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COMMUNICATION

Metal free synthesis of 2,4-Diarylquinoline Derivatives with Enamides and Imines[†]

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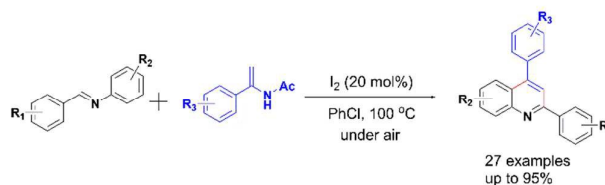
Yamin Li, Xiaoqiang Zhou, Zhaoyang Wu, Jinhui Cao, Chaowei Ma, Yongqin He and Guosheng Huang*

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A metal free I₂-catalyzed cyclization between enamides and imines has been developed. This approach is available for a broad range of substrates and provides an extremely simple and efficient way to construct heteroaromatic quinoline derivatives.

quinolines with more scopes of substrates.



Introduction

The synthesis of substituted quinolines has been a subject of great focus in organic chemistry.¹ The quinoline core is found in a large number of natural products, many of which have important biological activities and potential pharmaceutical applications.² Also, quinolines serve as crucial ligands in the composition of OLED materials³ and asymmetric catalysts.⁴ The increasing importance of substituted quinolines has spurred considerable researches for the development of new synthetic methods.⁵ In the past few years, many transition-metal-catalyzed processes have been developed for the construction of quinolines.⁶ For example, some excellent previous work have been done for the formation of quinolines from nitrobenzene and aldehydes catalyzed by ruthenium,⁷ rhodium,⁸ palladium,⁹ and iron¹⁰. Notably, the number of conventional metal-free paths for quinoline synthesis have also been growing.¹¹ Compared to transition-metal catalysts, reactions mediated by non-metal catalyst such as iodine have attracted great interest recently because of its low toxicity, the ability to operate under mild reaction conditions and its low cost.¹² More recently, The prominent works on construction of 2,4-diarylquinoline derivatives with styrenes had been reported by the group of Jia¹³ and Shah¹⁴, it's worth mentioning that I₂ was fully utilized as the only catalyst in Shah's work. Nevertheless, compared to Shah's excellent work, our method could provide a simple procedure generating

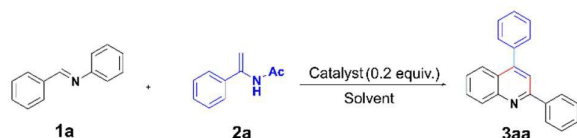
Enamides are versatile and powerful building blocks in organic synthesis,¹⁵ however, the method in construction of quinolines using enamides as reactant has still been rarely explored. In 2012, Zhao and co-workers developed a general method with coupling of enamides and arynes for the synthesis of substituted isoquinolines under transition-metal-free conditions.¹⁶ In this direction, we were intrigued to explore the possibility of a cyclization between enamides and imines. Inspired by the previous works on the formation of substituted quinolines and our experiences in development of efficient methods for the construction of heterocyclic compounds¹⁷, we report a concise approach to substituted quinolines from enamides and imines catalyzed by iodine.

Results and discussion

In a preliminary study of the reaction, we commenced our investigation with the *N*-phenylbenzaldimine (**1a**) and *N*-(1-phenylethenyl)acetamide (**2a**) in the presence of I₂ in toluene under air, to our gratification, the desired product (**3aa**) was observed in 35% yield (Table 1, entry 1). With unreacted **1a** and **1b** constituting the bulk of the remaining material, we suspected that the low temperature might have caused incomplete generation of the desired product. Therefore, we increased the reaction temperature from 80 °C to 100 °C, the results showed that the increasing in the reaction temperature was favorable to the transition (Table 1, entry 2). Screening of various solvents, such as 1,2-dichloroethane (DCE), PhCl, MeCN, DMF and DMSO, showed that PhCl was the most suitable solvent for this reaction (Table 1, entries 2-7). In order

State Key Laboratory of Applied Organic Chemistry, Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou, 730000, China. E-mail: hqs@lzu.edu.cn
Fax: +86-931-8912582

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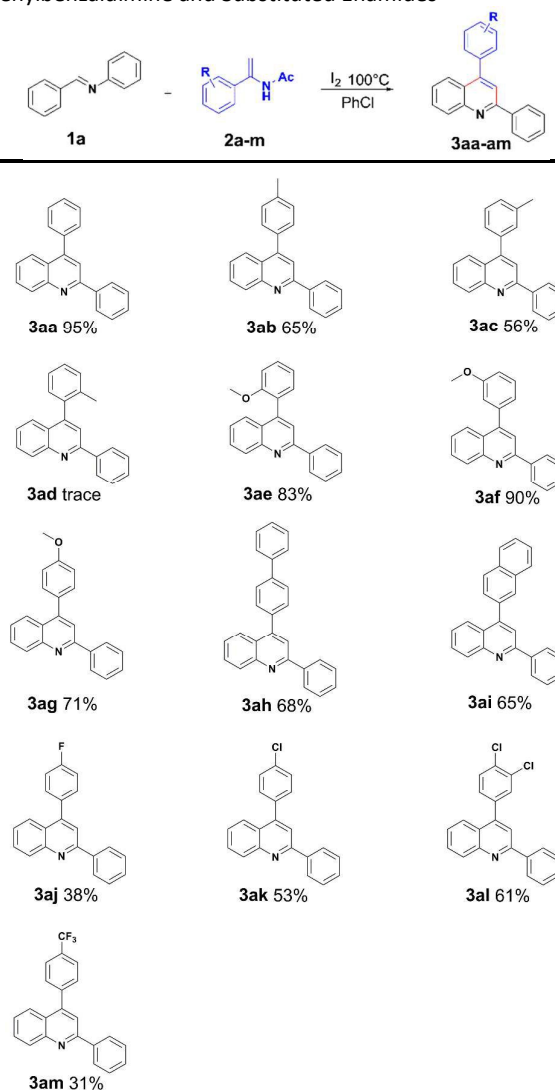
Table 1. Optimization of Reaction Conditions^a

Entry	Catalyst	T(°C)	Solvent	Yield(%) ^b
1	I ₂	80	Toluene	35
2	I ₂	100	Toluene	51
3	I ₂	100	DMF	43
4	I ₂	100	DMSO	—
5	I ₂	100	CH ₃ CN	85
6	I ₂	100	DCE	69
7	I ₂	100	PhCl	95
8	TBAI	100	PhCl	—
9	NIS	100	PhCl	78
10	NCS	100	PhCl	—
11	NBS	100	PhCl	—
12	—	100	PhCl	—

^aReaction conditions: **1a** (0.15 mmol), **2a** (0.2 mmol), catalyst (20 mol %), solvent (2 mL), 1 h. ^bYields of isolated products.

to further improve the reaction efficiency, different kinds of catalysts were investigated, among all these catalysts tested including tetrabutylammonium iodide (TBAI), *N*-iodosuccinimide (NIS), *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS) and iodine, I₂ showed the highest activity, giving a 95% yield (Table 1, entry 7). Indeed, no reaction occurred in the absence of a catalyst like indine or *N*-iodosuccinimide (NIS) (Table 1, entry 12). After filtrating all parameters above, the optimized reaction system was established and illustrated in Table 1 as entry 7.

With the optimized reaction conditions in hand, the scope and generality of this reaction were investigated. First, we examined the compatibility of the substrates by using a broad variety of substituted enamides to synthesize quinolines, the results are summarized in **Scheme 1**. Both electron-rich and electron-deficient substituted enamides could be smoothly transformed into the desired products. In general, electron-donating groups gave higher yields of the desired products probably due to higher stability of the radical intermediate. The substrates bearing electron-donating groups, such as 2-methoxy, 3-methoxy and 4-methoxy, underwent smooth reactions with *N*-phenylbenzaldimine and afforded the corresponding products (**3ae–3ag**) in 83%, 90% and 71% yields, respectively. Enamides with groups of 3-methyl and 4-methyl, gave the corresponding products (**3ab–3ac**) in 65% and 56% yields, respectively. However, when using 2-methyl enamide as reactant, only a trace amount of product was detected from TLC measurement (**3ad**). Substituted enamides with 4-phenyl and 2-naphthyl groups could also be efficiently transformed into the corresponding products (**3ah–3ai**) in 68% and 65% yields. Furthermore, the reaction with halogenated enamides such as 4-fluoro, 4-chloro and 3,4-dichloro enamides gave the

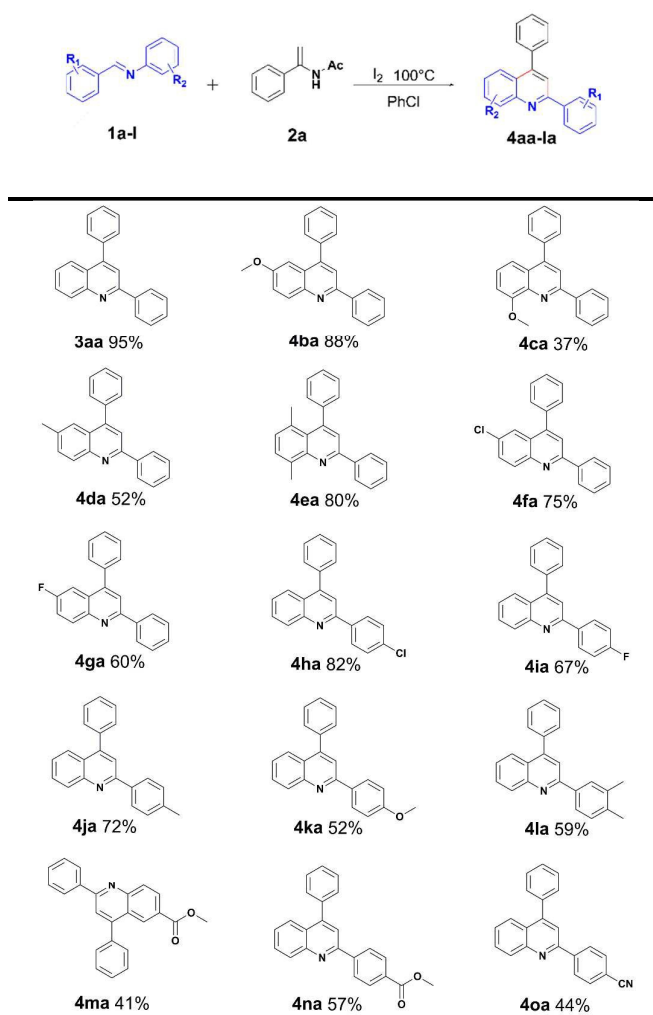
Scheme 1. Synthesis of 2,4-Diarylquinolines from *N*-phenylbenzaldimine and Substituted Enamides^a

^aReaction conditions: **1a** (0.15 mmol), **2a** (0.20 mmol), I₂ (20 mol %), PhCl (2 mL), 100 °C, 1 h.

corresponding products (**3aj–3al**) in 38%, 53% and 61% yields, respectively. Even with the more challenging 4-CF₃-substituted enamide, the reaction also gave the corresponding product in 31% yield.

To further explore the applicability of this method, we next examined the utility of this process to synthesize a range of quinolines with substituted imines. Various electron-donating and electron-withdrawing substituents on the imines were tolerated in this transformation. The results are illustrated in **Scheme 2**. The transformation showed good functional group tolerance and proved to be an efficient method for the preparation of substituted diarylquinolines. Imines with methyl, methoxyl, fluoro, and chloro groups on the aryl rings gave the desired diarylquinolines in moderate to good yields.

Scheme 2. Synthesis of 2,4-Diarylquinolines from Substituted Imines and *N*-(1-phenylethenyl)acetamide^a

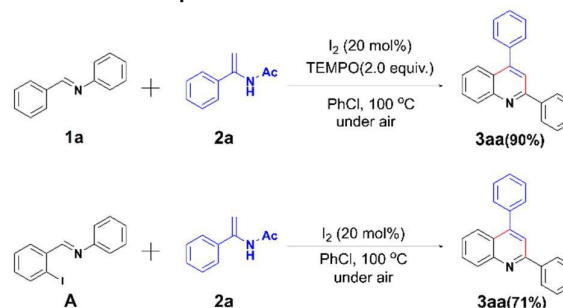


^a Reaction conditions: **1a-I** (0.15 mmol), **2a** (0.2 mmol), I_2 (20 mol %), PhCl (2 mL), 100 °C, 1 h.

As expected, the nature of the substituent on the aromatic rings did affect the yield of the product significantly (**4ba–4la**). Meanwhile, the position of substituents on the benzene ring had an obvious impact on the reaction yields. For example, 4-methoxyl-substituted imine gave the desired product (**4ba**) in 88% yield while the product synthesized from 2-methoxyl-substituted imine only yielded 37% (**4ca**). In particular, the imines bearing an electron-withdrawing group, such as F and Cl, generated the desired products yields in slightly difference with the electron-donating ones. Moreover, the substrates with methyl, dimethyl, ester and cyano groups proceeded well under optimized conditions and gave the corresponding products in moderate to good yields (**4ka–4oa**).

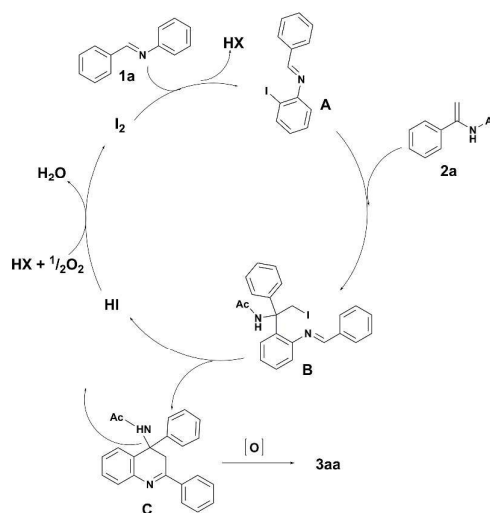
In order to obtain further insights into this reaction, several

Scheme 3. Control experiments



control experiments were investigated (**Scheme 3**). We first conducted the reaction of **1a** and **2a** in the presence of 2.0 equiv. of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under optimized conditions, 90% yield of **3aa** was obtained. Then, the substrate **2a** was employed to react with **A** under optimized conditions, the final product **3aa** was detected and isolated in 71% yield. Those above results reveal that the reaction may not undergo the radical pathway and the compound **A** should be the intermediate of the transformation.

On the basis of the experimental results and literature reports,^{13,18} a proposed reaction mechanism is outlined as shown in **Scheme 4**. The reaction is initiated by ortho iodination of **1a**, thus giving intermediate **A**. Subsequent insertion of an enamide into the C-I bond leads to intermediate **B** and followed by abstraction of the hydrogen atom of *N*-benzylideneaniline. Subsequent reductive elimination generates **C** and releases I^{-1} , which could be oxidized by O_2 to recover the I^0 catalyst. After further oxidation and aromatization, the desired quinoline skeleton was generated.



Scheme 4. Proposed mechanism.

Conclusions

In conclusion, we have developed a convenient and efficient metal-free procedure for the conversion of enamides and imines to quinolines. Various substituents of enamides and imines tolerated well in this approach and generated the desired products in moderate to good yields.

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