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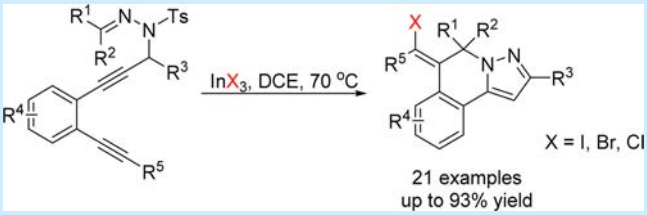
Synthesis of 5,6-Dihydropyrazolo[5,1-*a*]isoquinolines through Indium(III)-Promoted Halocyclizations of *N*-Propargylic Sulfonylhydrazones

Ren-Hao Li, Cheng-Ke Ding, Ya-Nan Jiang, Zong-Cang Ding, Xiao-Ming An, Hai-Tao Tang, Qi-Wei Jing, and Zhuang-Ping Zhan*

Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, People's Republic of China

Supporting Information

ABSTRACT: A novel method for the preparation of 5,6-dihydropyrazolo[5,1-*a*]isoquinoline via indium(III)-promoted halocyclizations of *N*-propargylic sulfonylhydrazones has been developed. The pyrazole and 3,4-dihydroisoquinoline moieties were synchronously formed via a cascade cyclization reaction using easily assembled open-chain compounds. The pyrazole and 3,4-dihydroisoquinoline moieties were formed via a cascade cyclization reaction using easily assembled open-chain compounds.



The pyrazole core is present in many pharmaceuticals,[1] agrochemicals,[2] biologically active compounds,[3] and other useful chemicals.[4] Among those pyrazole derivatives, compounds based on the pyrazolo[1,5-*a*]pyridine framework have attracted increasing attention due to their promising biological activities. Typical examples of bioactive pyrazolo[1,5-*a*]-pyridines include the well-known antiallergic and cerebroactive agent ibudilast,[5] the novel adenosine A1 receptor antagonist FK838,[6] the adenosine antagonist FK453,[7] and a series of highly selective D4 receptors ligands.[8] Although several strategies have been developed for the synthesis of 5,6-dihydropyrazolo[5,1-*a*] isoquinoline, they usually rely on the functionalization of substrates with the preinstalled pyrazole[9] or 3,4-dihydroisoquinoline[10] ring. As far as we know, methods that form both rings of the 5,6-dihydropyrazolo[5,1-*a*]isoquinoline via a domino reaction have not been reported.

Recently, Lewis acid promoted cyclization of diynes have been actively studied for synthesis of 2,2-disubstituted tetrahydrofurans,[11] indeno[1,2-*c*]chromenes,[12] and indene derivatives.[13] In this context, Snyder and co-workers[14] have recently shown that cyclization of 1,6-diynes promoted by stoichiometric Ga(III) halides produces iodotetrahydropyridines. Indium is widely used in the fields of organic synthesis.[15] We have reported the selective transformations of *N*-propargylic sulfonylhydrazones to (1*E*,3*E*)-2-sulfonyl-1,3-dienes[16] and pyrazoles.[17] As part of our ongoing research, we discovered the synthesis of 5,6-dihydropyrazolo[5,1-*a*]-isoquinoline from *N*-propargylhydrazones bearing diynes via an indium(III)-promoted halocyclization method.

In our initial studies, the reaction of *N*-propargylic sulfonylhydrazone **1a** was investigated (Table 1). Under a nitrogen atmosphere, compound **1a** was reacted with GaI_3 (1.0 equiv) in DCE at 70 °C to give (*Z*)-5-(4-bromophenyl)-6-(iodo(phenyl)methylene)-5,6-dihydropyrazolo[5,1-*a*]-isoquinoline (**2a**) in 50% isolated yield (Table 1, entry 1). The structure of **2a** was confirmed by single-crystal X-ray structure analysis.[18] When we carried out the reaction in the presence of InI_3 (1.0 equiv), the yield was improved to 93% (Table 1, entry 2). Other reagents with halogen such as CuI, CuI_2, ZnI_2, SmI_3, $FeBr_3$, $AuCl_3$, AgBr, elemental iodine, elemental bromine, and ICl were not effective (Table 1, entries 3−12). A screen of In(III) salts revealed In(III) bromide and chloride were suitable catalysts. Under these conditions, the vinyl bromide **3a** and chloride **4a** were isolated in 80% and 64% yields (Table 1, entries 13 and 14). The reaction time required increased from InI_3 to $InBr_3$ to $InCl_3$. With the chloride salt, the reaction required heating at 70 °C in 1,2-dichloroethane (DCE) for 12 h to consume the starting material. InF_3 and $In(OAc)_3$ exhibited no activity in this reaction (Table 1, entries 15 and 16), which may be due to the weak nucleophilicity of F^- and AcO^- compared to other halide anions. Attempts to enhance the efficiency of product formation further by screening different amounts of InI_3 were unsuccessful (Table 1, entries 17 and 18). Some halide sources such as TMSI and KI were screened hoping to reduce the amount of In(III) salt used but without success (Table 1, entries 19 and 20). The formation of **2a** was suppressed by changing the solvents of DCM, acetonitrile, 1,4-dioxane, toluene, DMF, and DMSO.[19] Hence, the optimum conditions involved conducting the reaction in DCE at 70 °C with the use of stoichiometric In(III) halides as the promoter and halide source.

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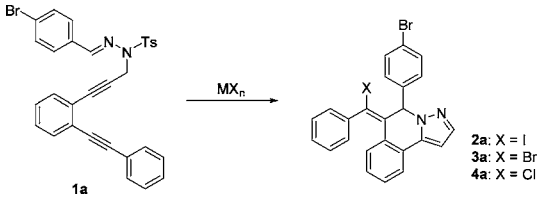
Table 1. Optimization of the Reaction Conditions[a,b]



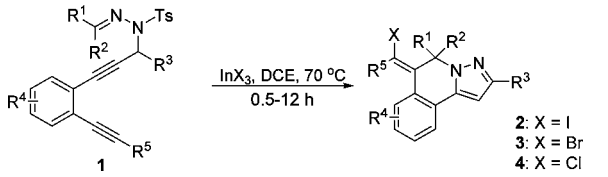
entry	MX_n	time (h)	yield (%)
1	GaI_3	0.5	50
2	InI_3	0.5	93
3	CuI	6	NR[c]
4	CuI_2	6	NR
5	ZnI_2	6	NR
6	SmI_3	6	NR
7	$FeBr_3$	6	NR
8	$AuCl_3$	0.5	complex
9	AgBr	0.5	NR
10	I_2	0.5	complex
11	Br_2	0.5	complex
12	ICl	0.5	complex
13	$InBr_3$	6	80
14	$InCl_3$	12	64
15	InF_3	6	NR
16	$In(OAc)_3$	6	NR
17	InI_3	12	41[d]
18	InI_3	0.5	91[e]
19	InI_3	0.5	complex[f]
20	InI_3	0.5	14[g]

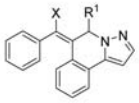
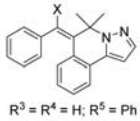
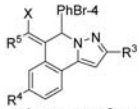
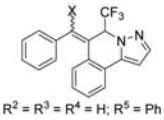
[a]Reaction conditions: **1a** (0.5 mmol), MX_n (0.5 mmol), DCE (5 mL), N_2 atmosphere, 70 °C. [b]Isolated yield. [c]NR = no reaction. [d]Run with 0.25 mmol of InI_3. [e]Run with 1.0 mmol of InI_3. [f]Run with 0.1 mmol of InI_3 and 0.5 mmol of TMSI. [g]Run with 0.1 mmol of InI_3 and 0.5 mmol of KI.

The range of *N*-propargylhydrazones amenable to this chemistry was then explored using InI_3 (Table 2). Hydrazones derived from a number of aldehydes including aryl aldehydes and alkyl aldehydes were all suitable substrates (Table 2, products **2a**–**h**, 54–93% yields). However, the reaction was somewhat sensitive to the electron-donating group and ortho-substitution of the aryl aldehydes. The low yields of **2b** and **2c** were probably caused by the steric hindrance of the *o*-bromo substituent for the former and the electron-donating effect of the −OMe group for the latter. A hydrazone synthesized from ketone was also cyclized (Table 2, product **2i**, 44% yield). *n*-Pentyl-terminated alkyne **1j** also reacted smoothly (Table 2, product **2j**, 40% yield). When R5 = H, the reaction led to a complex product mixture. Branching at the propargylic position (**1k**) or substitution at the linking aryl ring with a methyl group (**1l**) was tolerated (Table 2, products **2k**,**l**, 60–88% yields). The trifluoromethyl (CF_3) group is present in many pharmaceuticals and agrochemicals.[20] As a result, the synthesis of CF_3-substituted heterocycles has attracted considerable attention in recent years. The reaction of hydrazone derived from trifluoroacetaldehyde formed the desired product **2n** in excellent yield (Table 2, product **2n**, 92% yield, isomer ratio of the mixture = 4.0:1.0).

Conversion of hydrazones **1** to the vinyl bromide **3** and vinyl chloride **4** also proceeded smoothly using $InBr_3$ and $InCl_3$ but in diminished efficiency (Table 2). Hydrazones derived from aryl aldehydes were all suitable substrates (Table 2, product **3a**,

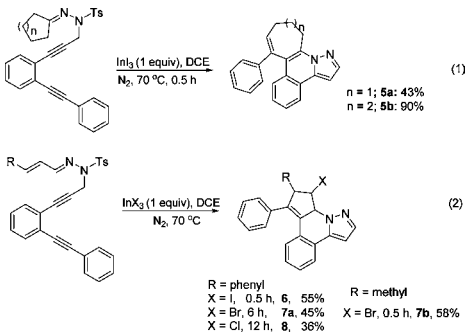
Table 2. Halocyclization Substrate Scope[a,b]



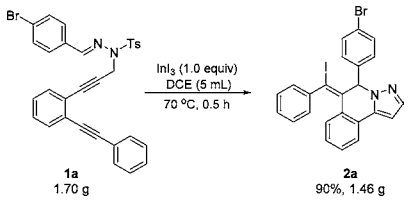
entry	reactant	product	yield (%)
1	**1a** (R^1 = 4-BrPh)		93 (**2a**) 80 (**3a**) 64 (**4a**)
2	**1b** (R^1 = 2-BrPh)		70 (**2b**)
3	**1c** (R^1 = 4-MeOPh)		66 (**2c**) 52 (**3c**) 40 (**4c**)
4	**1d** (R^1 = 4-NO_2Ph)	R^2 = R^3 = R^4 = H; R^5 = Ph	85 (**2d**)
5	**1e** (R^1 = Ph)		78 (**2e**)
6	**1f** (R^1 = 2-Thiophenyl)		55 (**2f**)
7	**1g** (R^1 = 2-Naphthyl)		71 (**2g**)
8	**1h** (R^1 = ethyl)		54 (**2h**)
9	**1i** (R^1 = R^2 = methyl)	 R^3 = R^4 = H; R^5 = Ph	44 (**2i**)
10	**1j** (R^3 = R^4 = H; R^5 = n-pentyl)		40 (**2j**)
11	**1k** (R^3 = methyl; R^4 = H; R^5 = Ph)		60 (**2k**) 54 (**3k**) 46 (**4k**)
12	**1l** (R^3 = H; R^4 = methyl; R^5 = Ph)		88 (**2l**)
13	**1m** (R^3 = R^4 = H; R^5 = 4-BrPh)	R^1 = 4-BrPh; R^2 = H	35(**3m**)
14	**1n** (R^1 = trifluoromethyl)	 R^2 = R^3 = R^4 = H; R^5 = Ph	92 (**2n**) isomer ratio 4.0:1.0[c] 80 (**3n**) isomer ratio 1.6:1.0[c] 71 (**4n**) isomer ratio 1.6:1.0[c]

[a]Reaction conditions: **1** (0.5 mmol) and InX_3 (0.5 mmol) in DCE (5 mL), N_2 atmosphere, 70 °C, 0.5–12 h. [b]Isolated yields. [c]Determined by ^{1}H NMR.

Scheme 1. Tetracyclic Scaffold Products



Scheme 2. Reaction Carried out on Gram Scale



80% yield; product **3c**, 52% yield; product **4a**, 64% yield; product **4c**, 40% yield). Additionally, substrates bearing methyl at the propargylic, 4-BrPh group at the terminated alkyne all

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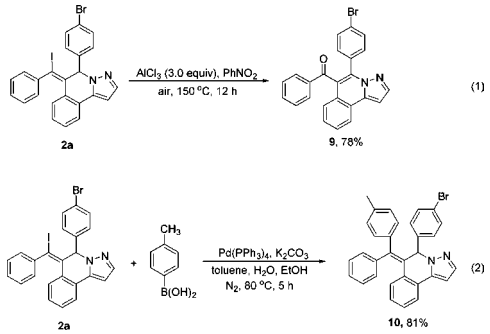
Scheme 3. Synthesis of Pyrazolo[5,1-*a*]isoquinoline 9 and Suzuki−Miyaura Coupling Product 10



reacted smoothly to afford the desired products (Table 2, product **3k**, 54% yield; product **4k**, 46% yield; product **3m**, 35% yield). Notably, cyclization of hydrazones synthesized from trifluoroacetaldehyde produced vinyl bromide and chloride in good yield (Table 2, product **3n**, 80% yield, isomer ratio of the mixture = 1.6:1.0; product **4n**, 71% yield, isomer ratio of the mixture = 1.6:1.0). With the use of indium halides as promoters, the yield increased from $InCl_3$ to $InBr_3$ to InI_3.

However, hydrazones derived from cyclopentanone and cyclohexanone gave the tetracyclic scaffold derivatives **5** followed by a ring-expansion reaction (Scheme 1, eq 1). When the catalyst was reduced to 0.1 equiv, the desired tetracyclic product **5a** was obtained in similar yield (40% yield). And hydrazones derived from cinnamaldehyde and butenal gave the tetracyclic scaffold products **6**−**8** followed by electrophilic addition (Scheme 1, eq 2).

The scalability of this novel 5,6-dihydropyrazolo[5,1-*a*]-isoquinoline synthesis was evaluated by performing the iodocyclization of **1a** on a gram scale. The reaction furnished the desired product **2a** in 90% yield (Scheme 2), similar to that obtained on a smaller scale.

Vinyl halides had been utilized broadly in drug development and natural product synthesis.[21] The vinyl iodide moiety of the product can participate in further transformations. For example, the reaction of 5,6-dihydropyrazolo[5,1-*a*]isoquinoline **2a** with $AlCl_3$ under air afforded ketone **9** in 78% yield (Scheme 3, eq 1). In addition, Suzuki−Miyaura coupling of **2a** with *p*-methylphenylboronic acid produced the tetrasubstituted alkene **10** in good yield (Scheme 3, eq 2).

A plausible mechanism for the reaction is proposed and depicted in Scheme 4. The coordination of the indium(III) catalyst with the alkyne activates the triple bond for nucleophilic attack by the imine nitrogen atom, leading to the cyclized intermediate **11**. Subsequently, intramolecular nucleophilic attack of the alkyne unit of **11** produces tricyclic vinyl cation **12**. Trapping of this vinyl cation by a halide ion leads to **13**. Proto-demetalation and aromatization through elimination of a molecule of TsH results in the generation of the 5,6-dihydropyrazolo[5,1-*a*]isoquinoline products **2**, **3**, or **4**. When R^1, R^2 are cyclopentyl or cyclohexyl, this mechanism also anticipates the formation of ring-expansion product **5** via an intramolecular rearrangement and elimination reaction. When R^1 is hydrogen and R^2 is styryl or propenyl, the vinyl cation **12** proceeds with an electrophilic addition reaction with styryl or propenyl and produces tetracyclic scaffold products **6**−**8**.

In conclusion, we have developed a highly efficient indium(III)-promoted halocyclization method for the synthesis of 5,6-dihydropyrazolo[5,1-*a*]isoquinolines, and the product can be oxidized to afford pyrazolo[5,1-*a*]isoquinolines. In addition, hydrazones derived from cyclic ketones or olefin aldehydes gave the tetracyclic scaffold products followed by ring-expansion or electrophilic addition. Application of the bicyclization protocol for the synthesis of other heterocycles is underway in our laboratory.

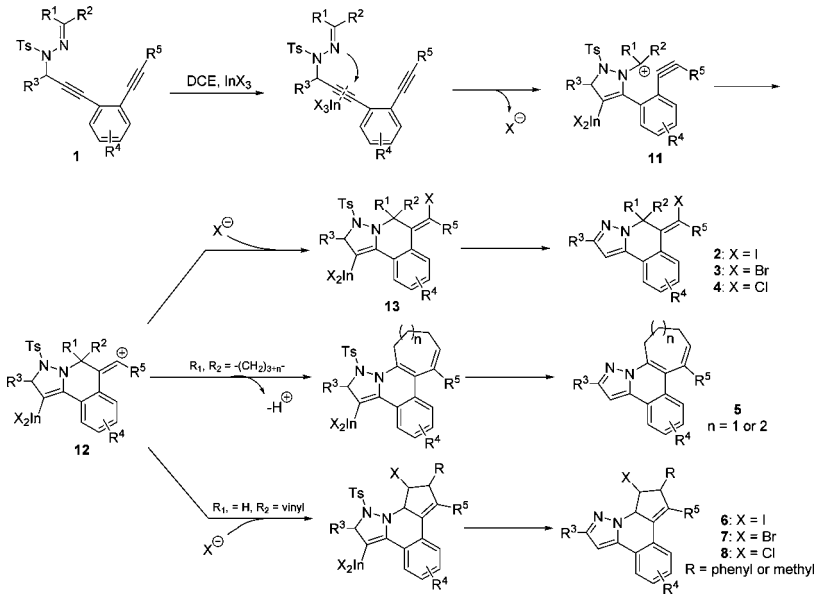
■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00534.

Experimental procedures and characterization of compounds **2a**−**l**,**n**, **3a**,**c**,**k**,**m**,**n**, **4a**,**c**,**k**,**m**, **5a**,**b**, **6**, **7a**,**b**, **8**−**10**, and **1a**−**r** (PDF)

Scheme 4. Proposed Mechanism



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Crystallographic data for **2a** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: zpzhan@xmu.edu.cn.

Notes

The authors declare no competing financial interest.

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(18) See the Supporting Information (Figure S1).

(19) See the Supporting Information (Table S1).

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