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Cerium(III)-catalyzed C3-acylation of indoles with nitroolefins

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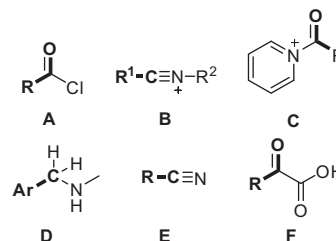
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ABSTRACT

A novel and efficient cerium(III)-catalyzed C3-selective acylation of N–H indoles using nitroolefins as acylating reagents was first developed. It was found that the use of CeCl₃ as a catalyst achieves an unexpected and highly efficient C–C bond cleavage.

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The indole skeleton is present in many pharmaceuticals and biologically active alkaloids, and a great deal of attention has been paid to the synthesis of substituted indoles by either de novo indole ring construction or modification of indole ring.¹ Among reports on indole rings, 3-acylindoles and their derivatives show some special properties, and some of which serve as potent agents to treat HIV, diabetes, and cancer.² They are also used as valuable intermediates in a variety of functional group transformations.³ Traditional strategies for the synthesis of 3-acylindoles typically involved the use of acyl chlorides (Scheme 1, A) as acylated reagents, which suffer from some limitations, including the use of stoichiometric amounts of Lewis acid, the requirement of a protecting functional group on nitrogen and strict exclusion of moisture. In addition, these reactions often have low selectivity, N1 acylation or N1/C3 diacylation were observed.⁴ The reactions of indoles with nitrilium salts (Scheme 1, B)⁵ or N-(ahaloacyl)-pyridinium salts (Scheme 1, C) were also demonstrated.⁶ Recently, a series of new acylating reagents have been developed to construct 3-acylindoles. Wu and Su found that indoles could be acylated via ruthenium- or ferrum-catalyzed oxidative coupling using anilines as carbonyl equivalents (Scheme 1, D), whereas the use of organic peroxides could cause explosion hazards.⁷ Nitriles were another valuable acyl source for the acylation of indoles, but these reactions required an expensive Pd salt as the catalyst (Scheme 1, E).⁸ α -Oxocarboxylic acids were also used as acylating reagents (Scheme 1, F), Wang et al. reported a novel copper-promoted decarboxylative acylation of indoles with α -oxocarboxylic acids, however stoichiometric amounts of copper salt were necessary

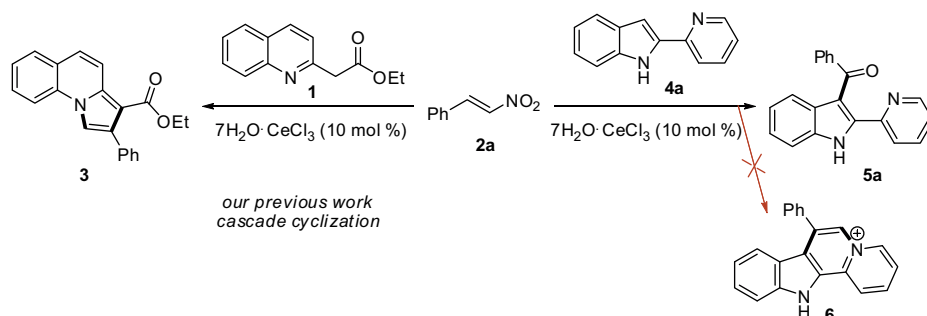


Scheme 1. Representative acylating reagents.

for the success of the reactions.⁹ To address such issues, it is highly desirable to develop new acylating reagents and reaction conditions for the acylation of indoles with free N–H.

Nitroolefins, which are inexpensive and broadly available, are widely used as Michael acceptors because of the high electrophilicity of the double bond.¹⁰ They have been employed to synthesize a variety of interesting heterocyclic or acyclic compounds.¹¹ Our group developed a cerium catalyzed cascade cyclization of 2-alkyl-lazaarenes (1) with nitroolefins (2) to construct pyrrolo[1,2-*a*]quinoline derivatives (3).¹² Encouraged by the result, we then tried to realize the cascade cyclization of 2-(pyridin-2-yl)-1H-indole (4a) with nitroolefins (2) using cerium as catalyst (Scheme 2). Surprisingly, the expected product 7-phenylindolo[2,3-*a*]quinolizine (6) was not observed. Instead, we found that (E)-(2-nitrovinyl)benzene (2a) reacted with 2-(pyridin-2-yl)-1H-indole (4a) to give an unexpected C3 acylation product of phenyl(2-(pyridin-2-yl)-1H-indol-3-yl)methanone (5a) with 90% isolated chemical yield.

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Scheme 2. Cascade cyclization and acylation.

The applications of cerium compounds to organic transformations have been extensively studied.¹³ They have attracted much attention in organic synthesis because they are inexpensive, easy to handle, and highly tolerant to air and moisture. Therefore, the development of cerium-catalyzed methods would be of a great value. Herein, we report a cerium-catalyzed C3-selective acylation of N-H indoles using nitroolefins as acylating reagents. To our knowledge, this is the first example of using the nitroolefins as acylating reagents in acylation reactions.

To look into the prospect of this new acylation reaction, a model reaction using easily available 2-(pyridin-2-yl)-1H-indole (**4a**) and *trans*-(*Z*)-nitrostyrene (**2a**) was investigated in detail by varying the catalyst in order to develop appropriate conditions (Table 1). We screened various Lewis acids and found that other Lewis acids, including copper salt, iron salt, nickel salt, cobalt salt, are either ineffective or less effective than $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (Table 1, entries 1–6). The reaction gave a poor yield in the absence of catalyst (Table 1, entry 7). On the other hand, the organic solvent was also found to play an important role in the reaction. Among various solvents screened, ethanol was found to be the most suitable solvent. Other solvents reduced the yield of this reaction (Table 1, entries 8–13). The yield of **5a** decreased to 72% when lowering the temperature from 120 °C to 100 °C (Table 1, entry 14). In recent years, it has been found that the $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ –NaI system as an efficient Lewis acid activator has a wide range of interesting applications in organic chemistry.^{13b} However, the introduction of 0.1 equiv of NaI into the reaction system significantly suppressed the reaction (Table 1, entry 15).

With the optimal conditions in hand, the substrate scope and limitation of the reaction was explored. First of all, the substrate scope of nitroolefins **2** was examined. As illustrated in Table 2, aromatic nitroalkenes with both electron-rich (4-Me, 4-OMe, 4-NMe₂) and electron-deficient (CF₃) substituents on the aromatic ring participated in this reaction smoothly to afford the expected products in good to excellent yields. Generally, an electron-donating substituent on the aromatic ring has a negative effect on the yield. Unprotected phenol functions were well tolerated under the optimized conditions, when R¹ was replaced by a 2-OH group, the reaction gave a lower yield in comparison with that R¹ was a 4-OH group (Table 2, entries **5f** and **5n**). This implied that steric effect had an influence on the reaction. The reaction of ring-fused (**5o**) nitroalkene also afforded the corresponding product in good yields. However, less-reactive alkyl substituted nitroalkenes did not give the target products under the current reaction conditions.

Next, the effect of the substituents attached on the indole ring was examined. The halogen, including fluoro, chloro, or bromo group, had little influence on the reaction (Table 2, **5q–5s**), thus providing the possibility to allow additional coupling reactions. The electron-donating group at 5-position of the indole ring was also well tolerated, affording the corresponding product in excellent yield (Table 2, **5p**). But the introduction of an electron-donating

group to 7-position of the indole ring marginally reduced the reaction yield (Table 2, **5t**).

To gain insight into the possible mechanism of the reaction, a few control experiments were carried out. In the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a negative influence on the yield was observed (Scheme 3, Eq. 1). This implied that some radical intermediates should be involved in the reaction. Next, instead of nitroolefin, benzaldehyde was used to react with 2-(pyridin-2-yl)-1H-indole under the optimal reaction conditions. Almost no desired product was obtained in this case (Scheme 3, Eq. 2). When the reaction of 2-(pyridin-2-yl)-1H-indole (**4a**) and *trans*-(*Z*)-nitrostyrene (**2a**) was performed in the cerium catalytic system under argon gas, the desired product (**5a**) was obtained in 93% yield (Scheme 3, Eq. 3). This result indicated that the nitro group might act as an internal oxidant. When 2-phenyl-1H-indole (Scheme 3, Eq. 4) or 2-(pyridin-4-yl)-1H-indole (Scheme 3, Eq. 5) was used to react with nitroolefin (**2a**), Michael adducts were separated as major product. The above results suggest that the existence of pyridin-2-yl group has an unclear intramolecular effect on the product formation process.

Table 1
Optimization of the reaction conditions^a

Entry	Catalyst	Solvent	Yield ^b (%)
1	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	EtOH	32
2	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	EtOH	25
3	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	EtOH	38
4	$\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$	EtOH	Traces
5	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	EtOH	90
6	$\text{TsOH} \cdot \text{H}_2\text{O}$	EtOH	29
7	—	EtOH	36
8	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	H_2O	Traces
9	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	DMF	Traces
10	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	MeCN	21
11	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	THF	Traces
12	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	CH_2Cl_2	Traces
13	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	MeOH	85
14 ^c	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	EtOH	72
15 ^d	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$	EtOH	43

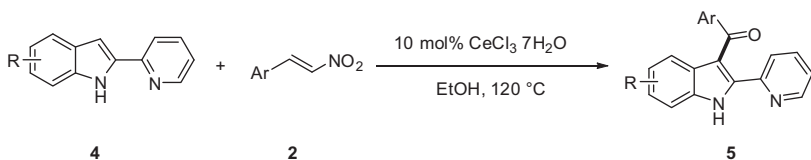
^a Reaction conditions: **4a** (0.20 mmol), **2a** (0.30 mmol), catalyst (0.02 mmol), solvent (2 ml), 120 °C, 12 h.

^b Isolated yield.

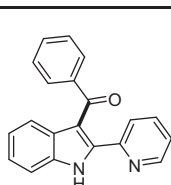
^c The reaction was at 100 °C.

^d 0.02 mmol of NaI was used.

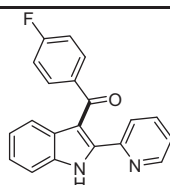
Table 2
Acylation of indoles with nitroolefins^a



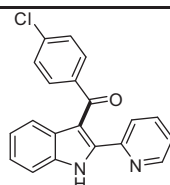
4 + **2** $\xrightarrow[\text{EtOH, 120 } ^\circ\text{C}]{10 \text{ mol\% CeCl}_3 \cdot 7\text{H}_2\text{O}}$ **5**



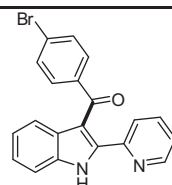
5a, 90%



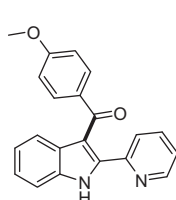
5b, 80%



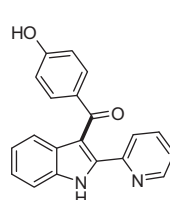
5c, 83%



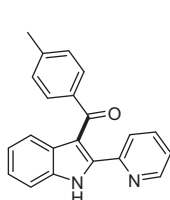
5d, 96%



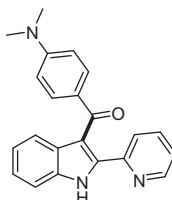
5e, 82%



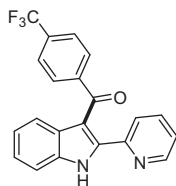
5f, 87%



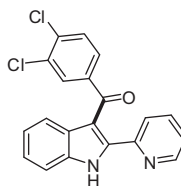
5g, 75%



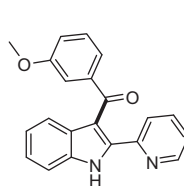
5h, 72%



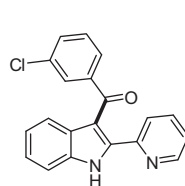
5i, 77%



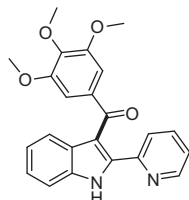
5j, 93%



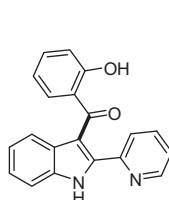
5k, 75%



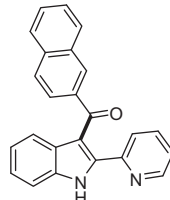
5l, 82%



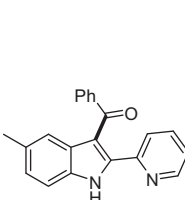
5m, 62%



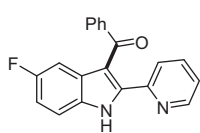
5n, 45%



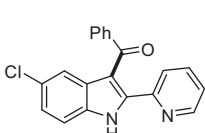
5o, 53%



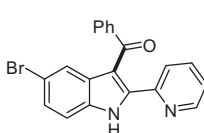
5p, 88%



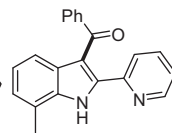
5q, 98%



5r, 91%



5s, 72%

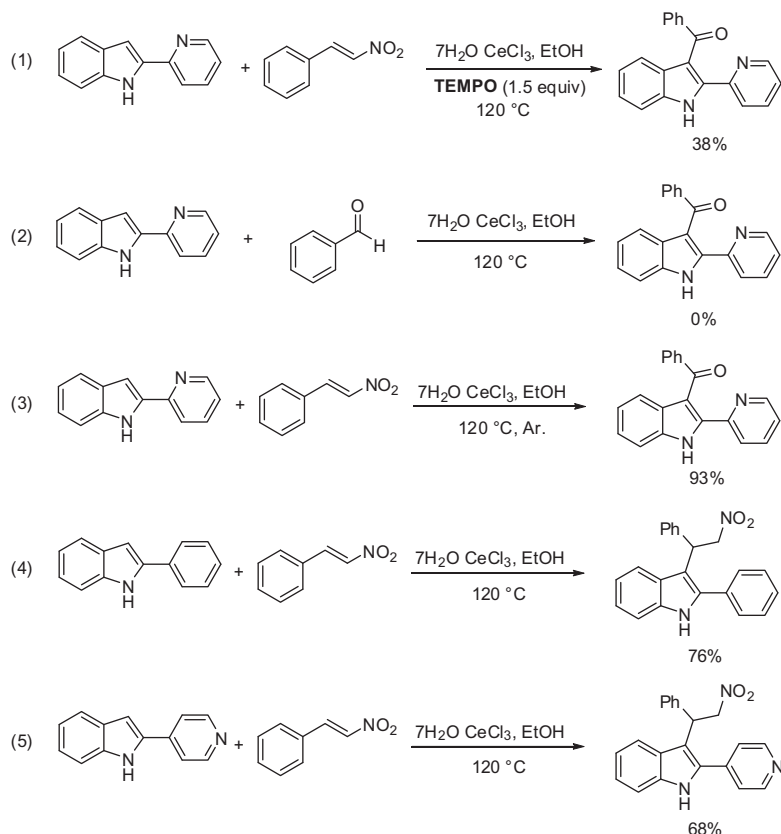


5t, 65%

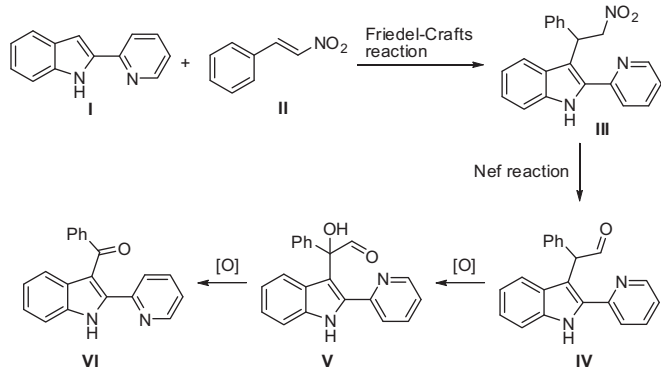
^a Standard reaction conditions: **4** (0.20 mmol), **2** (0.30 mmol), CeCl₃·7H₂O (0.02 mmol), 2 ml EtOH, 120 °C, 12 h, isolated yield.

On the basis of the control experiments and literature reports,^{10a,14} a plausible mechanism is outlined in Scheme 4. The first step of the reaction is the Friedel–Crafts reaction of 2-pyridyl-indole **I** with nitroolefin **II** to form the intermediate **III**. Ce(III) salt may accelerate the reaction by increasing the electrophilicity of the nitroolefin. Subsequently, the intermediate **III** is converted into intermediate **IV** by a Ce(III)-catalyzed Nef reaction. The intermediate **IV** is converted to **V** by oxidation reaction, further oxidation to the carbon–oxygen double bond **VI** is occurred via a carbon–carbon bond cleavage.

In conclusion, we have developed an unprecedented acylation reaction of indoles with nitroolefins through the cleavage of C–C bonds. In the presence of 10 mol % cerium(III) chloride heptahydrate, a range of aryl nitroolefins smoothly underwent acylation with unprotected indoles to give a wide range of 3-acylindoles in moderate to excellent yields with extremely high regioselectivity. The current research paves the way for the use of nitroolefins as unique acylating reagent in chemical synthesis.



Scheme 3. The control experiments to prove the mechanism.



Scheme 4. Plausible reaction mechanism.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2016.01.029>.

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