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Facile Assembly of *H*-Pyrazolo[5,1-*a*]isoquinolines *via* Silver Triflate-Catalyzed One-Pot Tandem Reaction of 2-Alkynylbenzaldehyde, Sulfonohydrazide, and Ketone or Aldehyde

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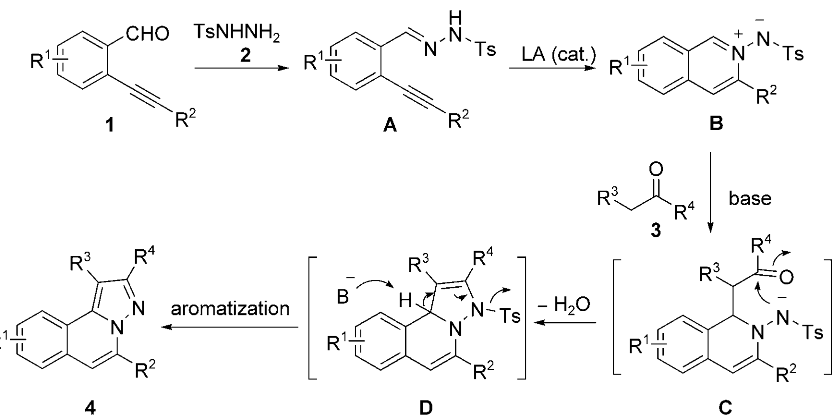
Abstract: A novel and efficient route for the generation of *H*-pyrazolo[5,1-*a*]isoquinolines *via* silver triflate-catalyzed one-pot tandem reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and ketone or aldehyde is described. This reaction proceeds with good functional group tolerance under mild conditions with high efficiency and excellent selectivity.

Keywords: aldehydes; 2-alkynylbenzaldehydes; ketones; *H*-pyrazolo[5,1-*a*]isoquinolines; silver triflate; sulfonohydrazide

Introduction

The availability of practical routes for the generation of small molecules-based natural products is of the utmost urgency and importance in biomedical research.[1] In the last decade, diversity-oriented synthesis has been widely used to efficiently generate diverse small molecules. Among the strategies employed in diversity-oriented chemical synthesis, multicomponent reactions are very attractive processes that push the limits of synthetic efficiency by using more than two reactants to create novel products with an optimal number of new bonds and functionalities.[2] These reactions are ideally suited for the construction of natural product-like libraries prone to display biological activity.[3] As a privileged fragment, isoquinoline is known to show a broad spectrum of biological activities[4,5] and the prominence of isoquinolines in natural products and biologically active molecules has prompted considerable efforts toward their preparation.[6–8] Among the family of isoquinolines, the fused isoquinolines have attracted much attention. For instance, the lamellarin alkaloids which constitute a family of novel marine natural products, contain a highly substituted fused 1,2-dihydroisoquinoline core.[9] Among these compounds, lamellarin D has been discovered as a potent inhibitor of human topoisomerase I[10] and lamellarin α-20-sulfate displays selective inhibition against HIV-1 integrase *in vitro*.[11] Thus, the development of novel and efficient routes for rapid access to functionalized isoquinolines under mild conditions is of high demand.

Recently, we have witnessed the important progress of cascade reactions[12] using 2-alkynylbenzaldehyde as a versatile building block for construction of heterocycles.[13] Based on these results, we have developed efficient routes for the construction of nitrogen-containing heterocycles starting from 2-alkynylbenzaldoxime or *N′*-(2-alkynylbenzylidene)hydrazide.[14] In order to build up a diverse library of fused isoquinolines for our subsequent biological assays, we are interested in the methodology development for the generation of fused isoquinoline compounds. Prompted by the advancement of multi-component reactions and our efforts in *N′*-(2-alkynylbenzylidene)hydrazide chemistry, we conceived that *H*-pyrazolo[5,1-*a*]isoquinolines might be easily accessible *via* a one-pot tandem reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and ketone or aldehyde (Scheme 1). 2-Alkynylbenzaldehydes **1** could be easily obtained *via* a Sonogashira reaction of 2-bromobenzaldehyde with alkyne. After condensation with sulfonohydrazide **2**, *N′*-(2-alkynylbenzylidene)hydrazide **A** would be afforded. Subsequently, the 6-*endo*-cyclization would occur to generate the isoquinolinium-2-yl amide **B** in the presence of suitable Lewis acid. In this step, the

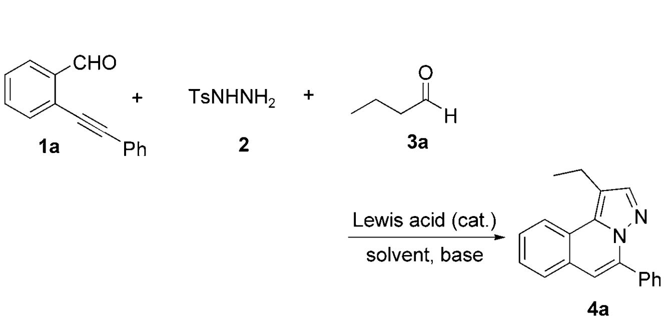


Scheme 1. Proposed route for one-pot tandem reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and ketone or aldehyde.

formation of a π-complex *via* coordination of the alkynyl moiety of **1** to the Lewis acid would be involved, thus activating the triple bond for further cyclization. Meanwhile, the *in situ* formed enolate (derived from ketone or aldehyde **3** in the presence of base) would attack the isoquinolinium-2-yl amide **B** to produce intermediate **C**. Subsequent intramolecular condensation and aromatization would give rise to the desired *H*-pyrazolo[5,1-*a*]isoquinoline **4**. However, there are several questions associated with the proposed synthetic route, such as selectivity, compatibility, and relative rates. Thus, to verify the practicability of the proposed route as shown in Scheme 1, we initiated the search for suitable conditions for this transformation.

Results and Discussion

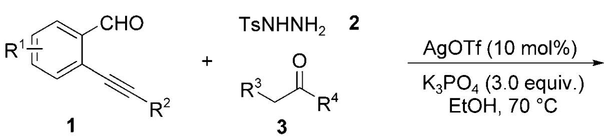
Initially, a set of experiments was carried out using 2-alkynylbenzaldehyde **1a**, sulfonohydrazide **2**, and butyraldehyde **3a** as model substrates (Scheme 2). Since the condensation worked efficiently in ethanol for the reaction of 2-alkynylbenzaldehyde **1a** with sulfonohydrazide **2**, and silver triflate was demonstrated as the most effective catalyst for the subsequent 6-*endo*-cyclization,[13] at the outset the reactions were catalyzed by AgOTf (10 mol%) in EtOH in the presence of different bases. To our delight, small amounts of product **4a** were formed when diisopropylamine, proline, piperidine, or 2,2,6,6-tetramethylpiperidine was utilized in the reaction. However, the large major product isolated was the isoquinolinium-2-yl amide. Elevating the reaction temperature or increasing the amount of butyraldehyde **3a** could not improve the result. We then shifted our focus on inorganic bases. Gratifyingly, the reaction proceeded smoothly in the presence of Na_2CO_3 at 70 °C, which gave rise to the desired product **4a** in 80% yield. Further investigation revealed that K_3PO_4 was the best choice with a 96% isolated yield. Reducing the amount of silver triflate retarded the reaction.



Scheme 2. Initial studies for one-pot tandem reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide **2**, and butyraldehyde **3a**.

Using the mild conditions [AgOTf (10 mol%), K_3PO_4 (3.0 equiv.), EtOH, 70 °C], the scope of this one-pot tandem reaction was investigated, and the results are shown in Table 1. All reactions proceeded smoothly leading to the desired *H*-pyrazolo[5,1-*a*]isoquinolines **4** in good to excellent yields. For instance, reaction of 2-alkynylbenzaldehyde **1a**, sulfonohydrazide **2**, and pentan-3-one **3b** afforded the expected product **4b** in 86% yield (Table 1, entry 2). A similar result was obtained when cyclohexanone **3d** was used as a replacement (83% yield, Table 1, entry 4). Various acetophenones **3e–3i** were employed in the reaction of 2-alkynylbenzaldehyde **1a** and sulfonohydrazide **2** as well (Table 1, entries 5–9). This silver-catalyzed *H*-pyrazolo[5,1-*a*]isoquinoline formation was found to be workable for acetophenones **3e–3i** with electron-withdrawing and -donating substituents on the aromatic backbone. Interestingly, it was found that the hydroxy group as substitution in the substrate **3f** or **3g** was well tolerated under these conditions and *H*-pyrazolo[5,1-*a*]isoquinoline **4f** or **4g** could be

Table 1. Silver triflate-catalyzed one-pot tandem reaction of 2-alkynylbenzaldehyde **1**, sulfonohydrazide **2**, and ketone or aldehyde **3**.



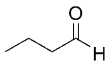
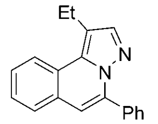
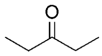
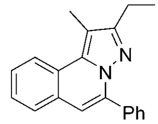
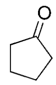
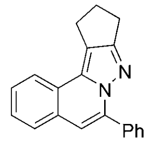
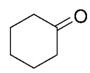
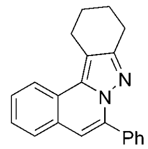
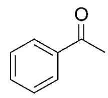
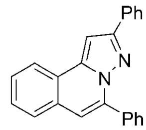
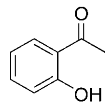
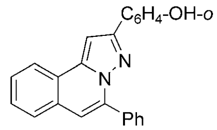
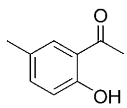
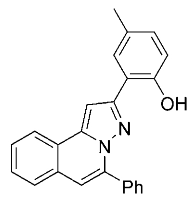
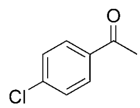
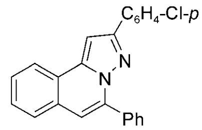
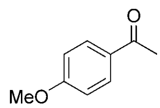
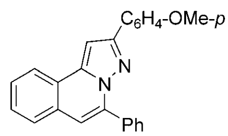
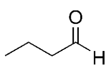
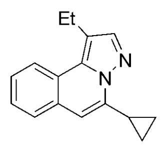
Entry	R^1, R^2	Compound **3**		Product **4**	Yield [%][a]
1	H, C_6H_5 (**1a**)	**3a**			96 (**4a**)
2	H, C_6H_5 (**1a**)	**3b**			86 (**4b**)
3	H, C_6H_5 (**1a**)	**3c**			67 (**4c**)
4	H, C_6H_5 (**1a**)	**3d**			83 (**4d**)
5	H, C_6H_5 (**1a**)	**3e**			81 (**4e**)
6	H, C_6H_5 (**1a**)	**3f**			77 (**4f**)
7	H, C_6H_5 (**1a**)	**3g**			70 (**4g**)
8	H, C_6H_5 (**1a**)	**3h**			63 (**4h**)
9	H, C_6H_5 (**1a**)	**3i**			68 (**4i**)
10	H, cyclopropyl (**1b**)	**3a**			98 (**4j**)

Table 1. (Continued)

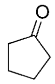
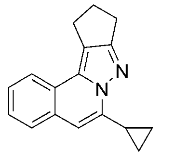
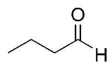
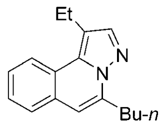
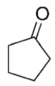
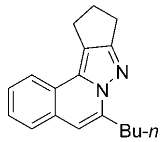
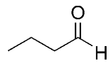
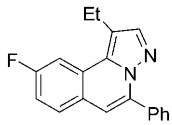
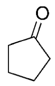
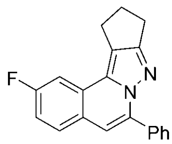
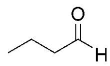
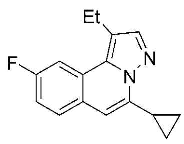
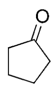
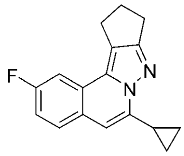
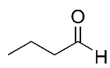
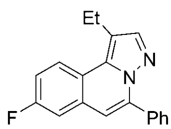
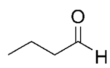
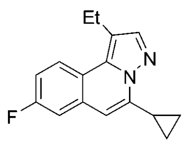
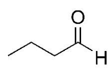
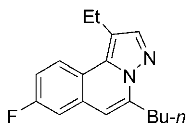
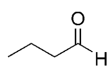
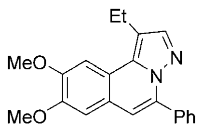
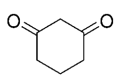
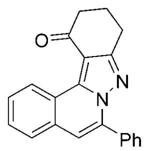
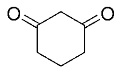
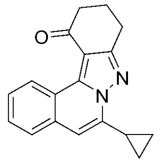
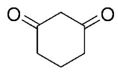
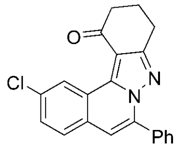
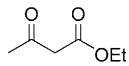
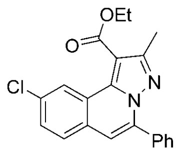
Entry	R^1, R^2		Compound **3**	Product **4**	Yield [%][a]
11	H, cyclopropyl (**1b**)	**3c**			80 (**4k**)
12	H, *n*-Bu (**1c**)	**3a**			91 (**4l**)
13	H, *n*-Bu (**1c**)	**3c**			81 (**4m**)
14	5-F, C_6H_5 (**1d**)	**3a**			98 (**4n**)
15	5-F, C_6H_5 (**1d**)	**3c**			68 (**4o**)
16	5-F, cyclopropyl (**1e**)	**3a**			86 (**4p**)
17	5-F, cyclopropyl (**1e**)	**3c**			90 (**4q**)
18	4-F, C_6H_5 (**1f**)	**3a**			95 (**4r**)
19	4-F, cyclopropyl (**1g**)	**3a**			90 (**4s**)
20	4-F, *n*-Bu (**1h**)	**3a**			85 (**4t**)
21	4,5-$(OMe)_2$, C_6H_5 (**1i**)	**3a**			67 (**4u**)
22	H, C_6H_5 (**1a**)	**3j**			40 (**4v**)

Table 1. (Continued)

Entry	R^1, R^2	Compound **3**		Product **4**	Yield [%][a]
23	H, cyclopropyl (**1b**)	**3j**			71 (**4w**)
24	5-Cl, C_6H_5 (**1j**)	**3j**			35 (**4x**)
25	5-Cl, C_6H_5 (**1j**)	**3k**			31 (**4y**)

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

isolated in 77% and 70% yield, respectively (Table 1, entries 6 and 7). Other 2-alkynylbenzaldehydes were tested meanwhile. In addition to the phenyl group attached to the C≡C triple bond, 2-alkynylbenzaldehydes with a cyclopropyl or *n*-butyl group were found to be suitable as well to generate the desired products in good yields (Table 1, entries 10–13). The conditions have also proven to be useful for 2-alkynylbenzaldehydes with substituents in the aromatic ring. For example, an almost quantitative yield of compound **4n** was isolated for the reaction of 2-alkynylbenzaldehyde **1d** with sulfonohydrazide **2** and butyraldehyde **3a** (98% yield, Table 1, entry 14). Cyclopentanone **3c** was also a suitable partner in this reaction, which furnished the expected product **4o** in 68% yield (Table 1, entry 15). A good yield was observed as well in the reaction of methoxy-substituted 2-alkynylbenzaldehyde **1i** with sulfonohydrazide **2** and butyraldehyde **3a** (Table 1, entry 21). The structure of compound **4r** was verified by X-ray diffraction analysis meanwhile (Figure 1). Reactions employing 1,3-dicarbonyl compounds **3j** and **3k** as substrates were examined as well (Table 1, entries 22–25). For example, reaction of 2-alkynylbenzaldehyde **1b**, sulfonohydrazide **2**, and cyclohexane-1,3-dione **3j** gave rise to the corresponding product **4w** in 71% yield (Table 1, entry 23). The yield was decreased to 35% when 2-alkynylbenzaldehyde **1j** was used as a replacement in the reaction (Table 1, entry 24). A similar result was generated when ethyl 3-oxobutanoate **3k** was tested (Table 1, entry 25).

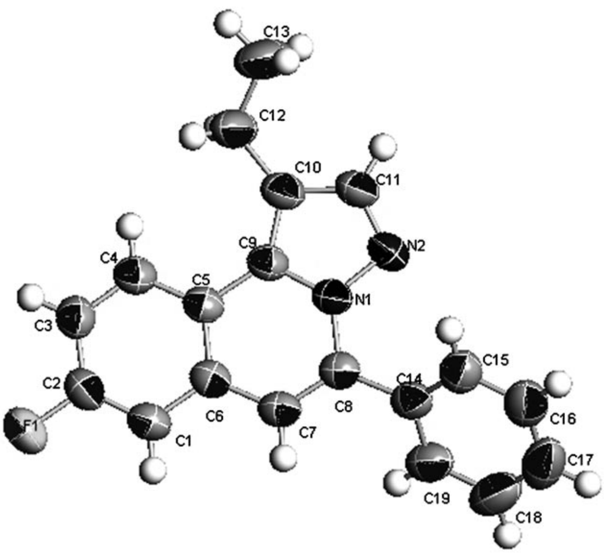


Figure 1. ORTEP illustration of compound **4r** (30% probability ellipsoids).

Conclusions

In conclusion, we have described a novel and efficient route for the generation of *H*-pyrazolo[5,1-*a*]isoquinolines *via* the silver triflate-catalyzed one-pot tandem reaction of 2-alkynylbenzaldehyde **1**, sulfonohydrazide **2**, and ketone or aldehyde **3**. This reaction proceeded with good functional group tolerance under mild conditions with high efficiency and excellent selectivity. Currently, the related library construction and screening for biological activity of these small molecules are ongoing, and the results will be reported in due course.

Experimental Section

General Procedure for AgOTf-Catalyzed One-Pot Tandem Reaction of 2-Alkynylbenzaldehyde 1, Sulfonohydrazide 2, and Ketone or Aldehyde 3

2-Alkynylbenzaldehyde **1** (0.3 mmol) was added to a solution of sulfonohydrazide **2** (0.3 mmol) in EtOH (1.0 mL). The mixture was stirred at room temperature for 10 min. Then AgOTf (7.7 mg, 10 mol%) was added and the reaction mixture was heated to 70 °C. Subsequently, ketone or aldehyde **3** (0.6 mmol) and K_3PO_4 (0.9 mmol) were added in the mixture. After completion of reaction as indicated by TLC, the mixture was diluted with ethyl acetate (5.0 mL) and quenched with water (5.0 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by flash chromatography column on silica gel (eluting with PE/EA = 60/1 to 20/1) to provide the desired product **4**.

1-Ethyl-5-phenyl-*H*-pyrazolo[5,1-*a*]isoquinoline (4a): yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.45$ (t, $J = 7.3$ Hz, 3H), 3.07–3.13 (m, 2H), 6.95 (s, 1H), 7.46–7.57 (m, 5H), 7.70 (d, $J = 7.3$ Hz, 1H), 7.83–7.85 (m, 3H), 8.24 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 19.6, 112.5, 117.2, 123.3, 125.5, 127.2, 127.3, 127.4, 128.4, 129.3, 129.5, 129.6, 134.2, 134.6, 138.7, 140.4; HR-MS: $m/z = 273.1380$, calcd. for $C_{19}H_{17}N_2$ ($M^+ + H$): 273.1392.

2-Ethyl-1-methyl-5-phenyl-*H*-pyrazolo[5,1-*a*]isoquinoline (4b): yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.3$ Hz, 3H), 2.54 (s, 3H), 2.80–2.85 (m, 2H), 6.83 (s, 1H), 7.39–7.49 (m, 5H), 7.61 (d, $J = 7.3$ Hz, 1H), 7.90–7.92 (m, 2H), 8.23 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.8$, 14.4, 20.2, 107.2, 111.5, 123.0, 125.6, 126.8, 126.9, 127.1, 128.3, 129.2, 129.6, 129.8, 134.3, 135.9, 138.4, 154.8; HR-MS: $m/z = 287.1530$, calcd. for $C_{20}H_{19}N_2$ ($M^+ + H$): 287.1543 (for details, please see Supporting Information)

Crystallographic data for the structure **4r** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 764298. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].

Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of compound **4** are available as Supporting Information.

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