Rapid Access to *H*-Pyrazolo[5,1-*a*]isoquinolines via Sequential Reaction of *N′*-(2-Alkynylbenzylidene)hydrazides

Zhiyuan Chen,[a] Xiaolin Pan,[a] Jie Wu*[a,b]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, P. R. of China
Fax +86(21)65641740; E-mail: jie_wu@fudan.edu.cn

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China

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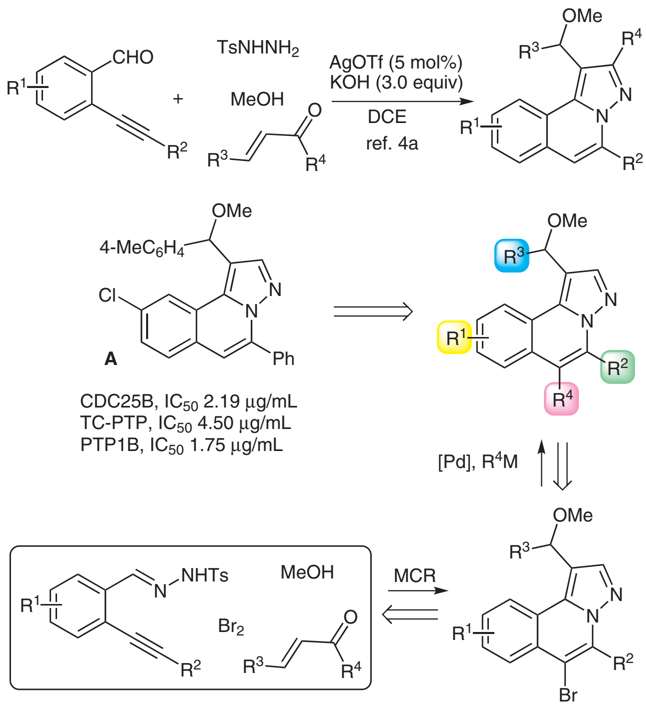
Abstract: Diverse *H*-pyrazolo[5,1-*a*]isoquinolines are efficiently synthesized via sequential reaction of *N′*-(2-alkynylbenzylidene)hydrazides. Bromo-containing isoquinolinium, generated from *N′*-(2-alkynylbenzylidene)hydrazide with bromine, reacts with α,β-unsaturated aldehyde and methanol under mild conditions, leading to 6-bromo-1-(methoxymethyl)-*H*-pyrazolo[5,1-*a*]isoquinolines in moderate to good yields. Further elaboration via palladium catalyzed Suzuki–Miyaura coupling or Heck reaction produces diverse *H*-pyrazolo[5,1-*a*]isoquinoline compounds.

Key words: alkynes, hydrazide, bromine, methanol, isoquinoline, α,β-unsaturated aldehyde

A multi-component reaction is a highly attractive device that can be used to generate complex and diverse small molecules in a one-pot procedure.[1] This strategy has been widely applied in drug discovery programs as a practical and efficient tool for providing large collections of natural-product-like compounds.[2] Over the last few years, we have been involved in the development of methodologies for accessing privileged scaffolds that can be used in a range of biological assays.[3,4] Very recently, we reported a multi-component reaction of 2-alkynylbenzaldehydes, sulfonohydrazides, alcohols, and α,β-unsaturated aldehydes or ketones.[4a] This reaction was highly efficient, leading to *H*-pyrazolo[5,1-*a*]isoquinolines in good yields. Moreover, promising biological results were obtained with these compounds, which acted as a CDC25B inhibitor, a TC-PTP inhibitor, and a PTP1B inhibitor (Scheme 1). The moderate activity prompted us to develop an efficient synthetic protocol and to evaluate the resulting analogues, with the expectation of finding improved inhibitors. Additionally, other biological assays would be performed,[5–7] because this skeleton could be regarded as a privileged scaffold. Thus, we initiated a program to explore a facile route for rapid access to diverse *H*-pyrazolo[5,1-*a*]isoquinoline molecules. The proposed synthetic route is presented in Scheme 1. Because *N′*-(2-alkynylbenzylidene)hydrazide could be easily cyclized with bromine under mild conditions, affording isoquinolinium-2-yl amide,[8] we expected that the bromo-containing *H*-pyrazolo[5,1-*a*]isoquinolines could be formed in a one-pot reaction of *N′*-(2-alkynylbenzylidene)hydrazide, bromine, methanol, and α,β-unsaturated aldehyde under suitable conditions. These compounds could be further decorated via palladium-catalyzed cross-coupling reactions to generate diverse *H*-pyrazolo[5,1-*a*]isoquinolines. With these considerations in mind, we started to investigate this transformation.



Scheme 1 Proposed synthetic route for the generation of diverse *H*-pyrazolo[5,1-*a*]isoquinolines

To establish the optimized conditions, we tested the reaction of *N′*-(2-alkynylbenzylidene)hydrazide (**1a**), bromine, methanol, and cinnamaldehyde (**2a**) in the presence of different bases and solvents (Table 1). To our delight, we obtained the desired product **3a** in 35% yield when the reaction was carried out in tetrahydrofuran (THF) with KOH as the base at 40 °C (Table 1, entry 1). A similar result was afforded when *t*-BuOK was used as base in the above reaction (Table 1, entry 2). Other inorganic bases, such as K_3PO_4, NaOH, and Cs_2CO_3 were then tested

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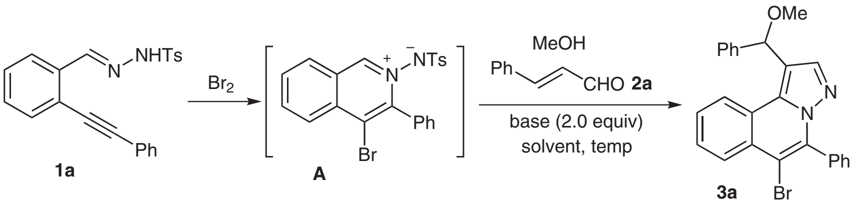
Table 1 Initial Studies for the One-Pot Reaction of *N*′-(2-Alkynylbenzylidene)hydrazide (**1a**), Bromine, Methanol, and Cinnamaldehyde (**2a**)



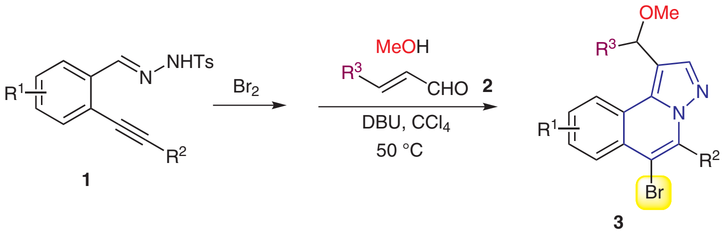
Entry	Base	Solvent[a]	Temp. (°C)	Time (h)	Yield (%)[b]
1	KOH	THF	40	48	35
2	*t*-BuOK	THF	40	48	32
3	K_3PO_4	THF	40	48	22
4	NaOH	THF	40	48	15
5	Cs_2CO_3	THF	40	48	9
6	DBU	THF	40	48	44
7	DBU	DCE	40	48	41
8	DBU	CH_2Cl_2	40	48	64
9	DBU	$CHCl_3$	40	48	39
10	DBU	CCl_4	40	48	73
11	DBU	DMF	40	48	trace
12	DBU	MeCN	40	48	55
13	DBU	toluene	40	48	65
14	DBU	1,4-dioxane	40	48	27
15	DBU	CCl_4	50	24	80
16	DBU	CCl_4	60	24	79

[a] DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide.
[b] Isolated yield based on *N*′-(2-alkynylbenzylidene)hydrazide (**1a**).

(Table 1, entries 3–5), however, all gave inferior results compared with KOH. The yield was increased to 44% when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base in the reaction (Table 1, entry 6). The solvent screening showed that CCl_4 was superior to other solvents, which furnished the corresponding product **3a** in 73% yield (Table 1, entry 10). The result could be improved further when the reaction was performed at 50 °C (80% yield, Table 1, entry 15). However, no difference was observed when the reaction was carried out at higher temperatures (Table 1, entry 16).

With the optimized conditions in hand, we investigated the scope of the one-pot reaction of *N*′-(2-alkynylbenzylidene)hydrazide **1**, bromine, methanol, and α,β-unsaturated aldehyde **2** (Table 2). Electronic variation of the aryl group of the cinnamaldehyde did influence the yield. For instance, when (*E*)-3-*p*-tolylacrylaldehyde (**2b**) or (*E*)-3-(4-methoxyphenyl)acrylaldehyde (**2c**) was employed in the reaction of *N*′-(2-alkynylbenzylidene)hydrazide (**1a**), bromine, and methanol, the desired product was formed in moderate yield (Table 2, entries 2 and 3). However, compound **3d** could be obtained in 87% yield when (*E*)-3-(4-bromophenyl)acrylaldehyde (**2d**) was used in the reaction (Table 2, entry 4). In addition, a good result was generated when (*E*)-3-(pyridin-3-yl)acrylaldehyde (**2e**) was employed as a substrate in the above reaction (Table 2, entry 5). To our surprise, in contrast to 3-arylacrylaldehyde, 3-alkylacrylaldehyde was not suitable for this transformation (Table 2, entry 6). Subsequently, we examined other *N*′-(2-alkynylbenzylidene)hydrazides with various substituents on the aromatic ring or attached to the triple bond. As can be seen, the substituents were tolerated, leading to the desired products in good yields (Table 2, entries 7–16).

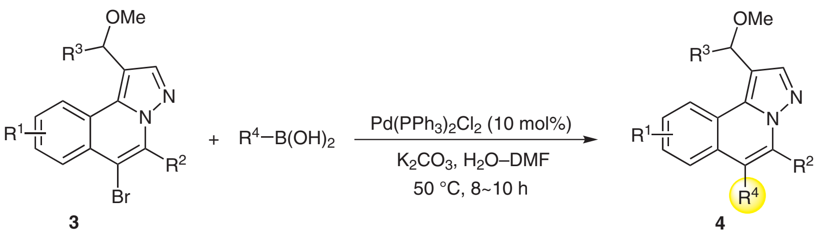
Table 2 One-Pot Reaction of *N'*-(2-Alkynylbenzylidene)hydrazide **1**, Bromine, Methanol, and α,β-Unsaturated Aldehyde **2**



Entry	R^1, R^2	R^3	Product	Yield (%)[a]
1	H, Ph (**1a**)	Ph (**2a**)	**3a**	80
2	H, Ph (**1a**)	4-MeC_6H_4 (**2b**)	**3b**	51
3	H, Ph (**1a**)	4-$MeOC_6H_4$ (**2c**)	**3c**	54
4	H, Ph (**1a**)	4-BrC_6H_4 (**2d**)	**3d**	87
5	H, Ph (**1a**)	pyridin-3-yl (**2e**)	**3e**	78
6	H, Ph (**1a**)	Et (**2f**)	**3f**	0
7	H, *n*-Bu (**1c**)	Ph (**2a**)	**3g**	70
8	H, *n*-Bu (**1c**)	pyridin-3-yl (**2e**)	**3h**	56
9	5-Me, Ph (**1d**)	Ph (**2a**)	**3i**	80
10	5-Me, Ph (**1d**)	4-MeC_6H_4 (**2b**)	**3j**	44
11	5-Me, Ph (**1d**)	4-$MeOC_6H_4$ (**2c**)	**3k**	40
12	5-Me, Ph (**1d**)	4-BrC_6H_4 (**2d**)	**3l**	73
13	5-Me, Ph (**1d**)	pyridin-3-yl (**2e**)	**3m**	63
14	4-F, cyclopropyl (**1e**)	pyridin-3-yl (**2e**)	**3n**	54
15	5-F, cyclopropyl (**1e**)	Ph (**2a**)	**3o**	50
16	5-F, cyclopropyl (**1e**)	4-BrC_6H_4 (**2d**)	**3p**	60

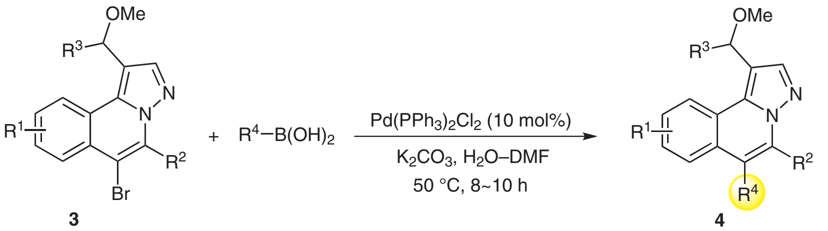
[a] Isolated yield based on *N'*-(2-alkynylbenzylidene)hydrazide **1**.

Table 3 Palladium-Catalyzed Suzuki–Miyaura Coupling Reaction of *H*-Pyrazolo[5,1-*a*]isoquinoline **3** with Arylboronic Acid



Entry	Compound **3**	R^4	Product **4**	Yield (%)[a]
1	**3a**	Ph	**4a**	99
2	**3a**	4-MeC_6H_4	**4b**	98
3	**3a**	4-$MeOC_6H_4$	**4c**	90
4	**3a**	4-$F_3CC_6H_4$	**4d**	94
5	**3e**	Ph	**4e**	98
6	**3i**	Ph	**4f**	96

Table 3 Palladium-Catalyzed Suzuki–Miyaura Coupling Reaction of *H*-Pyrazolo[5,1-*a*]isoquinoline **3** with Arylboronic Acid (continued)



Entry	Compound **3**	R^4	Product **4**	Yield (%)[a]
7	**3m**	Ph	**4g**	93
8	**3o**	Ph	**4h**	83

[a] Isolated yield based on *H*-pyrazolo[5,1-*a*]isoquinoline **3**.

We subsequently explored the application of bromo-containing *H*-pyrazolo[5,1-*a*]isoquinoline **3** in palladium-catalyzed Suzuki–Miyaura coupling reactions (Table 3).[9] The reactions worked efficiently with arylboronic acids in the presence of $[PdCl_2(PPh_3)_2]$ (10 mol%) and K_2CO_3 in DMF–H_2O at 50 °C. As expected, all products were afforded in good to excellent yields. For example, almost quantitative yield of product **4a** was obtained when *H*-pyrazolo[5,1-*a*]isoquinoline (**3a**) reacted with phenylboronic acid under the conditions described above (Table 3, entry 1). Interestingly, when compound **3l** was utilized as a substrate, product **4i** could be generated in the presence of 2.2 equivalents of phenylboronic acid (Scheme 2, eq. 1). *n*-Butyl acrylate was also used as a coupling partner in the reaction of *H*-pyrazolo[5,1-*a*]isoquinoline (**3a**), which furnished compound **4j** in 80% yield (Scheme 2, eq. 2).

In conclusion, we have described a one-pot reaction of *N′*-(2-alkynylbenzylidene)hydrazide, bromine, α,β-unsaturated aldehyde, and methanol that generates 6-bromo-1-(methoxymethyl)*H*-pyrazolo[5,1-*a*]isoquinolines in moderate to good yields. Further elaboration via palladium-catalyzed Suzuki–Miyaura coupling or Heck reaction produces diverse *H*-pyrazolo[5,1-*a*]isoquinoline compounds. Efforts to screen the biological activity of these small molecules are underway in our laboratory, and the results will be reported in due course.

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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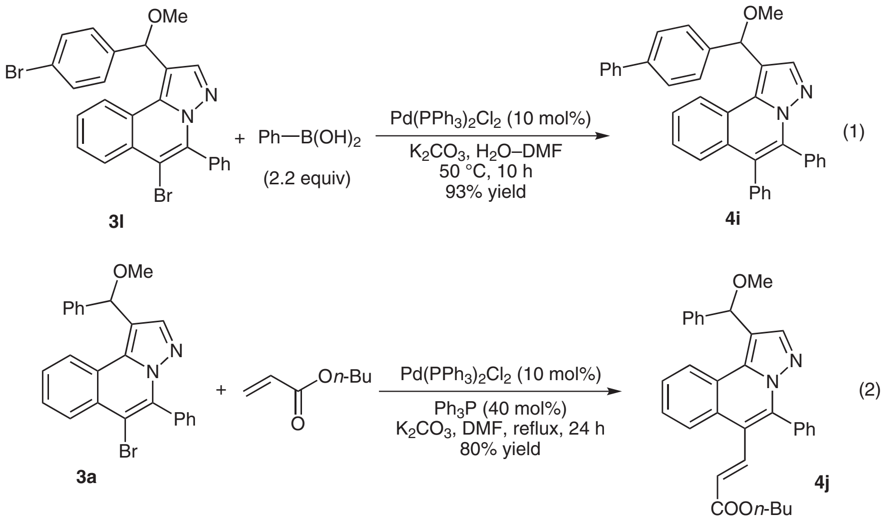

Scheme 2 Palladium-catalyzed Suzuki–Miyaura coupling or Heck reaction of *H*-pyrazolo[5,1-*a*]isoquinoline **3**

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