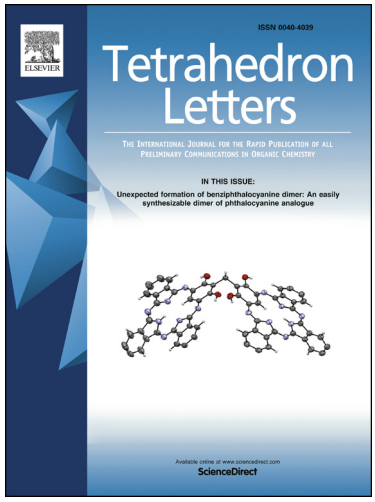

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Graphical Abstract

An Improved Pfitzinger Reaction: Eco-efficient Synthesis of Quinaldine-4-carboxylates by TMSCl-Mediated

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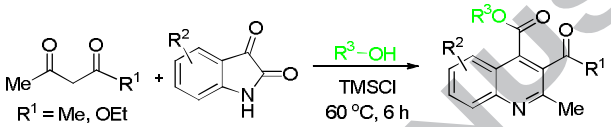

- Improved Pfitzinger reaction
- Large substrate scope
- Mild reaction conditions
- Gram scale synthesis

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ABSTRACT

We report herein an improved Pfitzinger reaction for the synthesis of highly functionalized quinaldines from 1,3-dicarbonyl compounds, isatins and alcohols mediated by TMSCl. This synthesis involves cyclization and esterification in one-step cascade process for the formation of a carboxylate (CO_2R) at the 4-position of quinaldine ring. Moreover, this procedure shows highly efficient, good functional group tolerance, operational simplicity, environment-friendly and feasibility of scale up.

Introduction

Quinaldine is one of the most important methyl derivative of quinoline, it exists in many natural products, pharmaceuticals, physiologically active molecules, and material chemistry (Fig. 1).[1] Thus, it is highly desirable to develop efficient and selective methods for the synthesis of such highly valuable molecules. Generally, quinaldine derivatives have been prepared by several conventional methods (Scheme 1A), including Friedlander reaction,[2] Doebner–Miller reaction,[3] Niementowski reaction,[4] and Combes reaction,[5] and others.[6] However, these typical reactions were often performed under harsh reaction conditions with high temperatures, strong acidic medium, toxic reagents and transitionmetal mediated. To the best of our knowledge, only a handful reports are available for the synthesis of quinaldines *via* Pfitzinger reaction.[7] Therefore, the development of new eco-friendly synthetic methods for the construction of quinaldine

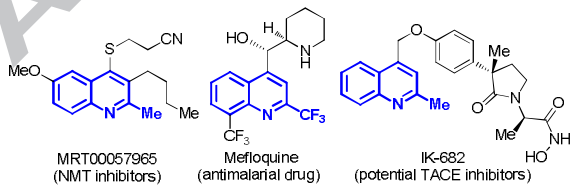
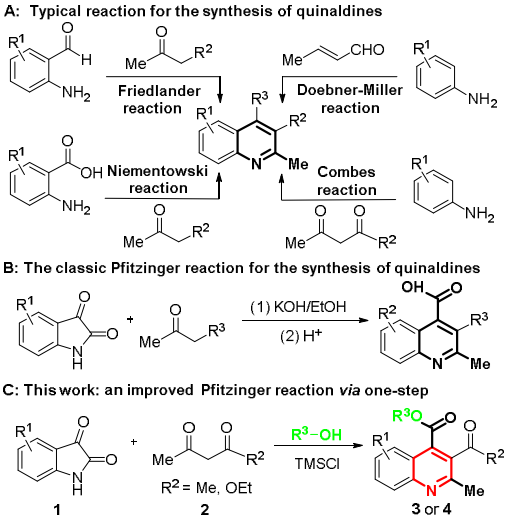


Fig. 1. Biologically active compounds containing a quinaldine ring.



Scheme 1. Synthesis of quinolines.

derivatives through Pfitzinger reaction are still of great interest.

Since its discovery in 1886,[8] the Pfitzinger reaction,[8b] involving the condensation of isatin and carbonyl compound, has arguably become one of the most utilized tools for the synthesis of biologically active quinoline-4-carboxylic acids.[7c,9.] However,

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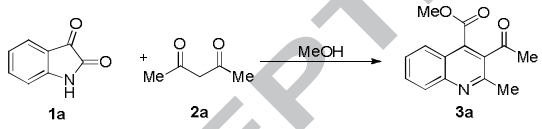
the classic chemical reaction is commonly performed in a two-step process based on strong base and subsequently acidified with strong acid, which can only generate quinoline-4-carboxylic acids and is unable to obtain the quinoline-4-carboxylates (Scheme 1B). Therfore, selective synthesis of the quinoline-4-carboxylate motifs under mild reaction condition (strong base- and acid-free) has remained a daunting challenge, especially through one-step method.

Based on our previous work on isatin-based heterocycle synthesis,[10] herein we wish to report a cyclization and esterification in one-step cascade protocol for the synthesis of functionalized quinaldines **3/4** *via* an improved Pfitzinger reaction (Scheme 1C). The three-component cascade reaction between readily available isatins **1** and 1,3-dicarbonyl compounds (acetylacetone or ethyl acetoacetate) **2** in the presence of alcohols mediated by trimethylchlorosilane (TMSCl), generates a carboxylate (CO_2R) at the 4-position of quinaldine ring.

Result and discussion

Initially, isatin (**1a**) and acetylacetone (**2a**) were selected as model substrates for screening the reaction conditions. (Table 1). Firstly, various catalysts were investigated in MeOH at 60 °C for 6 h. Et_3N, K_2CO_3, $CrCl_2$, $Bi(CF_3SO_3)_3$, AgOAc and AcOH afforded the desired product **3a** unsuccessfully (entries 1–6). To our delight, formation of **3a** was observed in reactions catalyzed by *p*-toluenesulfonic acid (*p*-TSA), HCl and *t*-butyldimethylchlorosilane (TBSCl) (47%, 43% and 62%, entries 7–9), and TMSCl was found more efficient (66%, entry 10). Next, the role of reaction temperature was also screened in the presence of TMSCl in MeOH (entries 9–12). It was found that the reaction at 60 °C still provided the best result (66%, entry 9 *vs* entries 11–13). Further investigation of the catalyst amounts showed that the reaction with 1.0 equiv TMSCl did not reach the complete conversion (entries 14), but higher catalyst loading (3.0 equiv.) had little impact on the results (entries 15). Thus, the reaction with 2.0 equiv. of TMSCl in MeOH at 60 °C was found the optimal condition.

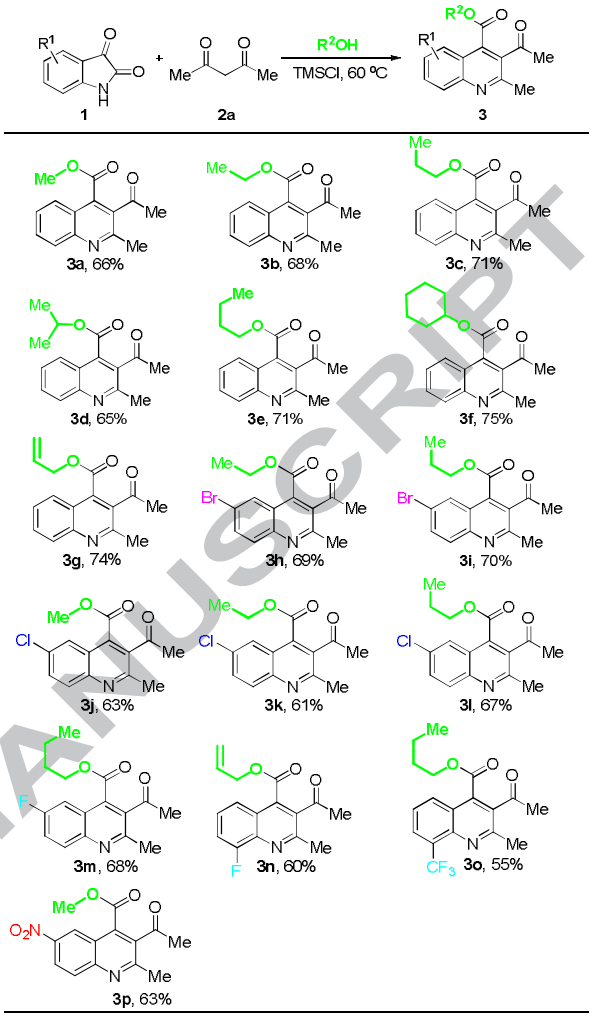
Table 1.
Optimization of reaction conditions.[a]



Entry	Catalyst (equiv.)	*T* (°C)	Time (h)	Yield (%)[b]
1	Et_3N (2.0)	60	6	n.d.[c]
2	K_2CO_3 (1.0)	60	6	n.d.[c]
3	$CrCl_2$ (0.5)	60	6	n.d.[c]
4	$Bi(CF_3SO_3)_3$ (0.2)	60	6	n.d.[c]
5	AgOAc (1.0)	60	6	n.r.[d]
6	AcOH (2.0)	60	6	n.d.[c]
7	*p*-TSA (1.0)	60	6	47
8	HCl [e]	60	6	43
9	TBSCl (2.0)	60	6	62
10	**TMSCl (2.0)**	**60**	**6**	**66**
11	TMSCl (2.0)	r.t.	8	29
12	TMSCl (2.0)	40	8	53
13	TMSCl (2.0)	80	6	63
14	TMSCl (1.0)	60	6	46
15	TMSCl (3.0)	60	6	67

[a] Reagents and conditions: isatin **1a** (0.5 mmol) and acetylacetone **2a** (0.7 mmol) in MeOH (3.0 mL); [b] Isolated yield based on isatin **1a**; [c] n.d. = no detected; [d] n.r. = no reaction; [e] 0.1 ml (1.0 M hydrochloric acid solution).

Table 2.
Substrate scope of the quinaldines **3**.[a,b]



[a] Reagents and conditions: isatins **1**, (0.5 mmol) acetylacetone **2a** (0.7 mmol) and TMSCl (1.0 mmol) in alcohols (3.0 mL), stirred at 60 °C for 6.0 h; [b] Isolated yield based on isatin **1**.

With the optimized reaction conditions in hand, the scope of isatins were examined when alcohols act as nucleophiles. The results summarized in Table 2. For most of the tested substrates, showed little impact on the results, and quinaldines were isolated in medium to excellent yields (55–75%). Generally, strong nucleophiles gave better results than weak nucleophiles (**3e**–**3f** *vs*. **3a**–**3d**, **3i** *vs*. **3h**, and **3l** *vs*. **3j**–**3k**), while weak nucleophiles **3g** gave better results than strong nucleophiles **3a**–**3e**. On the other hand, electron-neutral (5-H) and halogenated (5-Br, 5-Cl, 5-F and 7-F) isatins were smoothly converted to the corresponding products. When the substituent of isatins were changed to strong electron-withdrawing groups (5-NO_2 and 7-CF_3), the moderate yields were also obtained in certain cases (**3n**–**3p**, 55–62%).

As shown in Table 3, the reaction is not restricted to acetylacetone **2a**, and also can work with related substrates, such as ethyl acetoacetate **2b**. The expected quinaldines were obtained in good to excellent yields (**4a**–**4l**, 60–88%). Apparently, the reactivity of ethyl acetoacetate **2b** is higher than acetylacetone **2a**, and it gave better results. Moreover, the structure of one representative product **4j** was further conclusively confirmed by X-ray analysis (Fig. 2, CCDC 1506108).[11]

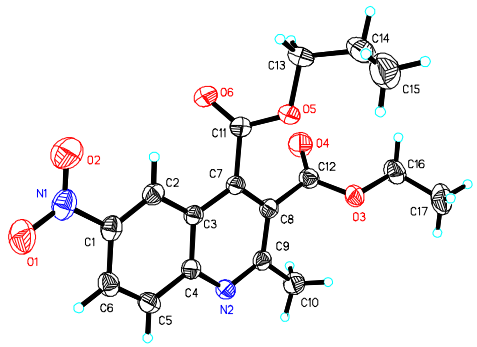
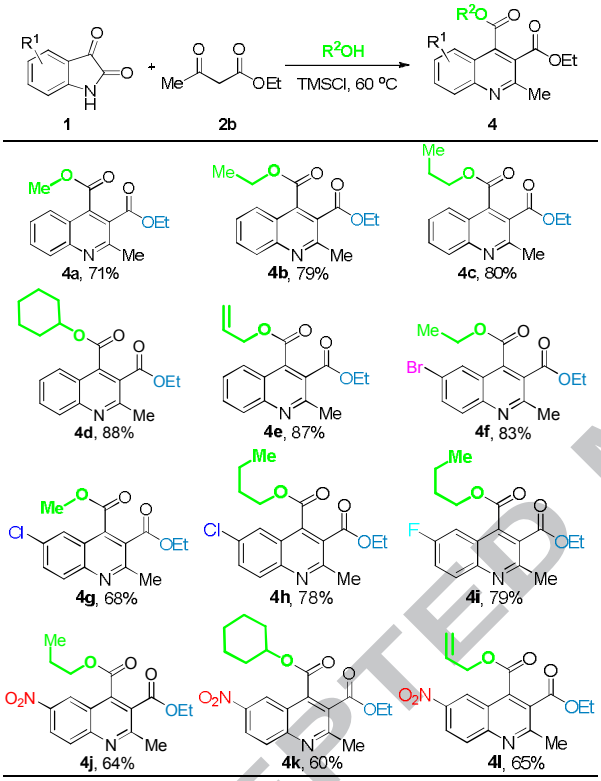
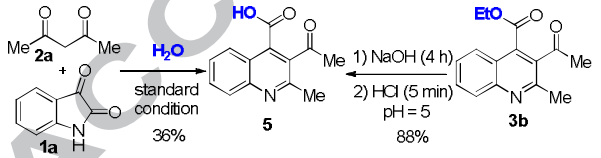


Fig. 2 X-ray structure of compound **4j**.

Table 3.
Substrate scope of the quinaldines **4**.[a,b]



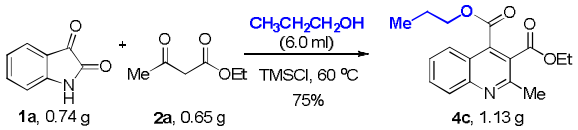
[a] Reagents and conditions: isatins **1** (0.5 mmol), ethyl acetoacetate **2b** (0.7 mmol) and TMSCl (1.0 mmol) in alcohols (3.0 mL), stirred at 60 °C for 6.0 h; [b] Isolated yield based on isatin **1**.



Scheme 2 Synthesis of 4-carboxyl- and α-methylenation of 3-carbonyl of quinaldine derivatives.

To broaden the potential application of this protocol, several derivatizations of products were conducted. The reaction between acetylacetone **2a** and isatin **1a** in the presence of water under standard condition, in which quinaldine-4-carboxylic acid **5** was obtained in 36% yield. Quinaldine-4-carboxylic acid **5** was also afforded in 88% yield by the esterolysis of quinaldine-4-carbethoxy **3b** (Scheme 2).[12]

To display the scalability and the practicality of the process, we also investigated a gram-scale reaction of isatin **1a** and



Scheme 3. Gram Scale Synthesis.

acetylacetone **2a** in propyl alcohol to provide the desired quinaldine **4c** (1.13 g, 75%) as show in Scheme 3.

In terms of the reaction mechanism, we checked the pH value of the quenched reaction system, which greatly reduced after. In fact, HCl is less efficient than TMSCl (entry 8 *vs.* entry 10, Table 1). Next, the desired product **3a** failed to obtain in 1.0 ml HCl and **3a** increased slightly catalyzed by 2.0 equivalent *p*-TSA (54%). Based on these observations, the reaction has likely gone through a proton acid mediated mechanism, but excess water inhibited the reaction. To confirm that TMSCl played an important role in the reaction, preprocessed TMSCl (dehydration and deacidification) also was carried out in this protocol, which found more efficient than unpreprocessed TMSCl (72% *vs.* 66% (entry 10, Table 1)). Thus, it is also likely that the reaction has experienced a TMSCl mediated mechanism. However, further evidences are necessary to disclose the details.

Conclusion

In conclusion, we developed a first improved Pfitzinger reaction for the synthesis of highly functionalized quinaldine-4-carboxylates, from isatins with 1,3-dicarbonyl compounds in alcohols mediated by TMSCl. Moreover, this green approach provided a rapidly strategy to construct molecularly diverse quinaldine-4-carboxylate derivatives library with good yields under mild conditions. The reaction can be scaled up to produce grams of quinaldine-4-carboxylates. Attempts to further understand to the reaction mechanism and applications are underway in our laboratory.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/xx.xxx/j.tetlet.xxxx.xx.xxx.

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11 CCDC 1506108 contain the supplementary crystallographic data for compound **4j**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

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Highlights:

- The first an improved Pfitzinger reaction for synthesis of quinaldines.
- It involves cyclization and esterification in one-step cascade process.
- A novel library of quinaldines in moderate to good yields under mild conditions.
- This method shows environment-friendly, easy to operate, feasibility of scale up.

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† L. Lu. and P. Zhou. contributed equally.