Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Cerium(III)-Catalyzed Cascade Cyclization: An Efficient Approach to Functionalized Pyrrolo[1,2-a]quinolines

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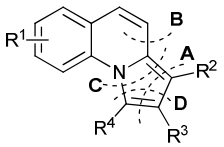
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A general and practical route to the synthesis of mutisubstituted pyrrolo[1,2-*a*]quinolines has been described from 2-alkylazaarenes and nitroolefins using cerium chloride as a catalyst *via* a tandem Michael addition, Cyclization and Aromatization. This protocol featured ready availability of the starting materials, the operational simplicity and high regioselectivity to access multifunctionalized pyrrolo[1,2-*a*]quinolines with the formation of multiple C-C and C-N bonds in one-pot. In addition, various substitution patterns and functional group were found to be compatible under the optimized conditions, which was lacking in existing procedures.

The chemistry of fused nitrogen heterocycles is of great importance due to their wide applications.[1] Among these compounds, the pyrrolo[1,2-*a*]quinoline derivatives raised special interest because of their potential biological activity[2] and physical properties.[3] Moreover, the skeleton of pyrrolo[1,2-*a*]quinoline exists in gephyrotoxin, a natural alkaloid which conduct to numerous studies regarding its biological activity.[4] However, only a few relevant synthetic methodologies were reported, which mainly relied on 1,3-dipolar cycloaddition of quinolinium N-ylides with electron-deficient alkynes or alkenes (**A**),[5] transition-metal-catalyzed intramolecular cycloisomerizations of pyrroles with specific C-2 functionalization (**B**).[6] Recently published reports involved a copper-catalyzed [3+2] cyclization of quinolines with alkenyldiazoacetates (**C**),[7] copper-catalyzed annulation of 2-alkylazaarenes with *α*, *β*-unsaturated carboxylic acids (**D**).[8] Besides, a muticomponent approach for the synthesis of pyrrolo[1,2-*a*]quinoline derivatives was also reported.[9] Despite the great successes achieved in this field, these methods still suffer from some limitations, such as harsh reaction conditions, limited substrate scope and substitution pattern, and involvement of multistage synthesis. Recently, a comprehensive structure–activity relationship (SAR) study in drug design has raised a growing demand for a variation of substitution patterns of target molecule. Therefore, developing more practical synthetic approaches to pyrrolo[1,2-*a*]quinolines with a variety of substitution patterns is highly desired.

A domino reaction is a consecutive series of intramolecular or intermolecular organic reactions. It allows the organic synthesis of complex multinuclear molecules from acyclic precursors.[10] Benzylic C-H bond of 2-alkylazaarenes has been functionalized with a variety of unsaturated bonds by various groups including our own.[11,12*d*] Among these reports, only acyclic compounds were formed. If a suitable substrate combined with a suitable catalyst were chosen, subsequent amination process can provide a fused heterocycle. The domino reaction is a more attractive strategy to construct polycyclic nitrogen heterocycles. Until recently, very few reports have appeared on this method (**D**).[8, 12*a*]



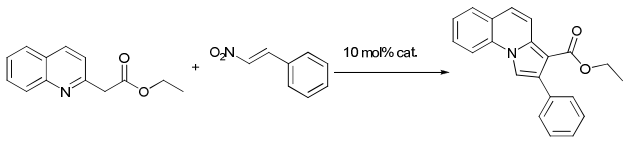
Scheme 1. The disconnection approaches to the pyrrolo[1,2-*a*]quinoline core.

Our group have reported a series of domino processes for synthesis of heterocycle compounds with the formation of multiple C-C and C-hetero bonds in one-pot.[12] As a continuous effort on these domino processes, herein, we report a general and practical domino reaction to access multifunctionalized pyrrolo[1,2-a]quinolines from readily available 2-alkylazaarenes with active methylene and nitroolefins using cerium(III) chloride as the catalyst under mild conditions.

Initially, trans-(Z)nitrostyrene (**2a**) and ethyl 2-(quinolin-2-yl)acetate (**1a**) were employed as model substrates to optimize the reaction conditions. Stirring a mixture of ethyl 2-(quinolin-2-yl)acetate **1a** (1.5 equiv), trans-(Z)nitrostyrene **2a** (1.0 equiv), and $TsOH{\cdot}H_2O$ (10 mol %) in EtOH at room temperature afforded pyrrolo[1,2-a]quinolines (**3a**) in 65% isolated yield (Table 1, entry 1). The use of iodine as a catalyst did not improve the yield (Table 1, entry 2). Then various metal Lewis acids were employed as potential catalysts for this transformation. The results showed that when $CeCl_3{\cdot}7H_2O$ was used as a catalyst, the reaction could gave the corresponding product with the highest yield of 88% (Table 1, entry 10). In view of excellent catalytic capacity, outstanding stability and low toxicity, $CeCl_3{\cdot}7H_2O$ was chosen as the effective catalyst for the domino reaction. On the other hand, solvent also played a crucial role in the reaction. Among various solvents examined, ethanol was

found to be the optimal. Other solvents reduced the yield of this reaction (Table 1, entries 13-18). Subsequently, we attempted to raise the temperature to 80℃. However, the yield decreased to 70% because of unknown side reactions (Table 1, Entry 19).

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



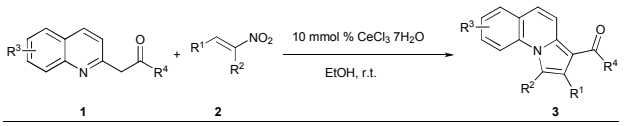
1a 2a 3a

Entry	Catalyst	Solvent	Yield (%)[b]
1	$TsOH·H_2O$	EtOH	65
2	I_2	EtOH	57
3	$MgCl_2·6H_2O$	EtOH	61
4	$NiCl_2·6H_2O$	EtOH	75
5	$AlCl_3·6H_2O$	EtOH	69
6	$ZrCl_4$	EtOH	82
7	$FeCl_3·6H_2O$	EtOH	73
8	$CoCl_2·6H_2O$	EtOH	81
9	$CuCl_2·2H_2O$	EtOH	62
10	**$CeCl_3·7H_2O$**	**EtOH**	**88**
11	$Ce(NO_3)_3·6H_2O$	EtOH	76
12	$Ce(SO_4)_2·4H_2O$	EtOH	52
13	$CeCl_3·7H_2O$	THF	38
14	$CeCl_3·7H_2O$	EtOAc	43
15	$CeCl_3·7H_2O$	Toluene	20
16	$CeCl_3·7H_2O$	DMSO	55
17	$CeCl_3·7H_2O$	DMF	46
18	$CeCl_3·7H_2O$	CH_3CN	50
19[c]	$CeCl_3·7H_2O$	EtOH	70

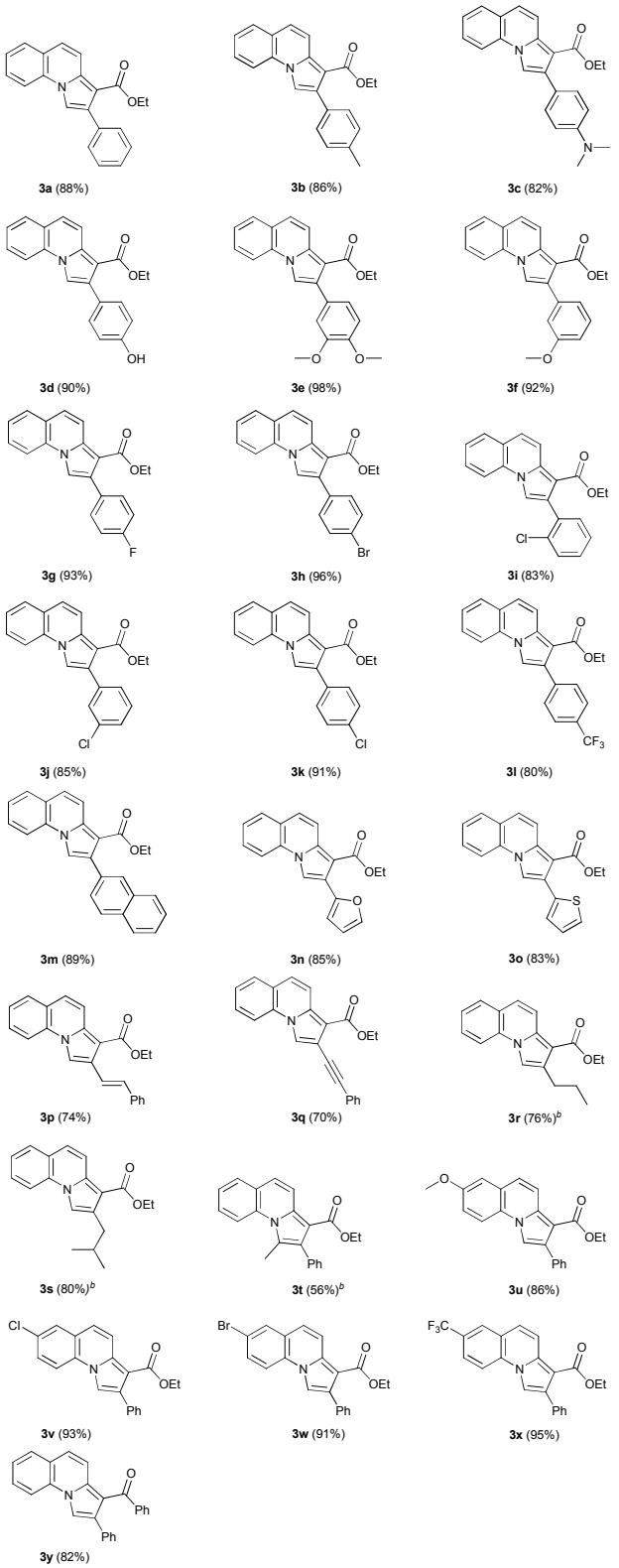
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.20 mmol), catalyst (0.02 mmole), solvent (2 mL), room temperature, 24 h. [b] Isolated yield. [c] The reaction was at 80℃.

With the optimal conditions in hand, the substrate scope of the reaction was extended. First of all, the substrate scope of nitroolefin **2** was screened. As illustrated in Table 2, aromatic nitroalkenes with both electron-rich (4-Me, 4-OMe, 4-NMe_2) and electron-deficient (CF_3) 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 positive effect on the yield. When R^1 was replaced by a 2-chlorophenyl group, the reaction gave a lower yield in comparison with that R^1 was a 4-chlorophenyl group (Table 2, entries **3i**, **3k**). This implied that steric effect had an influence on the reaction. Unprotected phenol moiety was also well tolerated under the reaction conditions, and **3d** was obtained in 90% yield. Pleasingly, the reaction of ring-fused (**2m**), heterocyclic (**2n** and **2o**), styryl (**2p**) and phenylethynyl (**2q**) nitroalkenes also afforded the corresponding products in good yields (Table 2, entries **3m-3q**). When R^1 group were replaced by aliphatic groups, the use of ultrasound was necessary to obtain good yields of the reaction (**3r** and **3s**). Notably, when disubstituted nitroalkene was employed as the substrate, the reaction also

Table 2. Synthesis of pyrrolo[1,2-a]quinolines.[a]



1 2 3

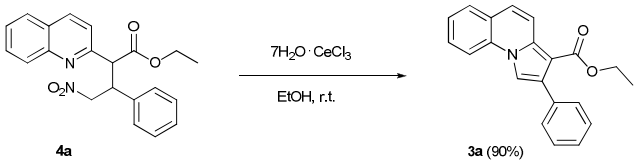


[a] Standard reaction conditions: **1** (0.25 mmol), **2** (0.20 mmol), $CeCl_3 \cdot 7H_2O$ (0.02 mmol), 2 mL EtOH, room temperature, 24 h, Isolated yield. [b] The reaction was performed at 40℃ under ultrasound for 3 h.

proceeded smoothly to provide the trisubstrated product **3t** in 56% yield.

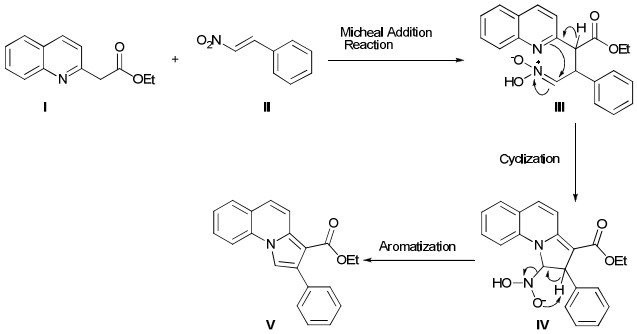
Subsequently, different quinoline derivatives **1** were investigated. Both electron-withdrawing and electron-donating substituents on the aromatic ring were tolerated in this reaction. The electron-rich group on the aromatic ring was unfavorable for the formation of pyrrolo[1,2-a]quinolines, while the electron-deficient substituents increased the reaction yields (Table 2, **3u** -**3x**). Additionally, when R^4 was a phenyl group, the product **3y** was obtained in 82% yield.

Presumably, this process involves Michael addition of 2-alkyl-quinolines to α, β-unsaturated nitroalkenes followed by a subsequent cyclization, thereby leading to the final product. We were able to isolate the intermediate **4a** from the reaction of ethyl 2-(quinolin-2-yl)acetate **1a** and trans-(Z)nitrostyrene **2a**. It is noteworthy that the Michael adduct **4a** gave the final product **3a** in excellent yield in the presence of $CeCl_3 \cdot 7H_2O$ in EtOH, as shown in Scheme 2. However, only trace of product **3a** was observed in the absence of catalyst under similar reaction conditions. Therefore, $CeCl_3 \cdot 7H_2O$ plays an essential role to enhance the rate of this transformation.



Scheme 2. The control experiment to prove the mechanism.

A plausible reaction mechanism is suggested on the basis of these preliminary date and literature precedents (Scheme 3). [13] The first step of the reaction is the Michael addition of 2-alkyl-quinoline **I** with nitroolefin **II** to form the intermediate **III**. Ce(III) chloride may accelerated the reaction by increasing the electrophilicity of the nitroolefin through coordination. Subsequently, the intermediate **III** is converted into intermediate **IV** by a Ce(III)-catalyzed intramolecular cyclization. Finally, the intermediate **IV** eliminate a water and nitroxyl (HNO) to form the final product **V**.[14]



Scheme 3. Plausible reaction mechanism.

In summary, we have developed a facile domino cyclization to construct pyrrolo[1,2-a]quinoline derivatives from α, β-unsaturated nitroalkenes with 2-alkyl-quinolines catalyzed by cerium chloride. Compared to previous reports, this present method has the advantages of general applicability, simple operation, mild condition and good yields. Therefore, considering the above feature, we believe this one-pot catalytic transformation would be an attractive approach for the synthesis of pyrrolo[1,2-a]quinoline derivatives.

We are grateful to National Nature Science Foundation of China (2127222, 91213303, 21172205, J1030412).

Notes and references

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† Electronic Supplementary Information (ESI) available(exprement procedure and NMR data). See DOI: 10.1039/b000000x/

1 (*a*) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles,* WILEY-VCH, Weinheim, 2003; (*b*) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.,* 2006, **4**, 2337-2347.

2 (*a*) A. Cappelli, G. Giuliani, M. Anzini, D. Riitano, G. Giorgi, S. Vomero, *Bioorg. Med. Chem.,* 2008, **16**, 6850-6859; (*b*) T. Ikeda, T. Yaegashi, T. Matsu-zaki, S. Hashimoto, S. Sawada, *Bioorg. Med. Chem. Lett.,* 2011, **21**, 342–345; (*c*) A. Hazra, S. Mondal, A. S. Maity, P. Naskar, R. Saha, K. B. Paira, P. Sahu, S. Paira, C. Ghosh, A. Sinha, A. Samanta, S. Banerjee, N. B. Mondal, *Eur. J. Med. Chem.,* 2011, **46**, 2132–2140.

3 (*a*) L. Leontie, I. Druta, R. Danac, G. I. Rusa, *Synth. Met.,* 2005, **155**, 138–145; (*b*) S. A. Ahmed, *J. Phys. Org. Chem.,* 2006, **19**, 402-414.

4 (*a*) T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly and B. Witkop, *Helv. Chim. Acta*., 1974, **57**, 2597-2604; (*b*) R. Fujimoto and Y. Kishi, *J. Am. Chem. Soc.,* 1980, **102**, 7154-7156; (*c*) L. -L. Wei, R. P. Hsung, H. M. Sklenicka and A. I. Gerasyuto, *Angew. Chem. Int. Ed.,* 2001, **40**, 1516-1518; (*d*) M. Santarem, C.Vanucci-Bacqué and G. Lhommet, *J. Org. Chem.,* 2008, **73**, 6466-6469.

5 For selected reviews, see: (*a*) H. E.-A. El-Sayed, I. El-Sayed, *Adv. Heterocycl. Chem.,* 2003, **84**, 71-190; (*b*) G. Yue, Y. Wan, S. Song, G. Yang, Z. Chen, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 453–458; (*c*) A. V. Butin, F. A. Tsiunchik, V. T. Abaev, K. V. Bosikova, *ARKIVOC*., 2009, 79-87; (*d*) D. Basavaiah, B. Devendar, D. V. Lenin, T. Satyanarayana, *Synlett*., 2009, **3**, 411-416.

6 For selected reviews, see: (*a*) V. Mamase, A. Furstner, *J. Org. Chem.,* 2002, **67**, 6264-6267; (*b*) D. G. Hulcoop, M. Lautens, *Org. Lett.,* 2007, **9**, 1761-1764; (*c*) D. I. Chai, M. Lautens, *J. Org. Chem.,* 2009, **74**, 3054-3061; (*d*) A. K. Verma, S. P. Shukla, J. Singh, V. Rustagi, *J. Org. Chem.,* 2011, **76**, 5670-5684; (*e*) S. Q. Ye, J. P Liu and J. Wu, *Chem. Commun*., 2012, **48**, 5028-5030; (*f*) S. Sarkar, K. Bera, S. Jalal, U. Jana, *Eur. J. Org. Chem.,* 2013, **27**, 6055–6061.

7 J. Barluenga, G. Lonzi, L. Riesgo, L. A. López, M. Tomás, *J. Am. Chem. Soc.,* 2010, **132**, 13200-13202.

8 Y. Z. Yang, C. S Xie, Y. J. Xie, Y. H. Zhang, *Org. Lett*., 2012, **14**, 957-959.

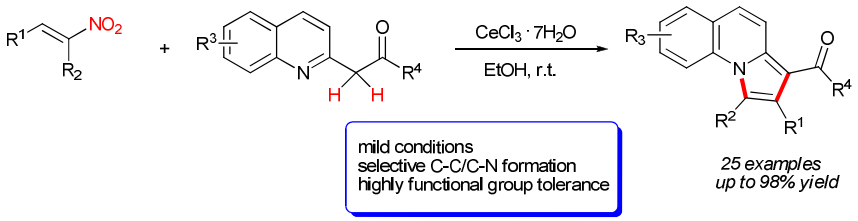
9 T.-J. Li, H.-M. Yin, C.-S. Yao, X.-S. Wang, B. Jiang, S.-J. Tu, G. Li, *Chem. Commun.,* 2012, **48**, 11966-11968.

10 For selected reviews, see: (*a*) L. Tietze, N. Rackelmann, *Pure Appl. Chem.,* 2004, **76**, 1967–1983; (*b*) B. Jiang, T. Rajale, W. Wever, S.-J. Tu, G. G. Li, *Chem. Asian. J.,* 2010, **5**, 2318-2335.

11 (*a*) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia, H. Huang, *J. Am. Chem. Soc.,* 2010, **132**, 3650-3651; (*b*) B. Qian, S. Guo, C. Xia, H. Huang, *Adv. Synth. Catal.,* 2010, **352**, 3195-3200; (*c*) M. Rueping, N. Tolstoluzhsky, *Org. Lett.,* 2011, **13**, 1095-1097; (*d*) H. Komai, T. Yoshino, S. Matsunaga, M. Kanai, *Org. Lett.,* 2011, **13**, 1706-1709; (*e*) B. Qian, P. Xie, Y. Xie, H. Huang, *Org. Lett.,* 2011, **13**, 2580-2583; (*f*) C. Fallan, H. W. Lam, *Chem. Eur. J.,* 2012, **18**, 11214-11218.

12 (*a*) Y. Z. Yan, Y. H. Zhang, Z. G. Zha, Z. Y. Wang, *Org. Lett.,* 2013, **15**, 2274-2277; (*b*)Y. Z. Yan, Y. H. Zhang, C. T. Feng, Z. G. Zha, Z. Y. Wang, *Angew. Chem. Int. Ed.,* 2012, **51**, 8077-8081; (*c*) Q. Wang, S. Zhang, F. F. Guo, B. Q. Zhang, P. Hu, Z. Y. Wang, *J. Org. Chem.,* 2012, **77**, 11161-11166; (*d*) Y. Z. Yan, K. Xu, Y. Fang, Z. Y. Wang, *J.*

Org. Chem., 2011, **76**, 6849-6855.(f) C. T. Feng, J. H. Su, Y. Z. Yan, F. F. Guo and Z. Y. Wang, *Org. Biomol. Chem.,* 2013, **11**, 6691-6694.
13 (*a*) H. Shiraishi, T. Nishitani, S. Sakaguchi, Y. Ishii, *J. Org. Chem.,* 1998, **63**, 6234-6238; (*b*) S. Maiti, S. Biswas, U. Jana, *J. Org. Chem.,* 2010, **75**, 1674-1683.
14 The nitrous oxide (N_2O) which originated from recombination of nitroxyl (HNO) was detected and identified by GC-MS, see supporting information.



mild conditions
selective C-C/C-N formation
highly functional group tolerance

25 examples
up to 98% yield