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Ytterbium(III) triflate catalyzed domino reaction of arylamines and styrene oxides: Synthesis of 2-benzyl-3-arylquinoline derivatives

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This work is dedicated to my teacher Professor Okhil Kumar Medhi, Former Vice-Chancellor, Gauhati University, upon his sudden passing away on February 2, 2021.

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Introduction

The quinoline structural unit is present in numerous naturally occurring alkaloids and well-known potent drugs [1]. These compounds exhibit a broad range of biological activities, such as antimalarial [2a], antiasthmatic [2b], antituberculosis [2c], antihypertensive [2d], anticancer [2e], and anti-HIV [2f] activities. In addition, naturally occurring compounds, namely quinine and cinchonidine, have been extensively used as chiral ligands for asymmetric synthesis [3]. Furthermore, quinoline and its derivatives have also been explored in materials science [4a,b]. Due to its wide applications in diverse fields, the synthesis of quinoline derivatives still attracts significant attention among synthetic organic chemists. Recently, Beller and co-workers reported a domino reaction for the synthesis of 2-benzyl-3-phenylquinoline derivatives from substituted anilines and styrene [5a]. Zhang and co-workers developed a method to access the 2-benzyl-3phenylquinoline scaffold using terminal alkynes and substituted anilines [5b]. Moreover, a few methods have been reported for the synthesis of 2-benzyl-3-phenylquinoline derivatives using substituted anilines and phenylacetaldehyde [6]. Zhang and

ABSTRACT

An efficient and straightforward method for the synthesis of 2-benzyl-3-arylquinoline derivatives is reported involving the domino reaction of substituted arylamines and styrene oxides in the presence of 10 mol% ytterbium(III) triflate in acetonitrile at 80 °C. Additionally, the reaction of aliphatic epoxides with *p*-anisidine provided 2,3-dialkylquinoline derivatives under identical reaction conditions. Important features of the protocol are ease of handling, broad substrate scope, good yields, and the formation of two C–N and two C–C bonds.

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co-workers [7a] further demonstrated the reaction of arylamines with styrene oxides in the presence of FeCl₃ to give 3-arylquinoline derivatives (Scheme 1). Using a mixture of Al_2O_3 and $MeSO_3H$, Sharghi and co-workers also reported the synthesis of 3-arylquinolines [7b] from the same starting materials. Some of the drawbacks of previously reported procedures are need for expensive catalysts, harsh reaction conditions, the requirement of an inert atmosphere, and low yields. Therefore, there is still scope to develop new methodology for the synthesis of 2-benzyl-3-phenylquinoline derivatives.

Very recently, Tepe and co-workers [7c] reported the synthesis of 2-benzyl-3-phenylquinoline derivatives using arylamines and styrene oxides in the presence of 0.5 equivalents of scandium(III) triflate (Scheme 1) under an inert atmosphere. Though this represents a good method to access 2,3-disubstituted quinolines, it has several disadvantages, such as requirement of a stoichiometric amount of TEMPO (1.0 equiv.), an excess amount styrene oxide (3 equiv.), high catalyst loading, molecular sieves, long reaction times (24 h), and an inert atmosphere of argon. Notably, the reaction does not proceed well with Yb(OTf)₃, which is mentioned in the supporting information. Herein, we report an efficient and straightforward method for the synthesis of 2-benzyl-3-arylquino-line derivatives *via* a domino reaction involving substituted







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Scheme 1. Previous reports and present work for the synthesis of quinoline derivatives.

arylamines and styrene oxides in the presence of 10 mol% ytterbium(III) triflate in acetonitrile at 80 °C (Scheme 1).

Result and discussion

To ascertain suitable reaction conditions, *p*-anisidine **1a** and styrene oxide **2a** were chosen as model substrates. Initially, the reaction was carried out with *p*-anisidine (**1a**, 1.0 mmol) and styrene oxide (**2a**, 2.0 mmol) in acetonitrile without a catalyst. However, the reaction did not proceed at room temperature or at 80 °C (Entries 1 and 2, Table 1). The reaction also did not proceed in the presence of 5 mol% Yb(OTf)₃ at room temperature (Entry 3, Table 1), however, upon heating at 80 °C for 6 h, **3a** was formed in 46% yield (Entry 4, Table 1).

When the catalyst loading was increased from 5% to 10% the reaction was complete within 3 h and the yield also increased from 46% to 81% (Entry 5, Table 1). However, further increasing the catalyst loading to 15 mol%, did not improve the yield (Entry 6, Table 1). To examine the efficiency of other metal triflates, the reaction was performed with Sc(OTf)₃, Bi(OTf)₃, and Cu(OTf)₂ (Entries 7–9, Table 1), and it was found that Sc(OTf)₃ and Bi

(OTf)₃ provided lower yields compared to Yb(OTf)₃. Additionally, the reaction did not proceed with Cu(OTf)₂.

Next, different solvents, such as water, methanol, tetrahydrofuran, 1,2-dichloroethane, dimethyl sulfoxide, *N*,*N*-dimethylformide and toluene were examined (Entries 10–16, Table 1), using 10 mol% Yb(OTf)₃ as the catalyst. In all these solvents, either the reaction did not take place or the yield was low. Hence, the best yield was obtained in acetonitrile. From all these observations, we concluded that the optimized reaction conditions were 10 mol% Yb(OTf)₃ in acetonitrile at 80 °C (Entry 5, Table 1) in terms of both the yield and reaction time.

With the optimal reaction conditions in hand, the scope and generality of the developed protocol were explored with various arylamines **1a-q** and styrene oxide **2a** (Table 2). The reaction of aniline **1b** with styrene oxide **2a** afforded 2-benzyl-3-phenylquino-line derivative **3b** in 73% yield. Likewise, arylamines containing electron-donating groups at the 4-position, such as 4-Me and 4-Et, gave the corresponding products **3c** and **3d** in 76% and 75% yield, respectively.

The reaction with arylamine **1e** containing a methyl group at the 2-position gave the desired product **3e** in 69% yield. Arylamines with substituents at the 3-position, such as 3-OMe and 3-Me, provided the expected products **3f** and **3 g** in 66% and 67% yield, respectively. Similarly, di-substituted arylamines, such as 2,4-Me, 3,5-Me, 3,4-Me, 3,5-OMe, and 3,4-OMe, also worked well and substituted quinoline scaffolds **3h-1** were obtained in 72–80% yield. Notably, the sterically crowded 3,4,5-OMe-aniline also furnished the desired product **3 m** in 70% yield. Gratifyingly, bicyclic arylamines, such as 2-naphthylamine, 1-naphthylamine, 5-aminoindan, and 3,4-(methylenedioxy)-aniline, afforded the corresponding fused quinoline derivatives **3n-q** in 64–72% yield. However, the reaction was unsuccessful with 4-substituted anilines containing electron-withdrawing groups, such as Cl, Br, I and NO₂.

Inspired by above-mentioned results, we further extended the scope and the generality of the method with substituted styrene oxides **2b** and **2c** as well as with aliphatic epoxides **2d-2f** (Table 3). The reaction of *p*-anisidine **1a** with styrene oxides **2b** and **2c** con-

Table 1

Optimization of the reaction conditions.^{a,b,c,d}



Entry	Catalyst	Loading (mol%)	Solvent	Time	Yield 3a (%) ^b
1 ^c	_	_	CH₃CN	10 h	NR
2	_	-	CH ₃ CN	10 h	NR
3 ^c	Yb(OTf) ₃	5	CH ₃ CN	10 h	NR
4	Yb(OTf) ₃	5	CH ₃ CN	6 h	46
5	Yb(OTf)₃	10	CH ₃ CN	3 h	81
6	Yb(OTf) ₃	15	CH ₃ CN	3 h	76
7	Sc(OTf) ₃	10	CH ₃ CN	6 h	46
8	Bi(OTf)3	10	CH₃CN	6 h	62
9	Cu(OTf) ₂	10	CH₃CN	6 h	NR
10	Yb(OTf) ₃	10	H ₂ O	6 h	NR
11 ^d	Yb(OTf) ₃	10	CH₃OH	6 h	NR
12 ^d	Yb(OTf) ₃	10	THF	6 h	43
13	Yb(OTf) ₃	10	(CH ₂ Cl) ₂	6 h	NR
14	Yb(OTf) ₃	10	DMSO	6 h	35
15	Yb(OTf) ₃	10	DMF	6 h	NR
16	Yb(OTf) ₃	10	toluene	6 h	NR

^a Reagents and conditions: p-anisidine (1a, 1.0 mmol), styrene oxide (2a, 2.0 mmol), solvent (1.0 mL), 80 °C.

^b Isolated yield.

^c Reaction performed at room temperature.

^d Reaction performed at reflux. NR (no reaction).

Table 2

Reaction of various arylamines 1a-q with styrene oxide 2a.^{a,b}



^a Reagents and conditions: arylamines (**1a-q**, 1.0 mmol), styrene oxide (**2a**, 2.0 mmol), Yb(OTf)₃ (10 mol%), CH₃CN (1.0 mL), 80 °C.

^b Isolated yield. NR: (no reaction).

Table 3

Reaction of *p*-anisidine **1a** with styrene oxides **2b** and **2c** and aliphatic epoxides **2d**- $\mathbf{f}^{a,b}$



^aReagents and conditions: *p*-anisidine (**1a**, 1.0 mmol), styrene oxides (**2b** and **2c**, 2.0 mmol) or aliphatic epoxides (**2d–f**, 2.0 mmol), Yb(OTf)₃ (10 mol%), CH₃CN (1.0 mL), 80 °C. ^bIsolated yield.

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Scheme 2. Plausible mechanism for the formation of product 3b.

taining Br and Cl substituents at the 4-position gave the desired products 3r and 3s in 75% and 72% yield, respectively. In order to incorporate aliphatic chains at the C-2 and C-3 positions of the quinoline derivatives, the reaction was performed with *p*-anisidine **1a** and 1,2-epoxybutane **2d** which gave the desired product 3-ethyl-6-methoxy-2-propylquinoline 3t in 79% yield.

Furthermore, the reaction was also carried out with epoxides containing extended alkyl chains (e.g. 1,2-epoxyhexane **2e** and 1,2-epoxydodecane **2f**), where the anticipated products 3u and 3v were isolated in 76% and 65% yield, respectively.

A plausible mechanism for product formation is outlined in Scheme 2. Initially, aniline **1b** reacts with styrene oxide **2a** in the presence of Yb(OTf)₃, which acts as a Lewis acid to provide β -amino alcohol **A** by attacking the less hindered side [6a]. Subsequently, removal of water from intermediate **A**, affords enamine **B** that can be tautomerized to the corresponding imine **C**. Based on the proposed mechanism by Beller and co-workers [5a], intermediates **B** and **C** react *via* an intermolecular Mannich reaction to generate intermediate **D**, which undergoes intramolecular electrophilic aromatic substitution followed by aromatization to give cyclized intermediate **F**. Finally, elimination of aniline **1b** from intermediate **F** forms dihydroquinoline **G**, which upon aerial oxidation gives the desired product **3b**.

In conclusion, we have developed a new, one-pot methodology for the straightforward access to a variety of 2-benzyl-3-arylquinoline scaffolds. In this protocol, we have utilized the domino reaction of readily available substituted arylamines and epoxide derivatives in the presence of 10 mol% Yb(OTf)₃ in acetonitrile at 80 °C under an air atmosphere. The advantages of this strategy are its ease of handling, consecutive formation of two C—N and two C—C bonds, and broad substrate scope with good yields. It is noteworthy that aliphatic epoxides also worked well to afford 2,3-dialkylquinoline derivatives.

Declaration of Competing Interest

The authors declare that they no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152981.

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