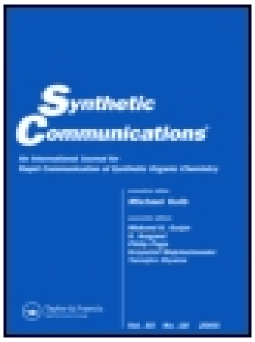

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

$CeCl_3 \cdot 7H_2O$ catalyzed $C(sp^2)$−CN bond construction on water: Synthesis of (*Z*)-2-(2-Oxoindolin-3-ylidene)-2-arylacetonitriles

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To cite this article: Yan Du & Zheng Li (2019): $CeCl_3 \cdot 7H_2O$ catalyzed $C(sp^2)$−CN bond construction on water: Synthesis of (*Z*)-2-(2-Oxoindolin-3-ylidene)-2-arylacetonitriles, Synthetic Communications, DOI: 10.1080/00397911.2018.1540050

To link to this article: https://doi.org/10.1080/00397911.2018.1540050

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$CeCl_3{\cdot}7H_2O$ catalyzed $C(sp^2)-CN$ bond construction on water: Synthesis of (*Z*)-2-(2-Oxoindolin-3-ylidene)-2-arylacetonitriles

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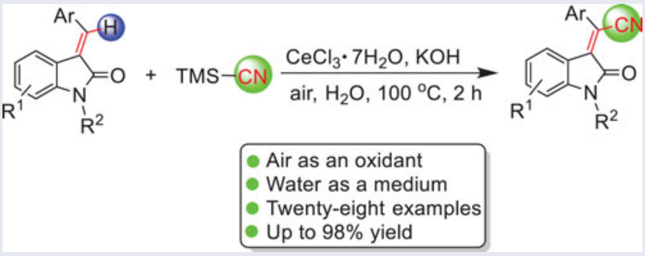
ABSTRACT
An environmentally friendly method for the construction of $C(sp^2)$–CN bond on water has been described, and (*Z*)-2-(2-oxoindolin-3-ylidene)-2-arylacetonitriles were synthesized by using $CeCl_3{\cdot}7H_2O$ as a catalyst. The reaction offers access to alkenyl nitriles in good-to-excellent yield. The investigations will be beneficial to reduce the use of toxic organic solvents and explore the efficient catalytic processes on water.

ARTICLE HISTORY
Received 31 August 2018

KEYWORDS
CeCl3·7H2O; on water; (*Z*)-2-(2-oxoindolin-3-ylidene)-2-arylacetonitrile

GRAPHICAL ABSTRACT



Introduction

Alkenyl nitriles are core structure motifs in natural products and pharmaceuticals (Fig. 1).[1] In addition, alkenyl nitriles also serve as precursors for a range of building blocks, such as amides, amidines, ketones, and heterocycles.[2] The reported typical synthetic methods for alkenyl nitriles include (i) the palladium-catalyzed cyanation of alkenyl halides;[3] (ii) the nickel-catalyzed carbocyanation of alkynes;[4] (iii) the ruthenium-catalyzed α-olefination of nitriles;[5] and (iv) the direct cyanation of indoles.[6] However, these methods use expensive catalysts, toxic solvents, and complex ligands. Therefore, it is of great importance to explore an easy and environmentally friendly way to synthesize alkenyl nitriles.

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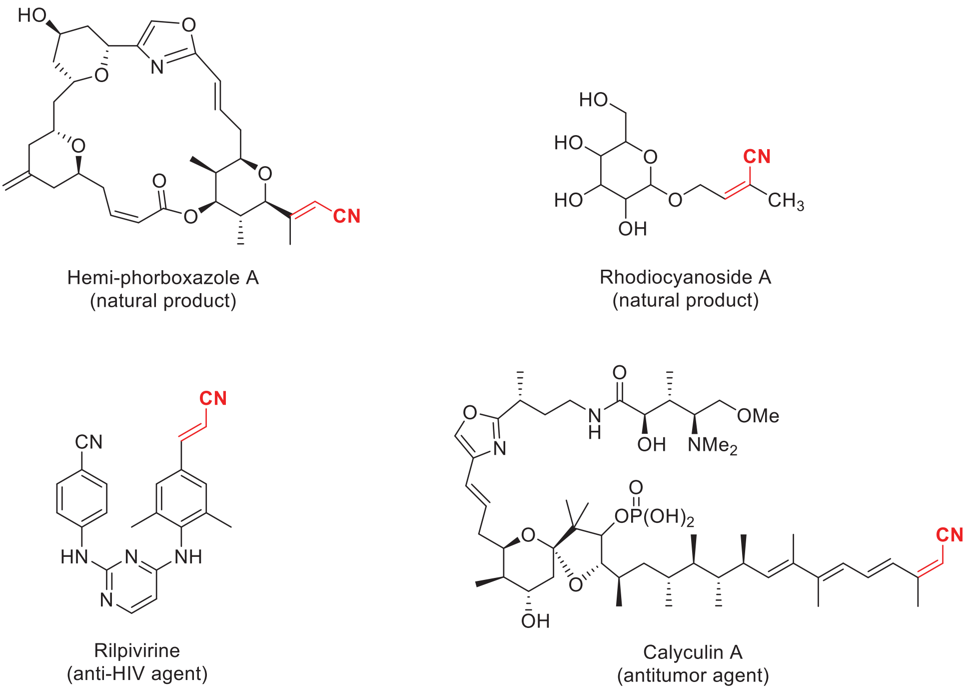


Hemi-phorboxazole A
(natural product)

Rhodiocyanoside A
(natural product)

Rilpivirine
(anti-HIV agent)

Calyculin A
(antitumor agent)

Figure 1. Representative examples bearing alkenyl nitrile structures.

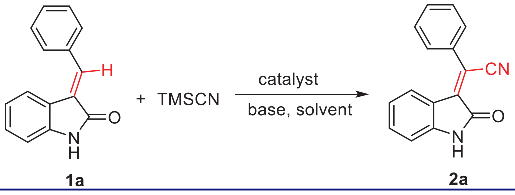
It is widely acknowledged that water serves as an important medium for all chemical reactions of life.[7] However, it was not applied to organic chemistry until early 1980s. Breslow found that water could promote the rate of some reactions which had made it possible for water to become solvent in organic reaction.[8] In contrast to classical traditional organic solvents that have the disadvantages of poisonous and difficult to handle, water has the obvious advantage of environmentally friendly, economic, and polar nature. Recently, "on-water" reactions have become one of the most potential areas of research in green chemistry.[9] Meanwhile, $CeCl_3.7H_2O$ has been demonstrated to be as a mild water-tolerable Lewis acid and green catalyst since the earlier introduction of $CeCl_3 \cdot 7H_2O$ by Luche.[10] Compared with traditional Lewis acid catalyst limited by strict anhydrous conditions, $CeCl_3.7H_2O$ outperforms on water and it serves as the most attractive Lewis acidic catalyst in organic synthesis.[11]

As an extension of our investigation on the various methods for the synthesis of compounds including cyano group,[12] herein, we report an environmentally friendly and efficient method for the synthesis of (*Z*)-2-(2-oxoindolin-3-ylidene)-2-arylacetonitriles through $C(sp^2)$–CN bond construction on water by using $CeCl_3 \cdot 7H_2O$ as a catalyst.

Results and discussion

Initially, the reaction of (*E*)-3-benzylideneindolin-2-one (**1a**) with trimethylsilyl cyanide (TMSCN) was selected as the model reaction to screen the optimal conditions, which included the use of different catalysts, bases, and solvents at a certain temperature for

Table 1. Optimization of the reaction conditions[a].



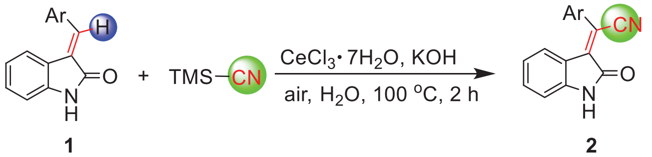
Entry	Catalyst	Base	Solvent	Yield [%][b]
1	None	KOH	H_2O	20
2	$NiCl_2$	KOH	H_2O	0
3	$FeCl_3$	KOH	H_2O	0
4	$InCl_3$	KOH	H_2O	41
5	$CeCl_3{\cdot}7H_2O$	KOH	H_2O	93
6	$CeCl_3{\cdot}7H_2O$	$NaHCO_3$	H_2O	25
7	$CeCl_3{\cdot}7H_2O$	K_2CO_3	H_2O	35
8	$CeCl_3{\cdot}7H_2O$	Cs_2CO_3	H_2O	16
9	$CeCl_3{\cdot}7H_2O$	*t*-BuOK	H_2O	trace
10	$CeCl_3{\cdot}7H_2O$	DBU	H_2O	0
11	$CeCl_3{\cdot}7H_2O$	DABCO	H_2O	0
12	$CeCl_3{\cdot}7H_2O$	Et_3N	H_2O	0
13	$CeCl_3{\cdot}7H_2O$	KOH	DMF	58
14	$CeCl_3{\cdot}7H_2O$	KOH	DMSO	52
15	$CeCl_3{\cdot}7H_2O$	KOH	THF	trace
16	$CeCl_3{\cdot}7H_2O$	KOH	PhMe	30
17	$CeCl_3{\cdot}7H_2O$	KOH	EtOH	23
18	$CeCl_3{\cdot}7H_2O$	KOH	MeCN	73

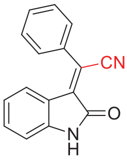
[a] Reaction conditions: **1a** (1 mmol), TMSCN (1.2 mmol), catalyst (0.1 mmol), and base (1 mmol) in solvent (5 mL) were refluxed for 2 h.
[b] Isolated yield.

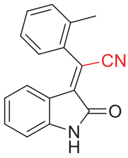
an appropriate time. The results are summarized in Table 1. It was found that the reaction readily proceeded on water using KOH as a base leading to produce (*Z*)-2-(2-oxoindolin-3-ylidene)-2-phenylacetonitrile (**2a**) in 20% yield (Table 1, entry 1). This result prompted us to further search for the optimal reaction conditions. Addition of 10 mol % of $NiCl_2$, $FeCl_3$, $InCl_3$, and $CeCl_3{\cdot}7H_2O$ as catalysts was tested (Table 1, entries 2 – 5). $CeCl_3{\cdot}7H_2O$ exhibited the best catalytic effect and gave the highest yield (93%) (entry 5). Some other bases, such as $NaHCO_3$, K_2CO_3, Cs_2CO_3, *t*-BuOK, DBU, DABCO, and Et_3N, were also tested for the reaction (entries 6 – 12). No improved yield of **2a** was observed. In addition, in our investigation of the organic solvents, such as DMF, DMSO, THF, PhMe, EtOH, and MeCN (Table 1, entries 13 – 18), it was found that the reaction in these solvents could not give higher yield of **2a** than the reaction on water.

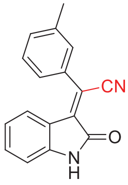
By using the optimized conditions, synthesis of (*Z*)-2-(2-oxoindolin-3-ylidene)-2-arylacetonitriles was conducted by reactions of various (*E*)-3-arylideneindolin-2-ones with TMSCN catalyzed by $CeCl_3{\cdot}7H_2O$ in the presence of KOH at reflux on water. The results are shown in Table 2. The reactions worked well for a wide range of substrates bearing both electron-donating (Me, MeO) and electron-withdrawing groups (F, Cl, Br, NO_2, and CF_3) on their aromatic rings, and afforded the desired products in good-to-excellent yields (**2b**–**2r**). Meantime, the substrates including fused aromatic ring (naphthalene), heterocycle (thiophene), and disubstituted aromatic rings also afforded the

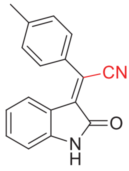
Table 2. Scope of Ar rings of **1** for the synthesis of **2**[a].

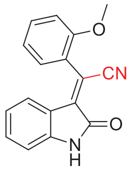



2a 93%


2b 96%


2c 95%


2d 98%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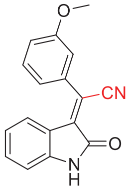
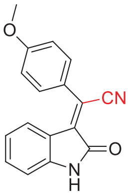
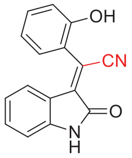

2f 94%


2g 87%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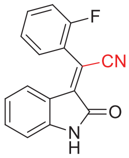
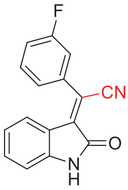
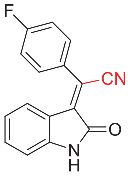

2i 96%


2j 85%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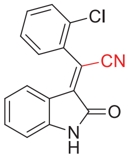
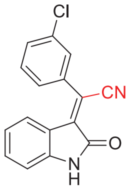
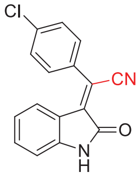
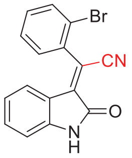
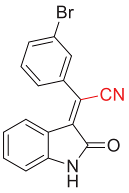
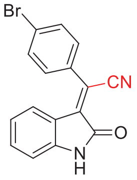

2l 90%

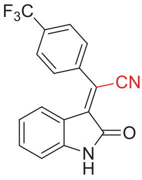

2m 88%

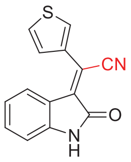

2n 89%

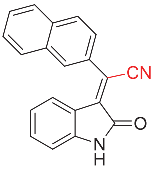

2o 95%


2p 92%


2q 85%


2r 78%


2s 52%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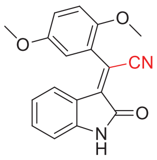
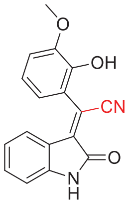
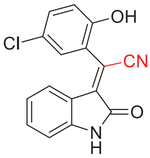

2u 73%


2v 75%

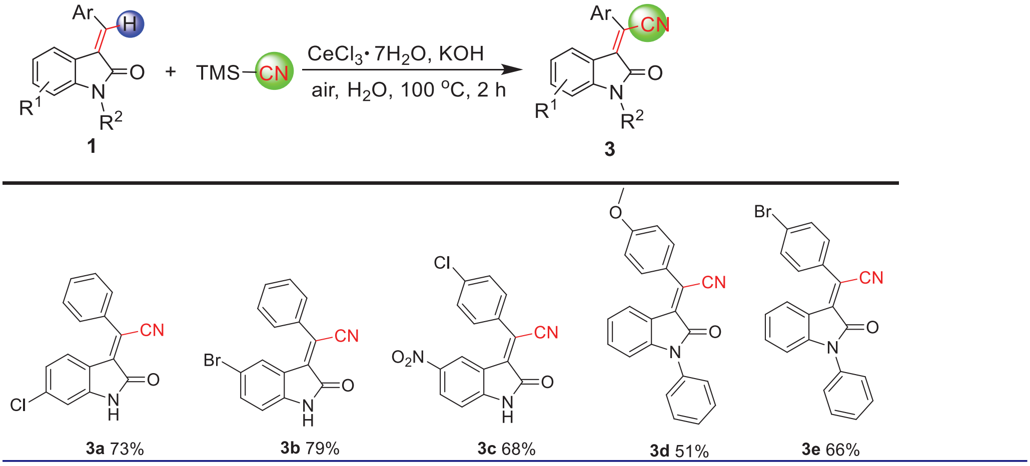

2w 80%

[a]Reaction conditions: **1** (1 mmol), TMSCN (1.2 mmol), $CeCl_3 \cdot 7H_2O$ (0.1 mmol), and KOH (1 mmol) in H_2O (5 mL) was refluxed for 2 h.

corresponding products in satisfactory yield (**2s**–**2w**). In addition, different scope of 2-oxoindoline rings was also tested. Representative alkenyl nitriles **3a**–**3e** could be achieved in good yield for all the tested cases (Table 3).

In order to gain insight into the reaction pathway, control experiments were performed (Scheme 1). Under N_2 atmosphere, the reaction of **1a** with TMSCN was attempted and only Michael addition product **4a** could be observed in 32% of yield. However, the further reaction of **4a** using the standard condition under air atmosphere

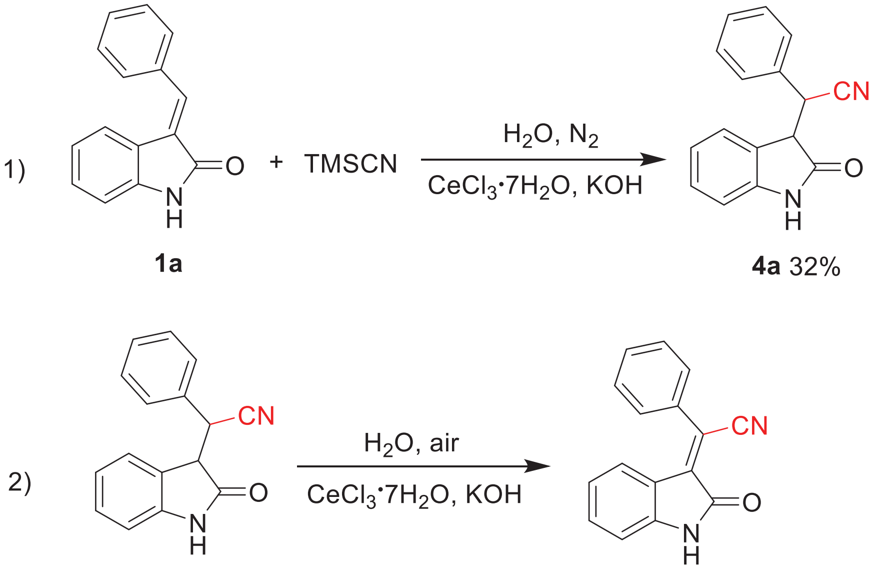
Table 3. Scope of 2-oxoindoline rings of **1** for the synthesis of **3**[a].



1 + → **3**

3a 73% **3b** 79% **3c** 68% **3d** 51% **3e** 66%

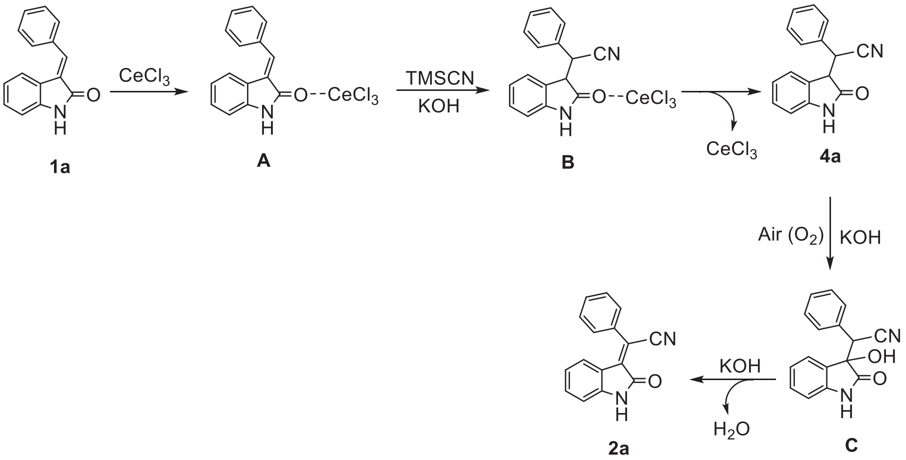
[a] Reaction conditions: **1** (1 mmol), TMSCN (1.2 mmol), $CeCl_3{\cdot}7H_2O$ (0.1 mmol), and KOH (1 mmol) in H_2O (5 mL) was refluxed for 2 h.



1a **4a** 32%

4a **2a** 99%

Scheme 1. Control experiments.



Scheme 2. Proposed mechanism for **2a**.

could produce **2a** in 99% yield. This result indicated that **4a** may be the intermediate of the reaction of **1a** with TMSCN to afford **2a**.

On the basis of the above results, a plausible mechanism is proposed for the synthesis of **2a** (Scheme 2). Firstly, **1a** was combined with $CeCl_3$ to form a complex **A**. **A** was attacked by cyanide from TMSCN in the presence of KOH to form an intermediate **B**. **B** released $CeCl_3$ to afford Michael addition product **4a**. Then, C–H hydroxylation of **4a** is promoted by KOH using atmospheric air as an oxidant to afford intermediate **C**. The similar reactions were also reported by Gnanaprakasam and coworkers.[13] Finally, intermediate **C** underwent dehydration to give **2a** as a final product.

Conclusions

In summary, a method for synthesis of (*Z*)-2-(2-oxoindolin-3-ylidene)-2-arylacetonitriles on water catalyzed by $CeCl_3{\cdot}7H_2O$ has been developed. The salient features of this protocol include high yield, high substrate adaptability, cheap and green catalyst, and environmentally friendly solvent. This method is a rare example of a reaction model of $C(sp^2){-}CN$ bond construction on water and conform to the green chemistry development and might be provide a better alternative to the synthesis of alkenyl nitriles.

Experimental

^1H NMR and ^{13}C NMR spectra were recorded on a Mercury-600MB instrument (Varian, USA) using $CDCl_3$ and DMSO-d_6 as solvents and Me_4Si as an internal standard. Elemental analyses were performed on a Vario El Elemental Analysis instrument (Elementar, Germany) . Melting points were observed in an electrothermal melting point apparatus. 3-Arylideneindolin-2-ones (**1**) were synthesized according to literature method.[14]

Typical experimental procedure for the synthesis of (Z)-2-(2-oxoindolin-3-ylidene)-2-arylacetonitriles

The mixture of (*E*)-3-arylideneindolin-2-ones (1 mmol), TMSCN (1.2 mmol), KOH (1 mmol), $CeCl_3 \cdot 7H_2O$ (0.1 mmol), and water (5 mL) was stirred at 100 °C for 2 h. The reaction was monitored by TLC. After the completion of the reaction, the solid was filtered and washed with 15 mL of water, and recrystallized from EtOAc to afford the pure products.

Funding

The authors thank the National Natural Science Foundation of China (21462038) for the financial support of this work.

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