,1-*a*]isoquinoline **3b** in 76% yield under the standard conditions (entry 2). A similar result was generated when (*E*)-3-(4-methoxyphenyl)acrylaldehyde **2c** was employed as a replacement (78% yield, entry 3). Cyclohex-2-enone **2d** was a suitable partner in the above reaction as well, which afforded the desired product **3d** in 72% yield (entry 4). When 2-alkynylbenzaldehyde **1b** was utilized as the substrate in this multicomponent reaction, not only 3-arylacrylaldehyde but also 3-alkylacrylaldehyde was workable in this transformation (entries 5−9). In addition, good results were obtained when (*E*)-3-(pyridin-3-yl)acrylaldehyde **2g** or (*E*)-3-(furan-2-yl)acrylaldehyde **2h** was employed as a substrate in the reaction of 2-alkynylbenzaldehyde **1b**, sulfonohydrazide, with methanol (entries 10 and 11). Subsequently we examined other 2-alkynylbenzaldehydes with various substituents on the aromatic ring or attached to the triple bond. As expected, all reactions worked well to furnish the desired *H*-pyrazolo[5,1-*a*]isoquinolines (entries 12−24).

Meanwhile, reactions with ethanol as a partner instead of methanol under the standard conditions were tested (Scheme 3). Compound **3y** was obtained in 45% yield in the reaction

Scheme 3. Multicomponent Reaction of 2-Alkynylbenzaldehyde, Sulfonohydrazide, Ethanol, and α,β-Unsaturated Aldehyde



of 2-(2-cyclopropylethynyl)benzaldehyde **1a**, 4-methylbenzenesulfonohydrazide, ethanol, and (*E*)-3-(4-methoxyphenyl)acrylaldehyde **2c**. 2-Alkynylbenzaldehyde **1g** reacted with (*E*)-3-(4-methylphenyl)acrylaldehyde **2e**, 4-methylbenzenesulfonohydrazide, and ethanol leading to the expected product **3z** in 33% yield.

As described above, the generated *H*-pyrazolo[5,1-*a*]isoquinoline, which incorporated both isoquinoline and pyrazolo[1,5-*a*]pyridine skeletons, should be regarded as a privileged scaffold as well. Thus, these compounds were screened with several biological assays. No active compounds were found for the DPP4 and SHP-1 assays. Compound **3t** shows an interesting result as an Aurora A inhibitor (IC_{50} 13.43 μM). Other assays including CDC25B, TC-PTP, and PTP1B assays were screened meanwhile, and the preliminary results were displayed in the Supporting Information. It is well-known that the inhibitor of CDC25B is recognized as one of the feasible channels of preventing and curing malignant tumors.[12] On the other hand, protein tyrosine phosphatase 1 B (PTP1B) has been proved to be a novel target for diabetes and obesity since it plays an important role in the negative regulation of insulin signaling pathway. Inhibition of PTP1B's activity could improve the sensitivity of insulin signaling.[13] From the screening, it was found that *H*-pyrazolo[5,1-*a*]isoquinolines showed promising results for the above assays. Among the compounds, *H*-pyrazolo[5,1-*a*]isoquinoline **3t** was the most effective one (CDC25B, IC_{50} 2.19 μg/mL; TC-PTP, IC_{50} 4.50 μg/mL; PTP1B, IC_{50} 1.75 μg/mL. (For details, please see the Supporting Information.)

In summary, we have described a novel and highly efficient route for the generation of diverse *H*-pyrazolo[5,1-*a*]isoquinolines via a multicomponent reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, alcohol, and α,β-unsaturated aldehyde or ketone. The advantages of this method include good substrate generality, mild conditions, and easy availability of starting materials. Subsequent biological assays show that some of these compounds display promising activities for inhibition of CDC25B, TC-PTP, and PTP1B. The focused library of *H*-pyrazolo[5,1-*a*]isoquinoline is constructed currently.

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

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