

Short communication

# Sc(OTf)<sub>3</sub>-catalyzed three-component cascade reaction: One-pot synthesis of substituted 3-oxoisindoline-1-carbonitrile derivatives



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## ARTICLE INFO

## Article history:

Received 21 September 2015

Received in revised form 10 November 2015

Accepted 13 November 2015

Available online 15 November 2015

## Keywords:

Isoindolinones

Cascade reaction

Amines

Sc(OTf)<sub>3</sub>

## ABSTRACT

A facile and efficient approach for the synthesis of *N*-substituted 3-oxoisindoline-1-carbonitrile derivatives has been developed, with a Sc(OTf)<sub>3</sub>-catalyzed three-component Strecker/Lactamization cascade reaction involving methyl 2-formylbenzoate, TMSCN and amines in ethanol at room temperature. Good to excellent yields for a broad scope of amine substrates were achieved.

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## 1. Introduction

Isoindolinone derivatives are important building blocks for the synthesis of a variety of natural products [1–3]. Due to their biological properties, such as antihypertensive [4], antipsychotic [5], anxiolytic [6], anticonvulsant [7], antiviral [8] and antileukemic [9] activities, isoindolinone derivatives extensively exist in the core structures of many commercial drugs (Fig. 1). Owing to the significant importance of this structural motif, the development of efficient routes for the synthesis of the isoindolinone derivatives is highly valuable. Conventional approaches for the synthesis of isoindolinone derivatives are usually unsatisfactory because of the requirement of harsh reaction conditions, complex starting materials and multistep synthesis [10–15]. In recent years, attribute to their ability to generate diverse and complex targets in fewer steps from readily available starting materials, multicomponent reactions (MCRs) have attracted extensive attention and emerged as powerful tools for the synthesis of complex compounds [16–17], like the construction of isoindolinone skeletons [18–25].

The Strecker reaction is regarded as one of the first multicomponent reactions and has been widely employed in the synthesis of  $\alpha$ -aminonitrile by the condensation of aldehyde, amine and hydrogen cyanide [26–27]. Bifunctional  $\alpha$ -aminonitrile compounds are versatile intermediates in a number of synthetic applications [28]. The cyano group can be transformed into primary amine [29], aldehyde [30] or carboxylic acid [26]. On the other hand, the amine function is nucleophilic and can undergo well-known reactions with electrophilic agents,

such as the intramolecular reactions that form the nitrogen heterocycles in the presence of a neighboring reactive site [31].

The Strecker reaction has been applied to the multicomponent synthesis of *N*-substituted 3-oxoisindoline-1-carbonitrile derivatives using 2-carbonyl benzaldehyde as the neighboring functionalized substrate. The Baum group first employed this method by reacting potassium cyanide with the 2-carbomethoxybenzylideneanilines in refluxing ethanol using equivalent acetic acid as the catalyst [18]. Subsequently, the Opatz group reported a similar route using methylamine hydrochloride as the substrate [32]. Both of these methods exhibited several shortages, such as the use of toxic cyanides and unsatisfied yields. Then Hu and co-workers developed a safer method for the synthesis of the isoindolinone derivatives utilizing trimethylsilyl cyanide (TMSCN) as the cyano source under acidic medium [33]. Though the yields have been improved, high temperature is still required in this protocol. And the substrates are limited to the benzyl and aliphatic amines. Recently, Bunce reported a mild and green approach for the synthesis of *N*-substituted 3-oxoisindoline-1-carbonitrile derivatives employing 5 mol% OSU-6, a MCM-41 type hexagonal mesoporous silica with high Lewis acid, as the catalyst. Both benzyl and aliphatic amines were suitable substrates and resulted in good to excellent yields at room temperature. However, aniline substrates failed to give the expected isoindolinones [24]. Thus, a more efficient method to facilitate the synthesis of *N*-substituted 3-oxoisindoline-1-carbonitrile derivatives is still needed.

Herein, we reported an improved Sc(OTf)<sub>3</sub>-catalyzed three-component cascade reaction for one-pot synthesis of *N*-substituted 3-oxoisindoline-1-carbonitrile derivatives from methyl 2-formylbenzoate, TMSCN and amines in ethanol at room temperature (Scheme 1).

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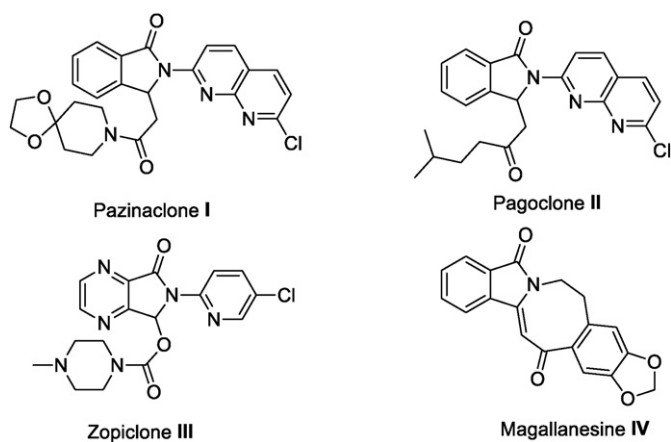


Fig. 1. Examples of biologically isoindolinone derivatives.

## 2. Experimental

### 2.1. General

All reagents were purchased from commercial sources and used without treatment. All known compounds were identified by appropriate technique such as  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and compared with previously reported data. The products were purified by column chromatography over silica gel (100–200 mesh).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AVANCE III 500 (500 MHz and 125 MHz) spectrometer, and tetramethylsilane (TMS) was used as a reference.

### 2.2. General procedure to prepare *N*-substituted 3-oxoisoindoline-1-carbonitrile derivatives

Methyl 2-formylbenzoate (0.5 mmol), amine (0.5 mmol), TMSCN (1.0 mmol) and 2.5 mol%  $\text{Sc}(\text{OTf})_3$  were dissolved in EtOH (1 mL), and the homogeneous solution was stirred at room temperature for 7 h. After completing the reaction (judged by running TLC), the mixture was concentrated in vacuo and the crude product was purified over silica gel by column chromatography (20–30% EtOAc in hexane).

## 3. Results and discussion

Our studies began by selecting the three-component cascade reaction of methyl 2-formylbenzoate, TMSCN and aniline as a platform for the identification of optimal reaction conditions (Table 1). Initially, the control experimental was conducted without catalyst and only trace amount of the target product was obtained (Table 1, entry 1). Then several transition-metal salts were screened as the catalysts, and 10 mol%  $\text{Sc}(\text{OTf})_3$  gave the product in excellent yield in 4 h, whereas all other Lewis acids investigated afforded only low yields (Table 1, entries 2–7). Given that  $\text{Sc}(\text{OTf})_3$  has been proven to be the most effective catalyst for the cascade reaction, we then turned our attention to examine catalyst loading. When the catalyst loading was decreased from 10 to 2.5 mol%, high yield (89%) still obtained, although long reaction times were necessary (Table 1, entries 2, 8–12). To further explore this reaction, the reaction medium was then screened, and EtOH afforded relatively higher yield than other solvents (Table 1,

Table 1  
Optimization of the reaction conditions<sup>a</sup>.

Entry	Catalyst (mol %)	Solvent	t (h)	Yield (%) <sup>b</sup>
1	/	MeCN	4	Trace
2	$\text{Sc}(\text{OTf})_3$ (10)	MeCN	4	95
3	$\text{Zn}(\text{OAc})_2$ (10)	MeCN	4	21
4	$\text{Zn}(\text{OTf})_2$ (10)	MeCN	4	25
5	$\text{Cu}(\text{OAc})_2$ (10)	MeCN	4	Trace
6	$\text{Cu}(\text{OTf})_2$ (10)	MeCN	4	30
7	$\text{NiCl}_2$ (10)	MeCN	4	Trace
8	$\text{Sc}(\text{OTf})_3$ (7.5)	MeCN	4	91
9	$\text{Sc}(\text{OTf})_3$ (5.0)	MeCN	4	76
10	$\text{Sc}(\text{OTf})_3$ (2.5)	MeCN	4	37
11	$\text{Sc}(\text{OTf})_3$ (2.5)	MeCN	7	89
12	$\text{Sc}(\text{OTf})_3$ (1.0)	MeCN	7	43
13	$\text{Sc}(\text{OTf})_3$ (2.5)	$\text{CH}_2\text{Cl}_2$	7	18
14	$\text{Sc}(\text{OTf})_3$ (2.5)	THF	7	65
15	$\text{Sc}(\text{OTf})_3$ (2.5)	MeOH	7	85
16	$\text{Sc}(\text{OTf})_3$ (2.5)	EtOH	7	94
17	$\text{Sc}(\text{OTf})_3$ (2.5)	1,4-Dioxane	7	57
18	$\text{Sc}(\text{OTf})_3$ (2.5)	DMF	7	50
19 <sup>c</sup>	$\text{Sc}(\text{OTf})_3$ (2.5)	EtOH	48	32

<sup>a</sup> Reaction conditions: methyl 2-formylbenzoate (0.5 mmol), aniline (0.5 mmol), TMSCN (1 mmol), catalyst and solvent (1 mL) were stirred at room temperature.

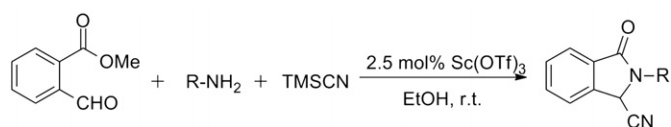
<sup>b</sup> Isolated yield.

<sup>c</sup> 2-Formylbenzoic acid was utilized as the starting material.

entries 11, 13–18), such as MeCN,  $\text{CH}_2\text{Cl}_2$ , MeOH, THF, 1,4-dioxane and DMF. At last, in contrast to methyl 2-formylbenzoate, a cheaper starting material, 2-formylbenzoic acid was utilized and resulted in a lower yield (32% vs. 94%), even the reaction time prolonged to 48 h (Table 1, entries 16 vs. 19).

After the establishment of the optimal reaction conditions, a broad range of amines were applied to define the substrate scope (Table 2). Initially, various anilines were evaluated. In the previous work reported by Bunce, anilines failed to give the expected isoindolinones, but instead, gave the isobenzofuranone derivatives [24]. Gratifyingly, in this protocol, almost all of the *para*- or *meta*-substituted anilines, including electron-rich and electron-deficient ones, afforded isoindolinones **3a–e**, **3g–h** in up to 97% isolated yields. It is worth noting that the anilines with electron-donating groups afforded relatively higher yields than the ones with electron-withdrawing groups. Unfortunately, when *p*-nitroaniline was employed in the cascade reaction, the yield of **3f** dramatically decreased and only trace product was obtained. Subsequently the *ortho*-substituted anilines were examined. Due to the steric hindrance effect, *o*-methoxyaniline resulted in lower yield than *p*-methoxyaniline and afforded isoindolinone **3i** in 82% yield. On the other hand, *ortho*-substituted anilines, such as *o*-methylaniline, *o*-chloroaniline, *o*-iodoaniline and *o*-nitroaniline, all resulted the sole uncyclized Strecker products in good yields, except that *o*-methoxyaniline and 2-fluoro-4-methylaniline afforded the cyclized products **3i** and **3j** in yields of 82% and 85% respectively, probably indicating that the increase of the size or electron-withdrawing ability of the *ortho*-substituents both have negative impact on the reactivity of anilines.

The protocol was then applied to the benzylamines. In all of the studied examples, benzylamines with electron-donating groups or electron-withdrawing ones were both well tolerated and could react smoothly to give the corresponding products **3k–3p** in good to excellent yields (87–93%). Furthermore, the heteroaromatic amines furan-2-ylmethanamine and pyridin-3-ylmethanamine both reacted efficiently to give products **3q** and **3r** in 86% and 90% yields, respectively. Some alkylamines, including phenethylamines and some aliphatic amines were also subjected to the conditions of this multicomponent



Scheme 1.  $\text{Sc}(\text{OTf})_3$ -catalyzed Strecker/Lactamization cascade reaction.

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