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Construction of 2-pyridones *via* oxidative cyclization of enamides: access to Pechmann dye derivatives†

Sivanna Chithanna[a] and Ding-Yah Yang *[a,b]

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An efficient protocol for the construction of structurally diverse 2-pyridone derivatives from imines and α,β-unsaturated acid chlorides in a single operation is reported. The target compounds, including coumarin-8-oxoprotoberbine analogues and lamellarin G isomers, were prepared *via* thermal cyclization of the *in situ* generated enamides followed by thermal dehydrogenation. The cyclization of enamides was achieved by the introduction of an electron-withdrawing group on the α-carbon of acid chlorides. This methodology allows quick access to polycyclic Pechmann dyes *via* rare double oxidative cyclizations of dienamides under mild conditions.

Introduction

2-Pyridones represent highly valuable and widely used heterocycles in the pharmaceutical industry. They are the core scaffolds present in milrinone,[1] 8-oxopseudopalmatine,[2] sempervilam,[3] camptothecin[4] and related alkaloidal natural products (Fig. 1).[5] The 2-pyridone derivatives exhibit a broad spectrum of biological activities, including antifertility,[6] antihistamine,[7] antitumor[8] and other biological activities.[9] In addition, 2-pyridones also serve as indispensable building blocks for the synthesis of some bioactive natural/unnatural products,[10] agrochemicals,[5b] functional materials[11] and fluorescence imaging agents.[12]

Owing to 2-pyridone's important biological properties, we have witnessed tremendous growth in the literature over the past few decades on the synthesis of 2-pyridone alkaloids and their derivatives.[13] Most synthetic strategies involved the use of transition-metal-catalyzed C–H activation,[14] N-heterocyclic carbenes (NHCs)[15] or multistep reactions to construct the 2-pyridone moiety.[16] For instance, Tanaka and coworkers have reported substituted 2-pyridones through gold-catalyzed cycloisomerization of *N*-alkenyl alkynylamides (Scheme 1, eqn (i)).[14h] Raji Reddy has reported the Rh(III)-catalyzed cascade annulations of *N*-(pivaloyloxy)benzamides with 1,5-enynes to access substituted and polycyclic 2-pyridone derivatives (Scheme 1, eqn (ii)).[14c] Recently, Zhong and coworkers described the chemo and enantioselective synthesis of 2-pyridones by an NHC-catalyzed [3 + 3] cyclization from γ-chloroenals and ketimines (Scheme 1, eqn (iii)).[15b] However, even with those strategies available, there is still a need to develop a one-pot, convenient and metal-free method to synthesize polycyclic-2-pyridone derivatives. On the other hand, enamides are useful organic substrates which can undergo a range of reactions due to delocalization of lone pair electrons on the nitrogen atom, thereby revitalizing the enaminic reactivity of the enamides. As a result, they have been used as versatile synthons in organic synthesis, including asymmetric hydrogenation, asymmetric catalytic reactions, and asymmetric and natural product synthesis.[17] Photocyclization of enamides is also well-studied for the synthesis of pyridine-containing natural products and other heterocyclic compounds, particularly alkaloids.[18] Although the nucleophilic addition of enamides to reactive electrophiles offers an attractive opportunity for the rapid construction of complex molecular skeletons, to our surprise, the chemistry of thermal annulation of enamides to the synthesis of 2-pyridones has not been thoroughly explored. While Ninomiya and co-workers have reported the first thermal cyclization of enamides in 1980 *via* introducing strong electron-withdrawing groups ($-NO_2 \times 2$) on aroyl chlorides for the synthesis of oxoberbines (Scheme 1, eqn (iv)),[19] limited information has been retrieved from the literature since then. Therefore, more in-depth examination on heat-promoted cyclization of enamides to expand the reaction scope remains desired. In the present study, we investigated the

[a]*Department of Chemistry, Tunghai University, No. 1727, Sec. 4, Taiwan Boulevard, Xitun District, Taichung 407224, Taiwan. E-mail: yang@thu.edu.tw*
[b]*Graduate Program for Biomedical and Materials Science, Tunghai University, No. 1727, Sec. 4, Taiwan Boulevard, Xitun District, Taichung 407224, Taiwan*

†Electronic supplementary information (ESI) available[1]H and [13]C spectra of **6a–m**, **8a–d**, **10a–d**, **11**, **12**, and **19a–b** and X-ray crystallographic data for **6a**, **6b**, **6j**, **8b** and **11** (PDF). CCDC 1900621, 2012710, 2036791, 2012685 and 2012684. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob02376k

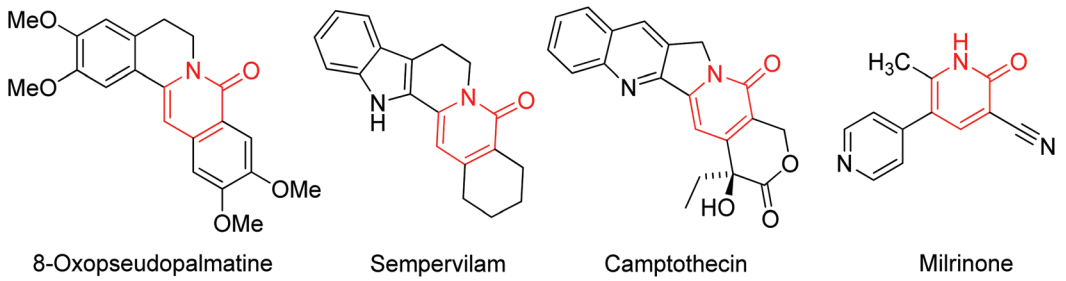
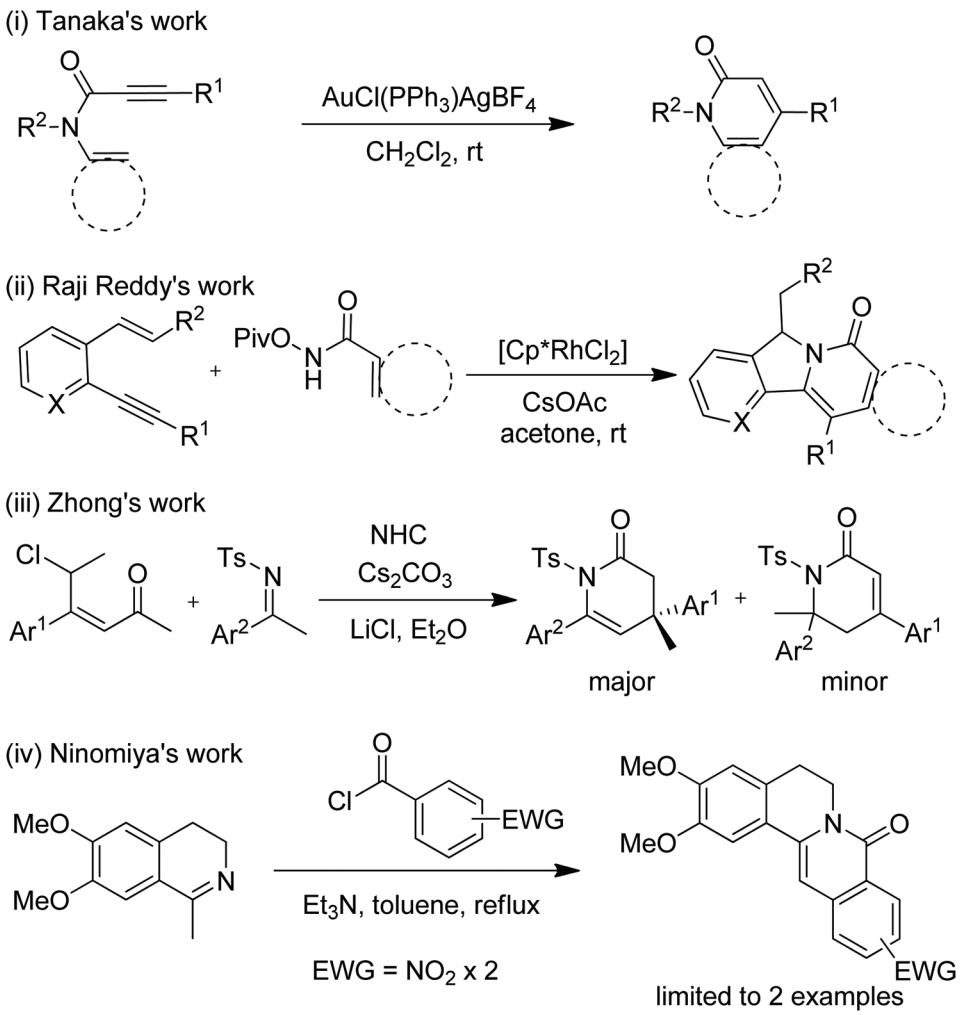


Fig. 1 Biologically important natural/unnatural products bearing a 2-pyridone moiety.

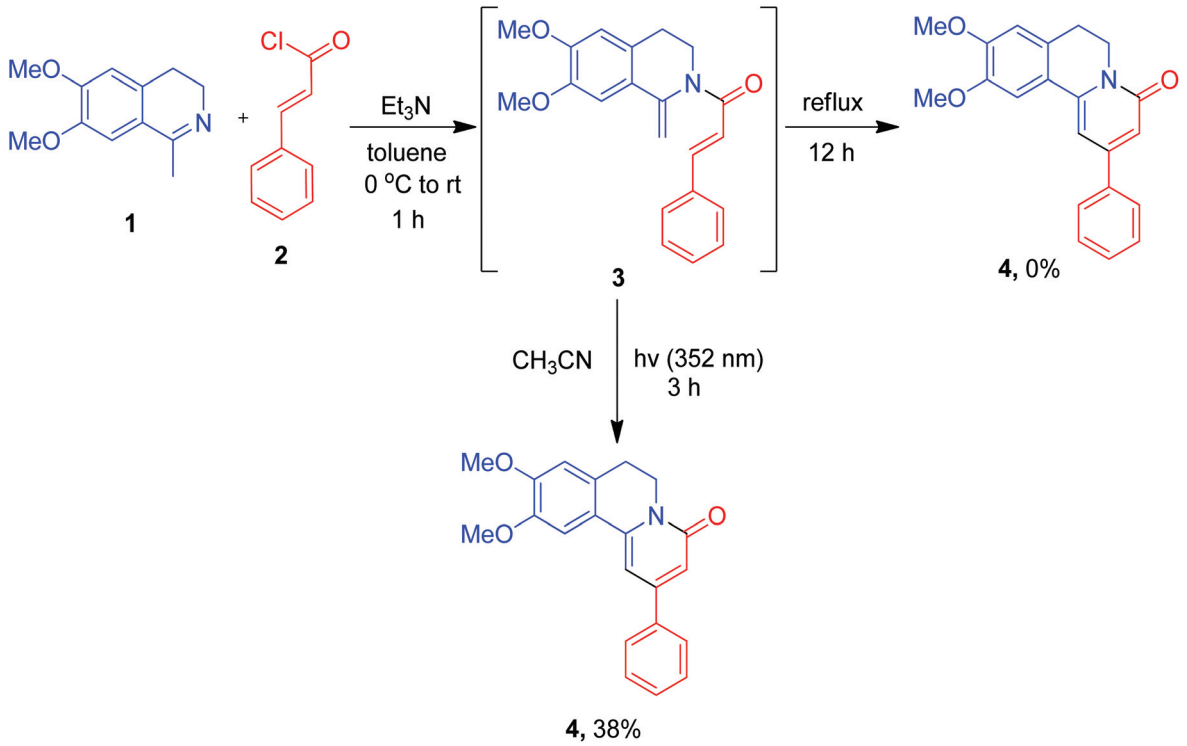


Scheme 1 Previous synthesis of 2-pyridone derivatives.

chemistry of thermal cyclization of enamides with the electronic effect of a substituent on α-carbon of α,β-unsaturated acid chlorides. The scope and mechanism of thermally promoted annulation were also explored. Furthermore, the potential application of this methodology to the one-pot synthesis of polycyclic Pechmann dyes was examined.

Results and discussion

To probe the feasibility of the thermal cyclization of enamides, we initially chose enamide **3** as the model compound. The enamide **3** was readily prepared by *N*-acylation of imine **1** with cinnamoyl chloride **2** in the presence of Et_3N as a

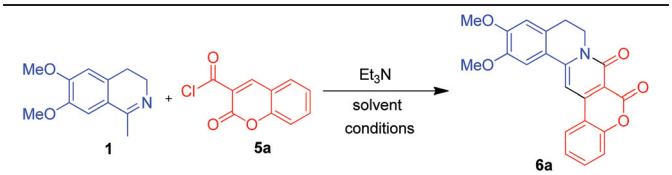


Scheme 2 Thermal and photocyclization of enamide **3**.

base in toluene. As expected, the enamide **3** failed to undergo cyclization and subsequent thermal dehydrogenation to obtain **4** when refluxed in toluene for 1–12 h (Scheme 2). However, the enamide **3** could be cyclized *via* photocyclization in acetonitrile to afford compound **4** in 38% yield.

The fact that enamide **3** failed to undergo cyclization under reflux conditions could be attributed to the presence of an electron-withdrawing carbonyl functionality on the nitrogen atom, resulting in low nucleophilic reactivity of enaminic carbon (a weaker Michael donor). We envisioned that the thermal cyclization of enamides might be facilitated by increasing the electrophilicity of the α,β-unsaturated carbonyl moiety (a stronger Michael acceptor) of enamides, which could be realized by introducing an electron-withdrawing group on the α-position of the acid chlorides. To test this hypothesis, we replaced the substrate cinnamoyl chloride (**2**) with coumarin-3-carboxylic acid chloride (**5a**) which bears an α,β-unsaturated carbonyl moiety and a lactone ring as the electron-withdrawing functionality on α-carbon. Interestingly, once compound **5a** was added to the reaction mixture of dihydroisoquinoline **1** and Et_3N in toluene at 0 °C, the formation of coumarin-derived 8-oxoprotoberbine **6a** (see Fig. 3 for the X-ray crystal structure) was observed immediately without the requirement of UV irradiation. To fully convert the unreacted enamide to **6a**, the reaction mixture was slowly brought to room temperature and then refluxed for 2 h. To our delight, compound **6a** was isolated in 72% yield (Table 1, entry 2). The prolonged reaction time and the excess of Et_3N were found to have little effect on the product yield (Table 1, entries 3, 4 and 5). Investigation on solvent effects indicates that xylene and dioxane gave lower

Table 1 Optimization conditions for thermal cyclization of enamides[a]



Entry	Base (mmol)	Solvent	Conditions	Yield of **6a**[b] (%)
1	1.5	Toluene	0 °C to rt for 2 h	53
2	**1.5**	**Toluene**	**0 °C to rt then reflux for 2 h**	**72**
3	1.5	Toluene	0 °C to rt then reflux for 6 h	73
4	2	Toluene	0 °C to rt then reflux for 6 h	73
5	3	Toluene	0 °C to rt then reflux for 6 h	73
6	1.5	Xylene	0 °C to rt then 110 °C for 6 h	58
7	1.5	Dioxane	0 °C to rt then 110 °C for 6 h	51
8	1.5	DMF	0 °C to rt then reflux for 6 h	Trace

[a] Reaction conditions: Imine **1** (0.5 mmol), triethylamine (1.5 mmol), and acid chloride **5a** (0.55 mmol) in toluene (3 mL) at 0 °C to rt and then reflux for 2 h. [b] Isolated yield.

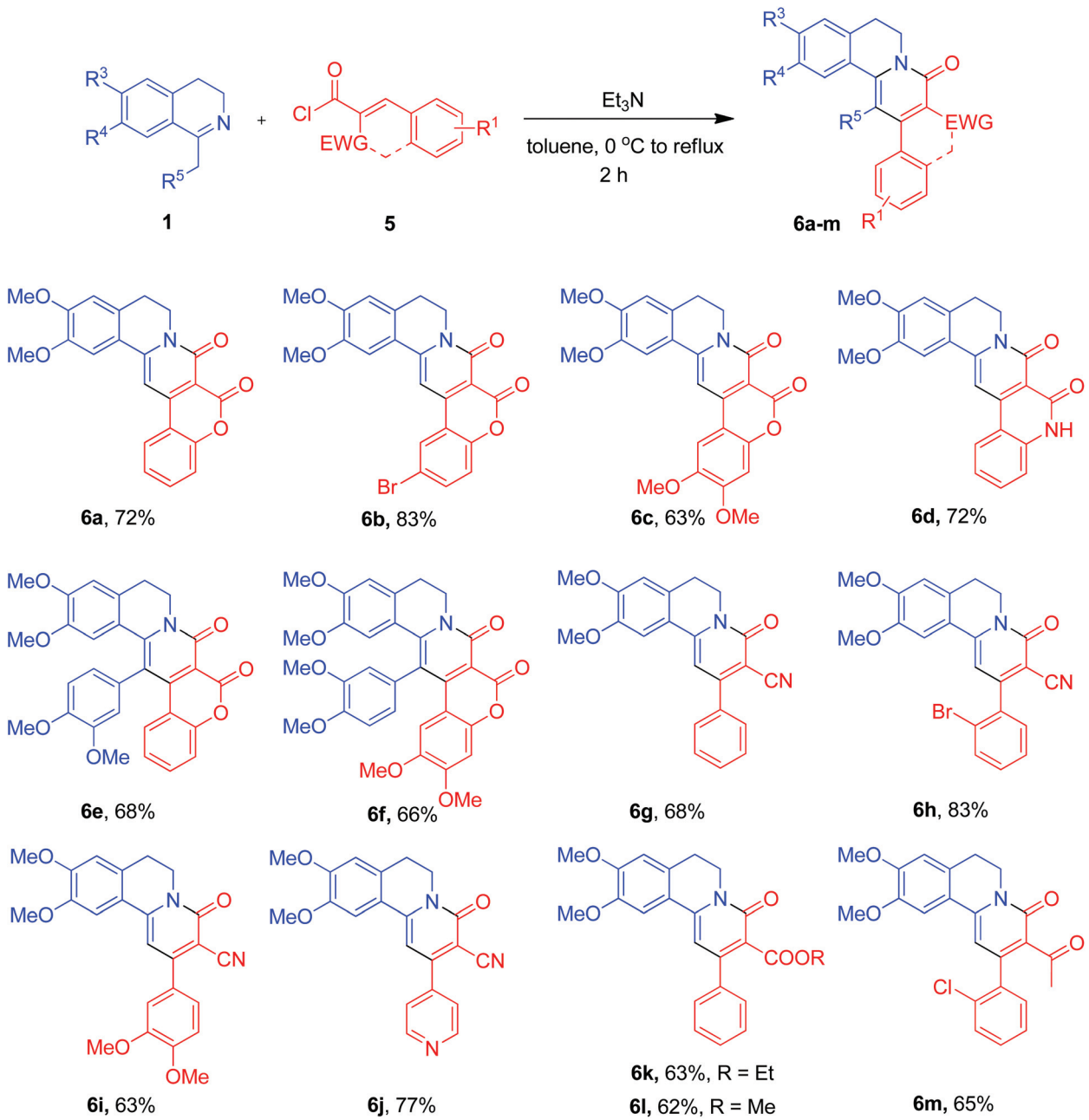


Fig. 2 Structures and yields of the prepared fused-2-pyridones **6a–m**.

yields than toluene (Table 1, entries 6 and 7), and DMF yielded a trace of product even with a prolonged reaction time (Table 1, entry 8). Thus, the reaction conditions shown in entry 2 in Table 1 were subsequently employed for the preparation of other polycyclic-2-pyridones with different substituents.

With the optimized reaction parameters in hand, we then focused our attention on the substrate scope of this reaction by the reaction of 1-methylisoquinolines with diverse acid chlorides under thermal conditions. As listed in Fig. 2, various α,β-unsaturated acid chlorides with an electron-withdrawing group substituted at the α-position could serve as substrates to prepare coumarin-8-oxoprotoberbine analogues **6a–d**, lamellarin G isomers **6e–f** and isoquinoline-fused 2-pyridone derivatives **6g–m**. The substrates with an electron-withdrawing substituent such as bromo on the benzene moiety of the acid chlorides generally gave better yields of the products (**6h** and **6j**) than their unsubstituted counterparts (**6g** and **6k**). The opposite was true for the electron-donating group such as OMe on the benzene moiety (**6f** and **6i**). Note that the potential bio-

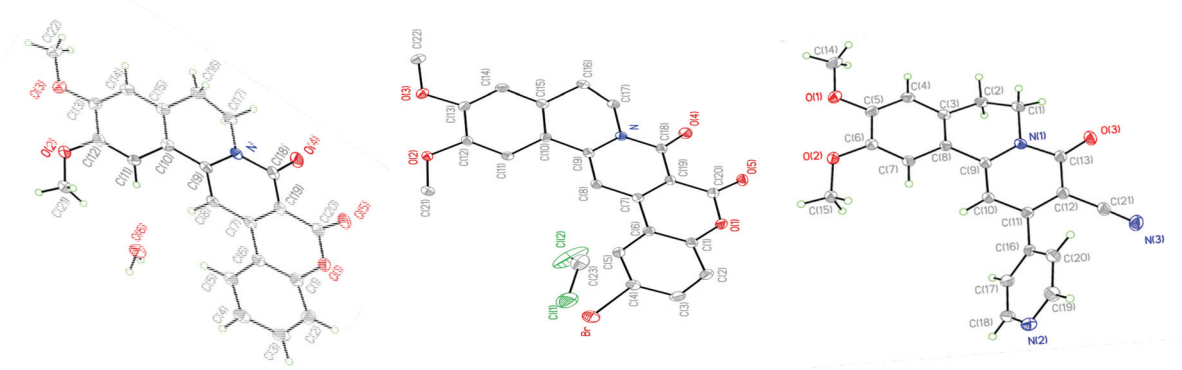


Fig. 3 X-ray crystal structures of **6a** (left, CCDC-1900621), **6b** (middle, CCDC 2012710†) and **6j** (right, CCDC 2036791†) with atomic displacement shown at 50% probability.

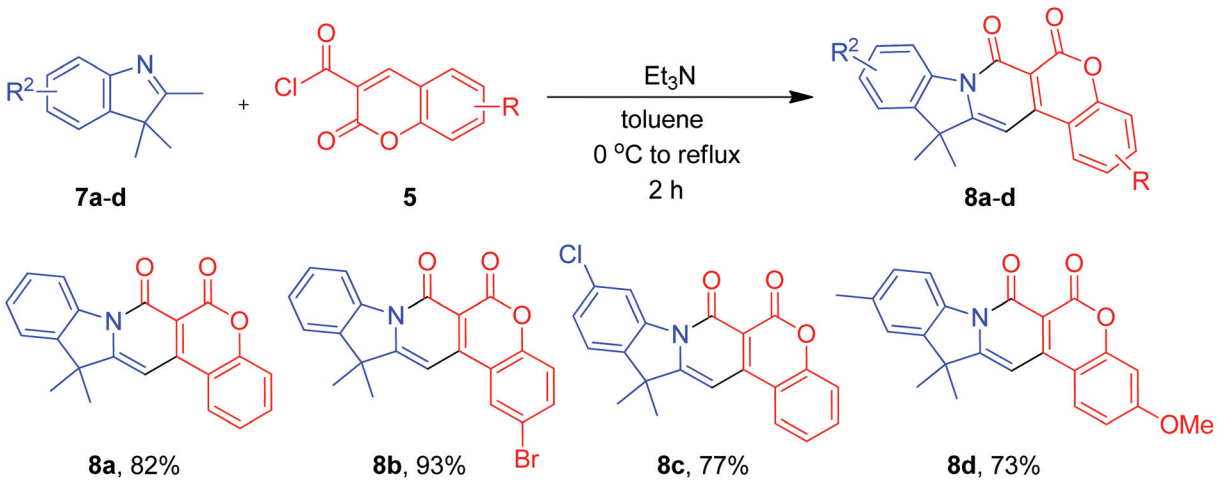


Fig. 4 Structures and yields of the prepared pentacycles **8a–d**.

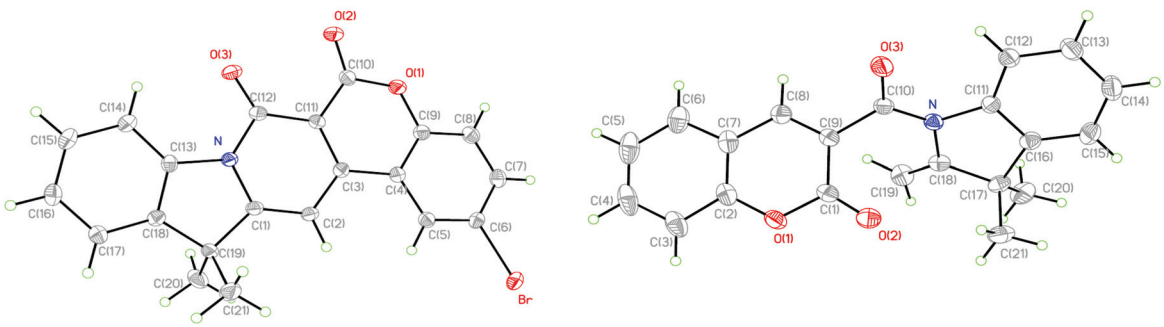


Fig. 5 X-ray crystal structures of **8b** (left, CCDC 2012685†) and **11** (right, CCDC 2012684†) with atomic displacement shown at 50% probability.

logically active isomeric lamellarin G **6e–f** could be efficiently prepared by direct coupling of 3,4-dihydropapaverine with coumarin-3-carboxylic acid chloride in one step with good yields. Furthermore, the molecular structures of compounds **6b** and **6j** were confirmed by X-ray crystallography analysis (Fig. 3).

The subsequent substrate scope screening for imines indicates that 1-methylisoquinolines could be replaced by 2-methylindoles as shown in Fig. 4. *N*-Acylation of different 2-methylindoles **7a–d** with functionalized coumarin-3-carboxylic acid chlorides **5** under the optimized reaction conditions gave the corresponding pentacycles **8a–d** in excellent yields. The molecular structure of **8b** was further confirmed by X-ray crystallography analysis (Fig. 5).

Further screening of the imine substrates suggests that enamino ester **9** could also react with functionalized α,β-unsaturated acid chlorides **5g–i** and **5n** to generate the tetra-substituted 2-pyridones **10a–d** under the optimized reaction conditions in moderate yields as shown in Fig. 6.

To gain more insights into the mechanistic details of this thermal cyclization of enamide reaction, a series of control experiments were conducted as outlined in Scheme 3. First, the reaction of 2,3,3-trimethylindolenine (**7a**) with coumarin-3-carboxylic acid chloride (**5a**) in the presence of trimethylamine as a base in toluene at 0 °C for 1 h provided the enamide **11** in 32% yield and the annulated product **8a** in 48% yield. This result indicates that the enamide was indeed the initial intermediate generated from *N*-acylation of imines with acid chlorides (Scheme 3, eqn (1)). The molecular structure of enamide **11** was further confirmed by single crystal X-ray crystallography analysis (Fig. 5). Second, upon refluxing of enamide **11** in toluene for 1 h, the pentacycle **8a** was obtained, quantitatively. This observation confirms that enamide **11** could undergo intramolecular cyclization to make the C–C bond and subsequent thermal dehydrogenation to form the pentacycle **8a** under thermal conditions (Scheme 3, eqn (2)). Third, the reaction of 1-methylisoquinoline (**1**) with α,β-unsaturated acid chloride **5k** in the presence of trimethylamine in toluene at 60 °C for 1 h provided the intermediate **12** in 38% yield. This proves that the thermal cyclization of enamides would undergo a [1,5] hydrogen shift to give the intermediate **12** rather than **13** (Scheme 3, eqn (3)). Fourth, upon refluxing of intermediate **12** in toluene for 1 h, the 2-pyridone **6k** was obtained in 95% yield, implying that intermediate **12** could undergo dehydrogenation to form dihydroquinoline fused 2-pyridone **6k** under thermal conditions (Scheme 3, eqn (4)).

On the basis of the aforementioned information, a plausible mechanism for the formation of **6a** from the thermal cyclization of enamide is depicted in Scheme 4. It presumably starts with the *N*-acylation of imine **1** with acid chloride **5a** to generate reactive enamide intermediate **14**. The *in situ* generated enamide **14** then undergoes intramolecular cyclization to give compound **15**, which then rearranges to the intermediate **16**, not intermediate **17**, *via* a [1,5] hydrogen shift. The final thermal dehydrogenation of **16** affords the target coumarin-8-oxoprotoberbine **6a**.

This thermally promoted cyclization of enamide methodology was further applied to the synthesis of polycyclic Pechmann dyes by replacing α,β-unsaturated acid chloride with fumaroyl chloride (Scheme 5). Fumaroyl dichloride was readily prepared from the corresponding fumaric acid. The Et_3N-mediated *N*-acylation of 3,4-dihydroisoquinolines (**1**, 2.0 eq.) with fumaroyl chloride (**18**, 1.0 eq.) in toluene at 0 °C to room temperature for 2 h provided the blue polycyclic Pechmann dyes **19a–b** in 77 and 63% yield, respectively. Although no electron-withdrawing group was substituted at the α-position of fumaroyl chloride, the Pechmann dyes **19a–b** were efficiently formed under mild conditions

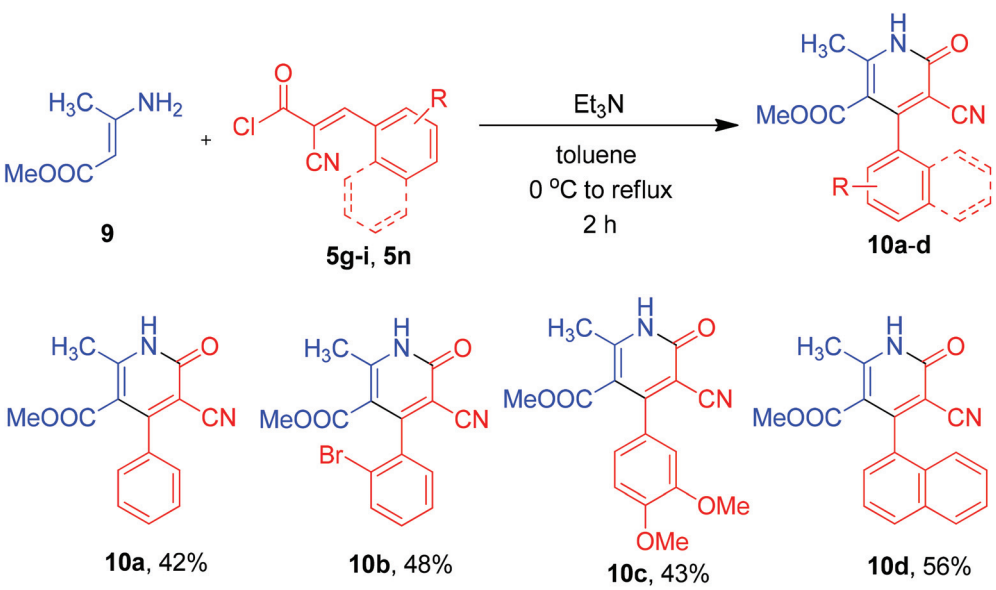
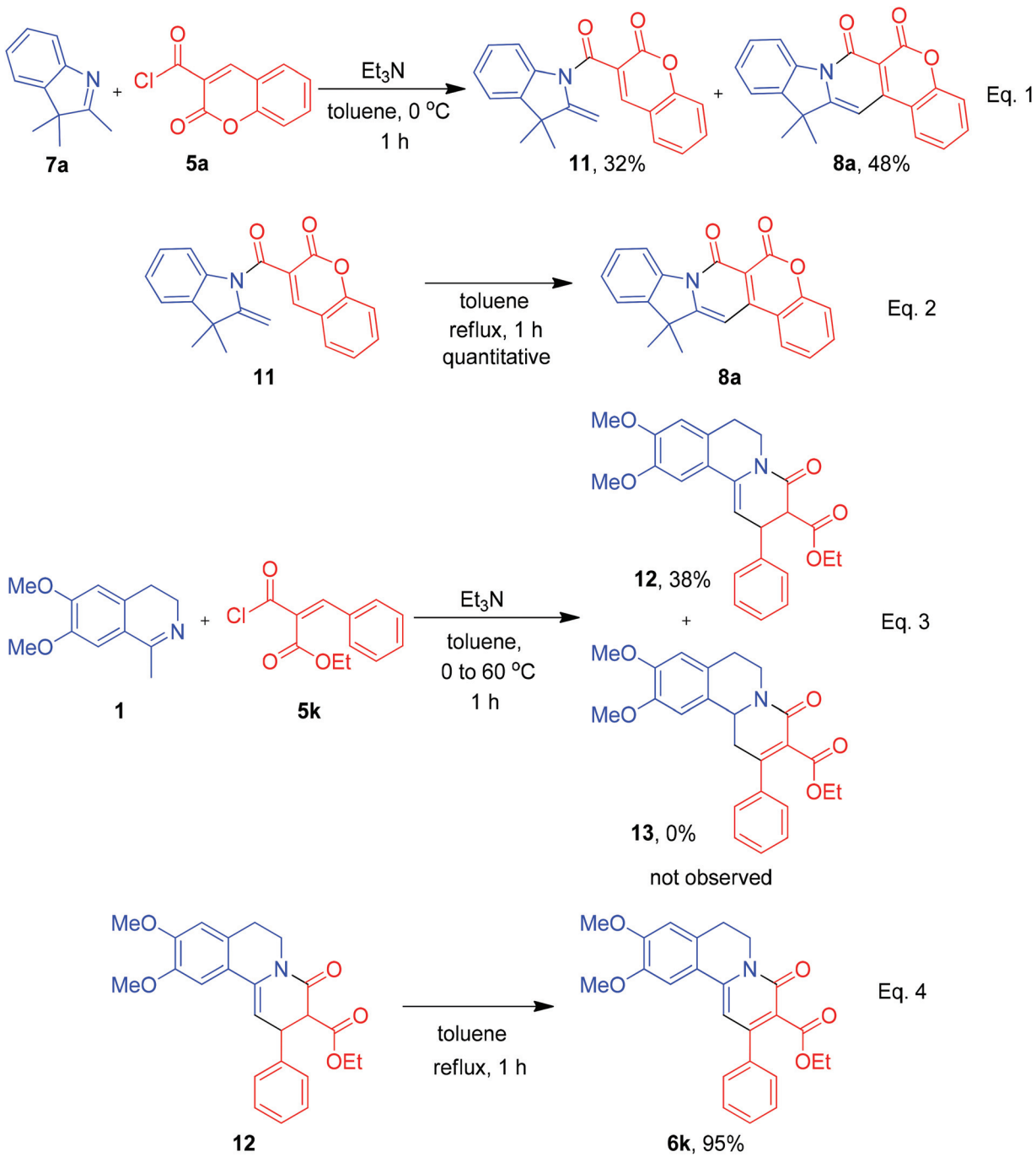


Fig. 6 Structures and yields of the prepared tetra-substituted 2-pyridones **10a–d**.

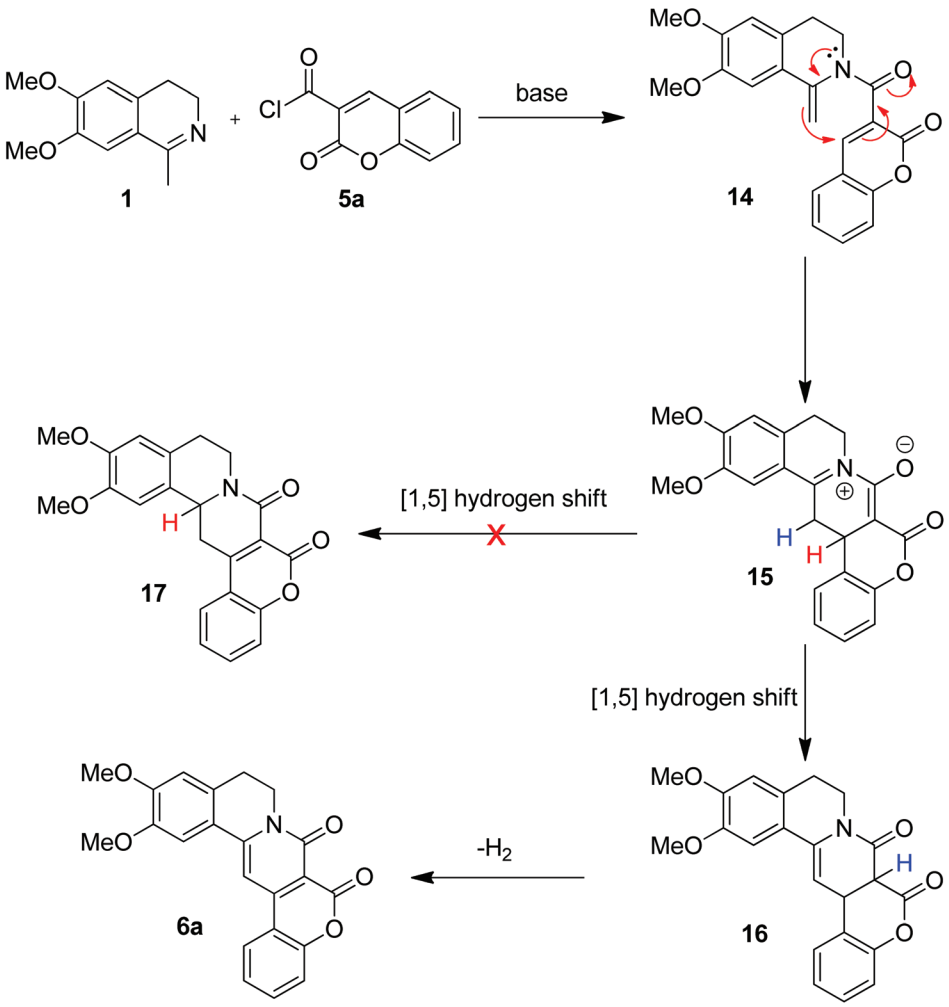


Scheme 3 Control experiments.

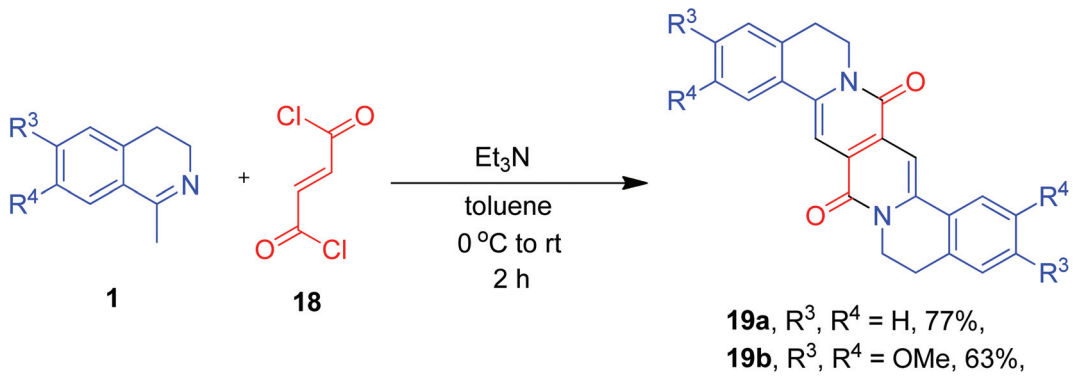
without the need for UV irradiation presumably due to its highly conjugated nature. Furthermore, this simple protocol could be performed on a gram scale. For instance, the preparation of compound **19a** was carried out on a 1 g scale to give the Pechmann dye in good yield, indicating the practical utility of this procedure. Since most of the reported Pechmann dye derivatives required multistep synthesis to be prepared,[20] this double oxidative cyclization of dienamide strategy provides quick access to Pechmann dye derivatives.

Conclusions

In summary, we have developed an efficient protocol for the construction of structurally diverse polycyclic-2-pyridone



Scheme 4 Proposed mechanism for the formation of **6a**.



Scheme 5 One-pot synthesis of Pechmann dye derivatives **19a–b**.

scaffolds *via* thermally promoted oxidative cyclization of the *in situ* generated enamides. The cyclization of enamides was facilitated by the presence of an electron-withdrawing group on the α-position of acid chlorides. A total of twenty-one examples (**6a–m**, **8a–d** and **10a–d**) were given to illustrate the scope of this cyclization, including the preparation of biologically important 8-oxoprotoberbine (**6a–d**) and isomeric lamellarin G (**6e–f**) derivatives. Finally, we have successfully applied

this methodology to the one-pot synthesis of blue polycyclic Pechmann dye derivatives **19a–b** *via* double oxidative cyclizations of fumaryl dienamide under mild conditions.

Conflicts of interest

The authors declare no competing financial interest.

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