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Lewis acid promoted three-component reactions of aziridines, arenes and aldehydes: an efficient and diastereoselective synthesis of *cis*-1,4-disubstituted tetrahydroisoquinolines

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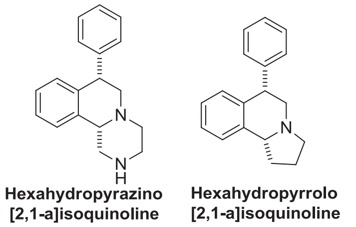
ABSTRACT

A new Lewis acid promoted three-component reaction between the aziridine, arene and aldehyde has been developed. This reaction involves sequential ring opening of aziridine and Pictet–Spengler condensation and gives a broad range of *cis*-1,4-disubstituted tetrahydroisoquinolines in moderate yields with good diastereoselectivities under mild conditions. The methodology provides a rapid and convergent synthesis for the scaffold of tetrahydroisoquinoline and serves as a good tool for constructing the libraries of substituted tetrahydroisoquinolines.

1. Introduction

Tetrahydroisoquinoline (THIQ) derivatives are structural motifs of many pharmaceutically relevant molecules and natural products and exhibit a variety of biological activities.[1] For this reason, they have attracted continuous interest to design the synthetic methods for the construction of all kinds of substituted THIQs.[2] In particular, 1,4-disubstituted THIQs have been paid much attention along with their physiological activities investigated in recent years. For example, hexahydropyrazino [2,1-*a*]isoquinolines[3] and hexahydropyrrolo [2,1-*a*]isoquinolines[4] were found to be associated with antidepressant activities (Scheme 1). Although several reports were available for the synthesis of 1,4-disubstituted THIQs,[5,6] most of them involved multistep syntheses employing two-component reactions. The reaction diversity and efficiency were often unsatisfactory. Moreover, the development of highly diastereoselective reactions for the synthesis of 1,4-disubstituted THIQs remains a challenging job.[6]



Scheme 1. 1,4-Disubstituted tetrahydroisoquinolines.

Because multiple chemical bonds in one-step reaction are formed, the multiple-component reaction allows an efficient and straightforward transformation from readily available materials to cyclic compounds with molecular complexity and structural diversity.[7] Due to avoiding the isolation and purification of intermediates, it saves a large number of efforts, times, and cost. Therefore, the multiple-component reaction has been widely used to the high-throughput screening in the discovery of modern new drug. Considering the continued importance of the THIQ derivatives in the field of organic and medicinal chemistry, developing efficient multiple-component reactions for the diastereoselective synthesis of THIQ derivatives is of great significance.

N-Sulfonylaziridine,[8] an readily accessible and good reactive organic intermediate, has been utilized for the ring-opening

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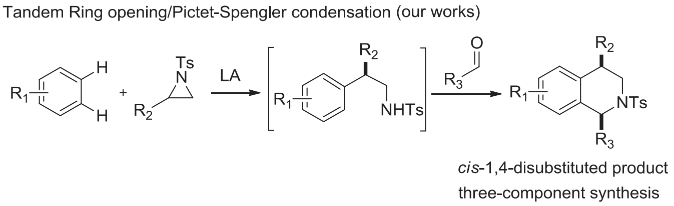
reactions with numerous heteroatom-nucleophilic reagents[9] and carbon-nucleophilic reagents.[10] Base on these ring openings, a series of tandem cyclizations involving two-components have been developed for the construction of nitrogen-containing heterocycles.[6a,11] But tandem multiple-component reactions are seldom seen.[12] We noticed that *N*-sulfonyl-β-arylamines were easily provided by Lewis acid promoted ring opening of *N*-sulfonyl aziridines with arenes.[13] If continuing to add aldehydes, *N*-sulfonyl-β-arylamines would further undergo Lewis acid catalyzed Pictet–Spengler condensation[14] in a cascade fashion leading to the three-component synthesis of 1,4-disubstituted tetrahydroisoquinolines (Scheme 2). To our best knowledge, few tandem three-component reactions were designed for one-step construction of the core skeletons of tetrahydroisoquinolines up to now.[15] This new three-component reaction undoubtedly provides a good choice for the rapid and convergent synthesis of tetrahydroisoquinolines. When carrying out this three-component reaction, we find that *cis*-1,4-disubstituted THIQ is isolated as the major isomer with a good diastereoselectivity. Herein, we hope to report about the results of the new *cis*-diastereoselective three-component reactions of aziridines, arenes and aldehydes.



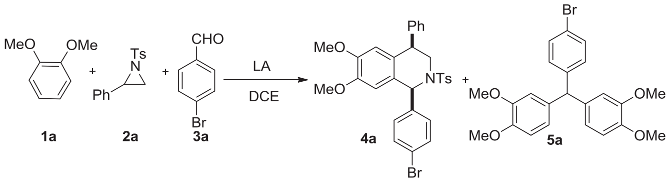
Scheme 2. Tandem three-component reactions between aziridines, arenes and aldehydes.

2. Results and discussion

Arene **1a**, aziridine **2a**, and aldehyde **3a** were selected as model substrates for optimizing the reaction conditions (Table 1). A screening of different acids was firstly carried out. $Sc(OTf)_3$, $In(OTf)_3$ and $AgPF_6$ failed to promote the three-component reaction (entries 1–3). To our delight, when $BF_3 \cdot OEt_2$ was used as the catalyst, **4a** was obtained in 32% yield with a good diastereoselectivity (*cis:trans*=86:14) (entry 4). In the three-component reaction byproduct **5a** was also obviously observed because of double arylation of aldehydes. The structure of *cis*-**4a** was unambiguously confirmed by X-ray crystal structure analysis.[16] $SnCl_4$ could also promote the three-component reaction, but a low yield was observed (entry 5). As additives, anhydrous $MgSO_4$ was found to be more beneficial for improving the yield of the three-component reaction than anhydrous Na_2SO_4 and 4 Å MS(entry 6–8). Then we attempted to raise the reaction temperature to 60 °C, the best result for the three-component reaction was obtained and **4a** was provided in 63% yield without the decrease of diastereoselectivity (entry 9). When the reaction temperature was further raised to 80 °C, a slightly low yield was observed (entry 10). Decreasing the amount of $BF_3 \cdot OEt_2$ from 300% to 200% gave a bad result and product **4a** was only isolated in 20% yield (entry 11). Then we tried to increase the amount of $BF_3 \cdot OEt_2$ to 400%, the result was similar with using 300 mol % of $BF_3 \cdot OEt_2$ (entry 12). We also tested the reaction using an increased amount of arenes (2 equiv), a slightly decreased yield was observed (entry 13). Besides, several different solvents were selected for optimizing the reaction conditions (entries 14–19). Unsatisfied yields were detected in DCM and $CHCl_3$. In THF, $MeNO_2$ and DMSO the reaction failed to afford product **4a**. In CCl_4 the reaction gave a similar result as in DCE. Considering the high toxicity of CCl_4, we preferred DCE as the reaction solvent at last.

With the optimized reaction conditions in hand, the substrate scope of the three-component reactions was firstly investigated with a series of aldehydes and aziridines. The results were outlined in Table 2. It was found that various substituted aldehydes **2** and aziridines **3** successfully reacted with arene **1a** affording product **4** in moderate yields and with good diastereoslectivities. *cis*-Diastereomers were isolated as the major isomers. The structures of *cis*-**4a** and *cis*-**4f** were confirmed by X-ray crystal structure analysis,[16] and the relative stereochemistry of other *cis*-diastereomers were determined by the analysis of NMR spectrum compared with *cis*-**4a** and *cis*-**4f**. Firstly, we fixed arene **1a** and aziridine **3a** as substrates to examine the scope of aldehydes. Aromatic aldehydes substituted with both electron-rich groups and electron-poor groups were suitable substrates for the three-component reaction (entries 1–5). The desired products **4a**–**4e** were obtained in moderate yields with good diastereoslectivities. The aliphatic aldehydes also reacted smoothly with arene **1a** and aziridine **3a** and led to the corresponding products **4f**–**4i** in moderate yields with good diastereoslectivities (entries 6–9). Subsequently, several aziridines were tested to react with arene **1a** and aldehyde **3** under the optimized reaction conditions. It was found that aziridines derived from aromatic alkenes could successfully undergo this reaction. Electron-withdrawing substituents on the benzene ring, such as F, Cl, Br gave similar product yields to **4a** (entries 10–12 and entry 16). Electron-donating substituents on the benzene ring led to harmful effect on the yields of products. Aziridine **2e** underwent the three-component

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Additive	T	Yield (**4a**)[b]	Dr[c]
1	$Sc(OTf)_3$	DCE	None	rt	0%	—
2	$In(OTf)_3$	DCE	None	rt	0%	—
3	$AgPF_6$	DCE	None	rt	0%	—
4	$BF_3 \cdot OEt_2$[d]	DCE	None	rt	32%	86:14
5	$SnCl_4$[d]	DCE	None	rt	12%	79:21
6	$BF_3 \cdot OEt_2$[d]	DCE	$MgSO_4$[h]	rt	49%	86:14
7	$BF_3 \cdot OEt_2$[d]	DCE	Na_2SO_4[i]	rt	35%	86:14
8	$BF_3 \cdot OEt_2$[d]	DCE	4 Å MS	rt	40%	86:14
9	$BF_3 \cdot OEt_2$[d]	DCE	$MgSO_4$	60 °C	63%	86:14
10	$BF_3 \cdot OEt_2$[d]	DCE	$MgSO_4$	80 °C	60%	86:14
11	$BF_3 \cdot OEt_2$[e]	DCE	$MgSO_4$	60 °C	20%	86:14
12	$BF_3 \cdot OEt_2$[f]	DCE	$MgSO_4$	60 °C	63%	84:16
13	$BF_3 \cdot OEt_2$[d,g]	DCE	$MgSO_4$	60 °C	60%	84:16
14	$BF_3 \cdot OEt_2$[d]	DCM	$MgSO_4$	40 °C	38%	86:14
15	$BF_3 \cdot OEt_2$[d]	$MeNO_2$	$MgSO_4$	60 °C	0%	—
16	$BF_3 \cdot OEt_2$[d]	THF	$MgSO_4$	60 °C	0%	—
17	$BF_3 \cdot OEt_2$[d]	DMSO	$MgSO_4$	60 °C	0%	—
18	$BF_3 \cdot OEt_2$[d]	CCl_4	$MgSO_4$	60 °C	62%	86:14
19	$BF_3 \cdot OEt_2$[d]	$CHCl_3$	$MgSO_4$	60 °C	25%	84:16

[a] Reaction conditions, unless otherwise stated: a solution of **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (0.04 mmol, 20 mol %) in solvent (2 mL) was stirred for 1 h at room temperature, then **3a** (0.4 mmol) was added and the mixture was further stirred for 18 h at set temperature.

[b] Combined yields of *cis*-**4a** and *trans*-**4a**.

[c] Determined by NMR analysis (*cis*/*trans*).

[d] Catalyst (300 mol %) was used.

[e] Catalyst (200 mol %) was used.

[f] Catalyst (400 mol %) was used.

[g] **1a** (0.4 mmol, 2 equiv) was used.

[h] Anhydrous $MgSO_4$ was used.

[i] Anhydrous Na_2SO_4 was used.