

Article

Isoquinolone Synthesis via Zn(OTf)₂-Catalyzed Aerobic Cyclocondensation of 2-(1-Alkynyl)-benzaldehydes with Arylamines

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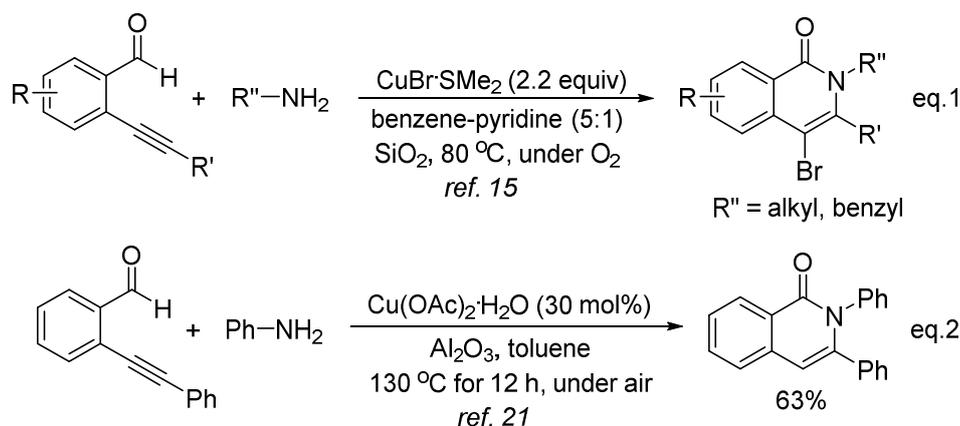
Abstract: A zinc(II) triflate-catalyzed cyclocondensation of *ortho*-alkynylbenzaldehydes with arylamines in the presence of base under an oxygen atmosphere affording isoquinolones in good to high yields has been developed. The advantages of the present catalyst system include the use of an air-stable and cheap commercially available Lewis acid as the catalyst, high atom utilization and easily available starting materials.

Keywords: zinc(II) triflate; *ortho*-alkynylbenzaldehydes; arylamines; isoquinolones

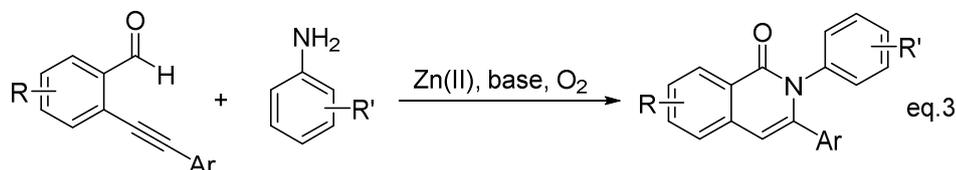
1. Introduction

Alkyne annulation is an important and efficient method for the synthesis of various heterocyclic compounds with high atom utilization [1–10]. Isoquinolones are one of the interesting and important nitrogen-heterocyclic compounds with versatile biological and physiological activities [11,12], and over the past decades, transition-metal-catalyzed isoquinolone formation through intermolecular annulation with the use of alkyne as one of the reaction partners has been well developed [13–26]. Among the different protocols for achieving this goal, the synthetic strategies starting from 2-(1-alkynyl)benzaldehydes are the most interesting due to their high atom utilization [15,21] (Scheme 1). Although the readily available 2-(1-alkynyl)benzaldehydes have been well-applied in the synthesis of benzo-fused six-membered heterocycles [27–33] and carbocycles [34–39], their applications for isoquinolone synthesis are very rare. As shown in Scheme 1, only two procedures have been reported to approach isoquinolones from the direct intermolecular cyclocondensation of 2-(1-alkynyl)-benzaldehydes with primary amines. One is the aerobic cyclocondensation of 2-(1-alkynyl)benzaldehydes with benzyl amines and primary aliphatic amines in the presence of an excess amount of CuBr·SMe₂ to afford 4-bromoisquinolin-1(2*H*)-ones, and no reaction example was given with the use of arylamines under the reaction conditions (Scheme 1, eq. 1) [15]. The other procedure focuses on the Cu(OAc)₂-catalyzed construction of isoquinolones by the reaction of H₂O with 2-(1-alkynyl)benzaldimines, giving one example from the direct cyclocondensation of 2-(1-phenylethynyl)benzaldehyde with aniline to produce 2,3-diphenylisoquinolin-1(2*H*)-one in 63% yield (Scheme 1, eq. 2) [21].

Previous works:



This work:



Scheme 1. Isoquinolone from cyclocondensation of 2-(1-alkynyl)benzaldehydes with amines.

Recently, we have been interested in the applications of 2-(1-alkynyl)benzaldehydes in the synthesis of benzo-fused cyclic compounds [28,33,39], air-stable Lewis acids as catalysts in organic transformation [40–44], and the development of synthetic methods for the formation of nitrogen-heterocyclic compounds via alkyne annulations [45–53]. Therefore, in continuation of our interests in the application of 2-(1-alkynyl)benzaldehydes, we herein describe a simple and efficient method for the construction of isoquinolone from the cyclocondensation of 2-(1-alkynyl)benzaldehydes with arylamines in the presence of a catalytic amount of Zn(OTf)₂ (Scheme 1, eq. 3).

2. Results and Discussion

The optimizing reaction conditions were performed by the reaction of 2-(1-phenylethynyl)benzaldehyde (**1a**) with 1.2 equivalents of aniline (**2a**) as the substrates under an oxygen atmosphere (Table 1). Initially, we performed the reaction without the use of any metal salts, in DMSO (dimethyl sulfoxide) at 120 °C for 24 h, no desired product was formed, but the dehydrated product **3aa'** between **1a** and **2a** could be obtained in 20% yield (entry 1). With K₂CO₃ as the additive, however, the reaction yielded 2,3-diphenylisoquinolin-1(2*H*)-one (**3aa**) in 50% yield and **3aa'** in 33% yield, indicating that the base displays an important role in the intermolecular cyclocondensation of **1a** with **2a**, due to the nucleophilic addition of **2a** to the carbonyl group of **1a** promoted by the base (entry 2). In addition, it is well-known that Lewis acid can promote the nucleophilic addition of nitrogen to alkyne via the intermolecular π -coordinating of carbon-carbon triple bonds to Lewis acids, thus repeating the same reaction in the presence of a catalytic amount of Fe(OTf)₂, ZnCl₂ and Zn(OTf)₂, which are not only cheap and easily available, but also air-stable Lewis acids (entries 3–5). Although Fe(OTf)₂ and ZnCl₂ showed no activity, Zn(OTf)₂ could greatly promote the formation of the desired product **3aa**, and **3aa** could be obtained in 87% yield. Decreasing the catalyst loading from 4.0 to 3.0 mol%, the yield was not changed at all (entry 6), and the use of 2.0 mol% of the catalyst resulted in a considerable decrease in the yield (78%) (entry 7). In addition, when KHCO₃ and KO^{*t*}Bu were used as the base to replace K₂CO₃, or when *N,N*-dimethylformamide (DMF) and 1,4-dioxane were employed as solvents instead of DMSO, all were found to be inferior, and the yields of **3aa** were significantly decreased (entries 8–11).

Table 1. Optimal conditions for the formation of 2,3-diphenylisoquinolin-1(2*H*)-ones (**2a**)^a.

Entry	Catalyst (mol%)	Base (2 equiv)	Solvent	Yield of 3aa (%) ^b
1 ^c	–	–	DMSO	trace
2 ^d	–	K ₂ CO ₃	DMSO	51
3	Fe(OTf) ₂ (4.0)	K ₂ CO ₃	DMSO	45
4	ZnCl ₂ (4.0)	K ₂ CO ₃	DMSO	50
5	Zn(OTf) ₂ (4.0)	K ₂ CO ₃	DMSO	87
6	Zn(OTf) ₂ (3.0)	K ₂ CO ₃	DMSO	87
7	Zn(OTf) ₂ (2.0)	K ₂ CO ₃	DMSO	78
8	Zn(OTf) ₂ (4.0)	KHCO ₃	DMSO	40
9	Zn(OTf) ₂ (4.0)	KO ^t Bu	DMSO	50
10	Zn(OTf) ₂ (4.0)	K ₂ CO ₃	DMF	60
11	Zn(OTf) ₂ (4.0)	K ₂ CO ₃	Dioxane	55

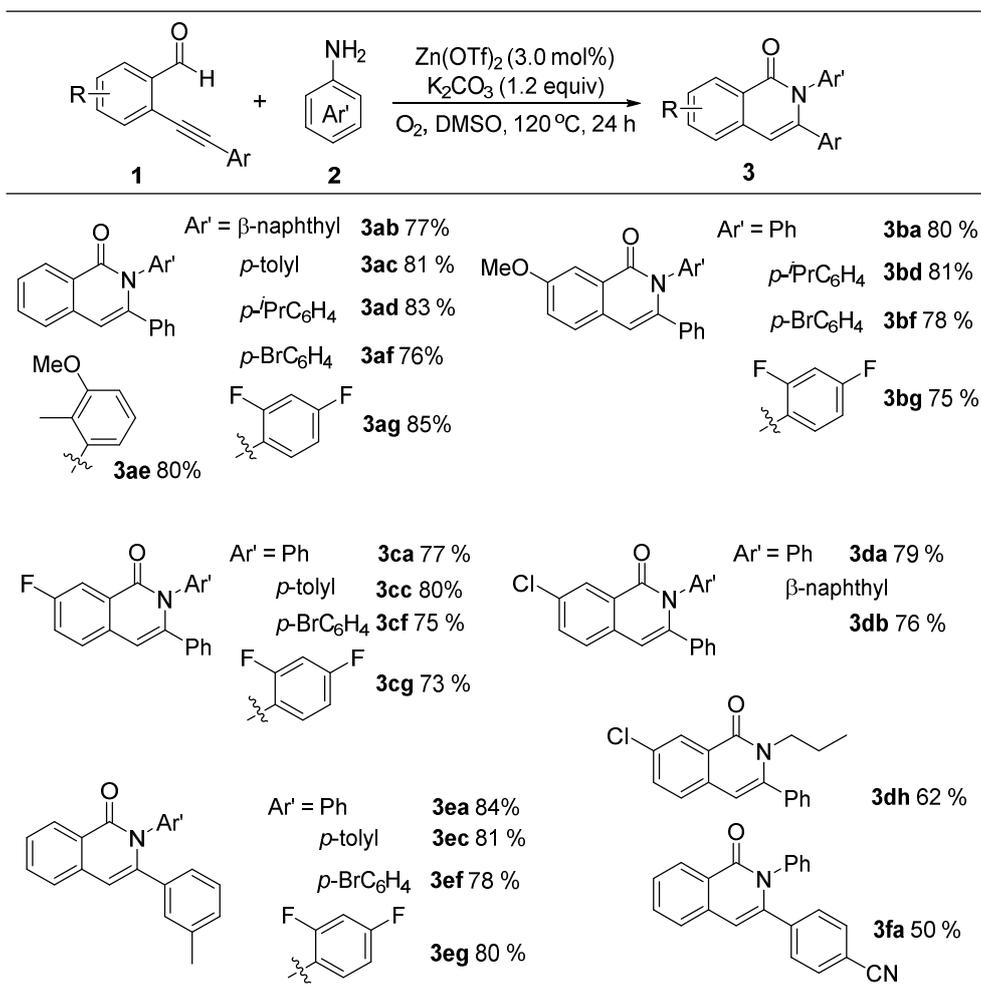
^a Reactions were carried out using 1.0 mmol of **1a**, 1.2 mmol of **2a**, and 2.0 mmol of base in 5.0 mL of solvent under oxygen atmosphere at 120 °C for 24 h. ^b Isolated yields. ^c 20% of **3aa'**. ^d 33% of **3aa'**.

Encouraged by the results obtained above, we studied the substrate scope for the formation of isoquinolin-1(2*H*)-ones using various *ortho*-alkynylbenzaldehydes and amines bearing different substituents under the conditions of entry 6 in Table 1. As can be seen from Table 2, β -aminonaphthalene (**2b**), *para*-substituted anilines (*para*-Me, **2c**; *para*-^{*i*}Pr, **2d**; *para*-Br, **2f**), 2-methyl-3-methoxyaniline (**3e**), and 2,4-difluoroaniline (**2g**) underwent cyclocondensation with **1a** affording the corresponding isoquinolin-1(2*H*)-ones (**2ab**–**2ag**) in 76%–85% yields, indicating that arylamines with electron-donating and electron-withdrawing group(s) show similar reactivity under the reaction conditions. When 5-methoxy-2-(1-phenylethynyl)benzaldehyde (**1b**), 5-fluoro-2-(1-phenylethynyl)benzaldehyde (**1c**), and 5-chloro-2-(1-phenylethynyl)benzaldehyde (**1d**) were used, reactions with **2a** and electron-rich and/or electron-poor arylamines also showed no significant difference in reactivity and gave the expected products in 73%–81% yields. In addition, the present catalyst conditions could be applied to primary alkylamine. For example, the reaction between **1d** and *n*-propylamine (**2h**) produced **3dh** in 62% yield.

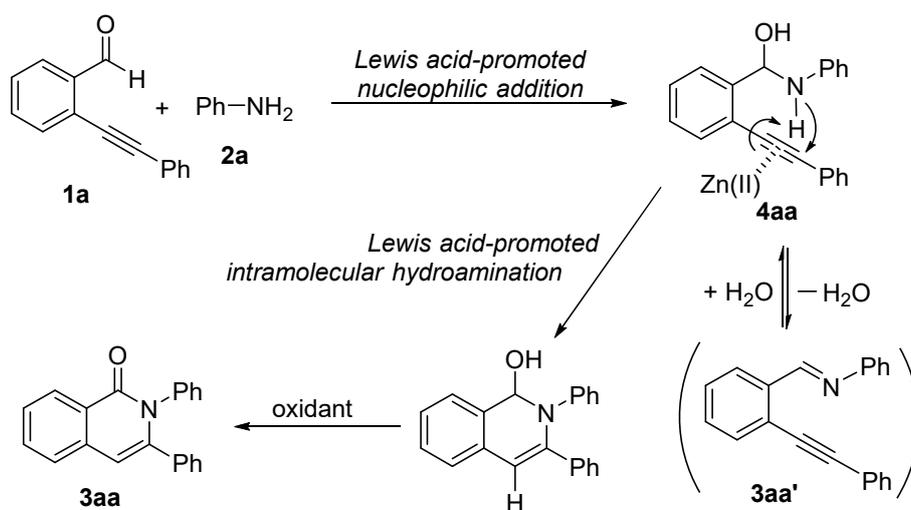
Moreover, we also tested the effects of electron-donating and electron-withdrawing groups by using *meta*-methylphenylethynyl (**1e**) and *para*-cyanophenylethynyl (**1f**) groups to replace the phenylethynyl group on **1a**. It was found that **1e** showed similar reactivity to **1a** in the cases of both the electron-rich and the electron-poor arylamines employed. However, it was apparent that **1f** bearing an electron-poor group of *para*-cyanophenylethynyl is not beneficial to the reaction with **2a** to give the corresponding product of **3fa** in 50% yield.

It should be noted that the present catalyst system is highly tolerant to various C(*sp*²)-X bonds, such as the C-O, C-Br, C-F, and CN groups, the products bearing these groups have important potential applications for further transformation.

A possible mechanism for the formation of isoquinolin-1(2*H*)-ones is shown in Scheme 2. It involves two well-known and normal steps: the nucleophilic addition of arylamines to aldehyde giving 1,2-aminoalcohol intermediate **4aa**, and intramolecular hydroamination followed by an oxidation reaction constructing isoquinolin-1(2*H*)-one **3aa**. Apparently, Zn(OTf)₂ plays an important role in promoting the nucleophilic addition of arylamines and the intramolecular hydroamination of carbon-carbon triple bonds. The formation of **3aa'** (Table 1, entries 1 and 2) is reasonable from the dehydration reaction of **4aa**.

Table 2. Substrate scopes for the formation of isoquinolin-1(2*H*)-ones ^a.

^a The reactions were carried out using 1.0 mmol of **1**, 1.2 mmol of **2**, and 2.0 mmol of K_2CO_3 in 5.0 mL of DMSO under an oxygen atmosphere.

**Scheme 2.** A possible mechanism for the formation of isoquinolin-1(2*H*)-ones.

3. Materials and Methods

3.1. General Methods

All commercial organic/inorganic reagents and solvents were analytically pure and used without further purification; 2-(1-alkynyl)benzaldehydes (1a–f) are known compounds and were prepared by cross-coupling reactions of 2-bromobenzaldehydes with terminal aryl acetylenes [39]. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECA-400 spectrometer (JEOL, Tokyo, Japan) using CDCl₃ as solvent at 298 K. The ¹H NMR (400 MHz) chemical shifts (δ) were referenced to internal standard TMS (for ¹H, δ = 0.00); ¹³C NMR (100 MHz) chemical shifts were referenced to internal solvent CDCl₃ (for ¹³C, δ = 77.16). High-resolution mass spectra (HRMS) with electron spray ionization (Supplementary Materials) were obtained with a micrOTOF-Q spectrometer (Agilent, CA, USA).

3.2. Typical Procedure for the Synthesis of 2,3-Diphenylisoquinolin-1(2H)-one (3aa)

A mixture of 2-(phenylethynyl)benzaldehyde (1a, 1.0 mmol), aniline (2a, 1.5 mmol), Zn(OTf)₂ (0.04 mmol), and K₂CO₃ (2.0 mmol) in DMSO (5.0 mL) under an oxygen atmosphere was stirred at 120 °C, and the reaction was monitored by GC-MS and TLC. After 24 h, the conversion of 1a was complete, and then the reaction mixture was cooled to room temperature. Water (10 mL) was added to the reaction mixture with vigorous stirring, and the mixture was then extracted with ethyl acetate three times (3 × 10 mL). The combined organic phases were dried overnight by anhydrous MgSO₄. The filtered solution was then concentrated by a rotary evaporator under reduced pressure, and the obtained crude residue was purified by column chromatography on silica gel (eluent solvents: petroleum ether/ethyl acetate with the gradient mixture ratio from 100:0 to 80:20) to afford 3aa (258.0 mg, 87%).

4. Conclusions

We have demonstrated that Zn(OTf)₂ is a very effective catalyst for the aerobic cyclocondensation of 2-(1-alkynyl)benzaldehydes with arylamines in the presence of base to afford 2,3-diarylisquinolin-1(2H)-ones in good to high yields. The present catalyst system is preferred over the known procedures starting from 2-(1-alkynyl)benzaldehydes to construct an isoquinolin-1(2H)-one ring with the use of an air-stable and cheap commercially available Lewis acid as the catalyst, high atom utilization and easily available starting materials.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/10/6/683/s1>, characterization data and copies of ¹H-NMR and ¹³C-NMR charts of products.

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