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An expeditious FeCl₃-catalyzed cascade 1,4-conjugate addition/annulation/1,5-H shift sequence for modular access of all-pyrano-moiety-substituted chromenes†

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ortho-Alkynyl quinone methides are well-known four-atom synthons for direct [4 + *n*] cycloaddition in constructing useful oxa-heterocyclic compounds owing to their high reactivity as well as the thermodynamically favored aromatization nature of this process. Herein we report an operationally simple and eco-friendly protocol for the modular and regioselective access of (*E*)-4-(vinyl or aryl or alkynyl)iminochromenes from propargylamines and *S*-methylated β-ketothioamides in the presence of FeCl₃, and particularly under undried acetonitrile and air atmosphere conditions. This method exhibits a broad substrate scope and displays nice functional group compatibility, thus providing an efficient access of 3,4-disubstituted iminochromenes.

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Introduction

The discovery of an advanced annulation strategy has received considerable attention in modern organic synthesis, notably in the area of polycyclic heteroarene assembly.¹ Indeed, ring formation involving cyclization² and late stage functionalization³ is a common protocol for accessing these structurally appealing frameworks, particularly in the synthesis of chromene systems.⁴ 2*H*/4*H*-Chromenes are privileged heterocyclic compounds with versatile properties that exhibit noteworthy potency, for instance anti-cancer, anti-microbial, anti-convulsant and anti-inflammatory activities.^{5,6} Among these chromene systems, iminochromene has been found as one of the best potential heterocycles for new drug discovery,⁷ for example MEKK2 inhibitors,⁸ caspase activators, apoptosis inducers⁹ and IRAP inhibitors (Scheme 1a).¹⁰ Indeed, there is an urgent demand to develop a new modular protocol for reaching these systems which allow good structural diversity.

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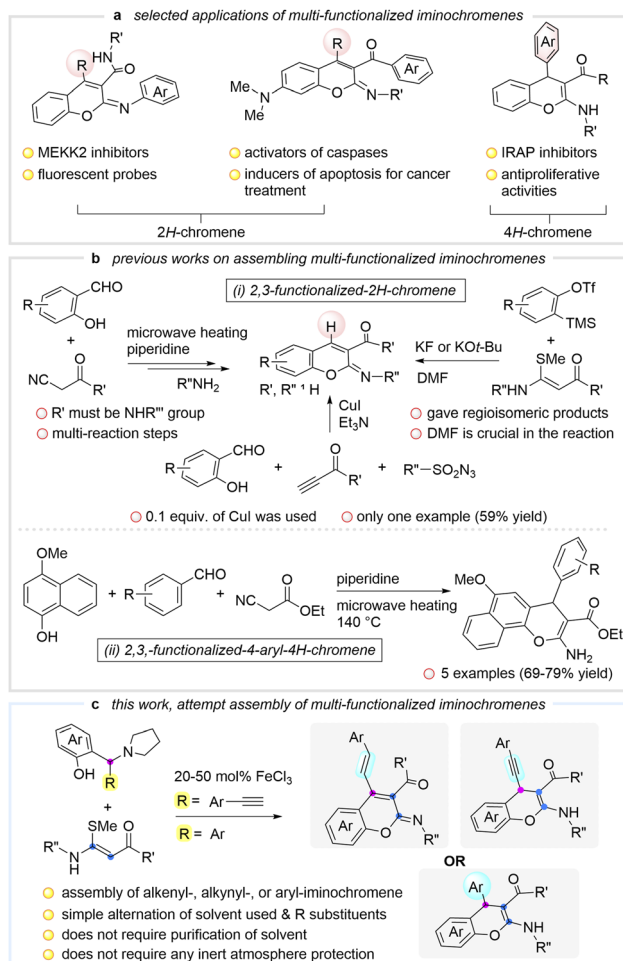
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Classical methods for constructing useful iminochromenes often employ salicylaldehyde as a typical synthon. Previous investigations showed the possible multicomponent reactions between terminal alkynes, sulfonyl azides and salicylaldehydes for affording 2,3-functionalized-2*H*-chromene using CuI as the catalyst (Scheme 1b(i)).¹¹ Recently, Li introduced a synthetic method to obtain 2,3-disubstituted-2*H*-chromene using a cascade three-component coupling of arynes, dimethylformamide and *N,S*-keteneacetals (Scheme 1b(i)).¹² In 2011, Liu and Wang reported the synthesis of 2-iminocoumarin-3-carboxamide from methyl cyanoacetate, aryl amines and salicylaldehydes *via* amidation and Knoevenagel condensation under microwave heating (Scheme 1b(i)).¹³ Remarkably, this skeleton displayed good photophysical properties for application in fluorescent intracellular imaging. Later, a modified multicomponent reaction of 4-methoxy-1-naphthol, substituted benzaldehyde and ethyl cyanoacetate allowed the formation of 2,3-functionalized-4-aryl-4*H*-chromenes (Scheme 1b(ii)).¹⁴ Certainly, the aforementioned methods have considerable merits in the assembly of multi-substituted iminochromenes. Nevertheless, the examples of all-pyran-functionalized iminochromenes were very limited. Only 5 relevant examples were reported. In fact, they are notable for having therapeutic potential as highlighted in Scheme 1a. Inspired by our pioneering results, in which highly reactive *ortho*-alkynyl quinone methide (*o*-AQM)¹⁵ displays the unique feature of cyclization,¹⁶ and in continuation of our interest in investigating the polyarene assembly,¹⁷ we herein report a new cascade reaction between alkylaminophenols and *N,S*-keteneacetals catalysed by FeCl₃ (Scheme 1c). This process provides a simple, rapid, and



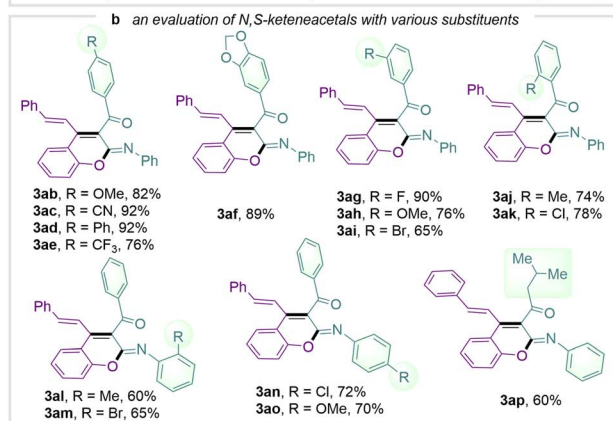
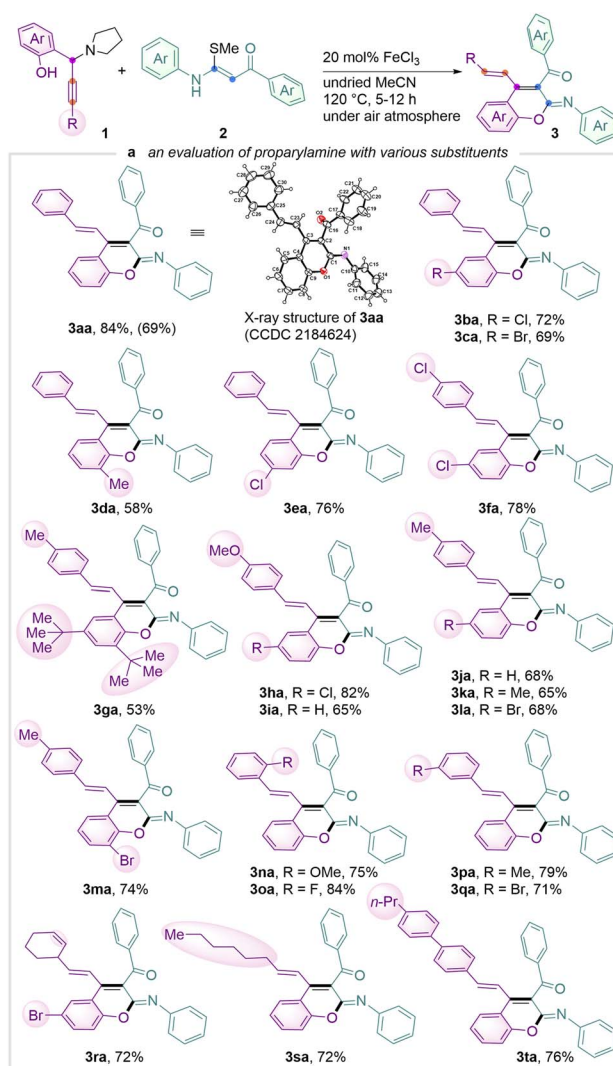


Scheme 1 Selected applications of multi-functionalized iminochromenes, previous methods and our design for the synthesis of such compounds.

direct approach to access alkenyl-, aryl- and alkynyl-iminochromene skeletons.

Results and discussion

Propargylic amine **1a** and *N,S*-keteneacetals **2a** were chosen as model substrates in our prototypical investigation (see Table S1 in the ESI[†]). Gratifyingly, in the presence of Lewis acid FeCl₃ in acetonitrile at 80 °C, the desired iminochromene **3aa** was generated in 82% yield with a ratio of *E/Z* isomer at 4:1. Switching the Lewis acids to Sc(OTf)₃, CuI, ZnI₂, AgNO₃ and others led to a dramatic drop in yields (entries 1–7), where no product was afforded in the absence of FeCl₃ (entry 8). Utilizing 1.0 or 2.0 equivalent of **1a** gave decreased yields of 72% and 76%, respectively (entries 1 vs. 9 and 10). A 20 mol% catalyst loading provided a comparable result (entries 1 vs. 11 and 12). Altering the solvent had a negative impact on the product yield (entries 11 vs. 13–17) and surprisingly the exclusion of water (*i.e.* anhydrous acetonitrile) proved to be unfavourable (entry 25). A survey of reaction temperature was also carried out. Decreasing the reaction temperature resulted in inferior yields and *E/Z* ratio

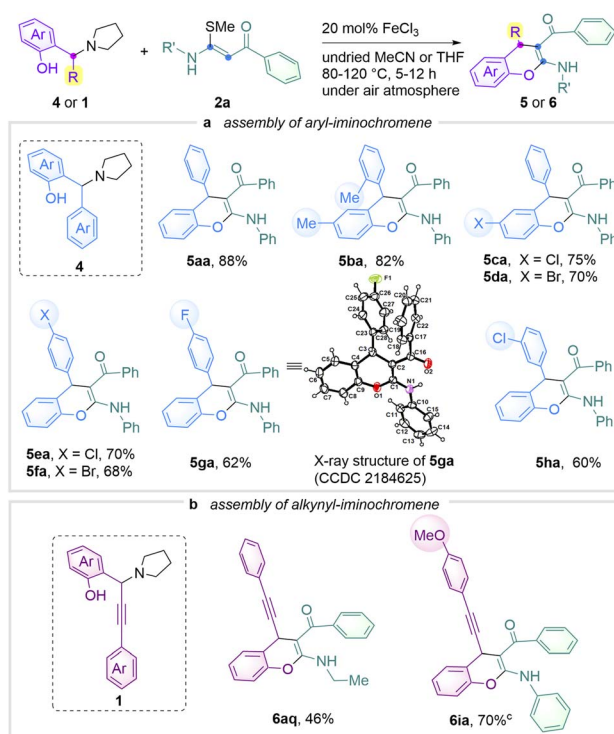


Scheme 2 Substrate scope of the formation of alkenyl-iminochromenes. Reaction conditions: (a) **1** (0.3 mmol), **2a** (0.2 mmol), and FeCl₃ (20 mol%) in undried MeCN at 120 °C for 12 h. Isolated yields were reported. Isolated yield of 12-fold scale in parenthesis. (b) **1a** (0.3 mmol), **2** (0.2 mmol), and FeCl₃ (50 mol%) in undried MeCN at 120 °C for 5 h. Isolated yields were reported.

(entries 11 vs. 18 and 19). Pleasingly, a 84% yield of **3aa** was obtained with an improved *E/Z* ratio (>20 : 1) at 120 °C (entries 11 vs. 20 and 21). It is worth noting that this cascade reaction proceeds well even under a bench-top air atmosphere.

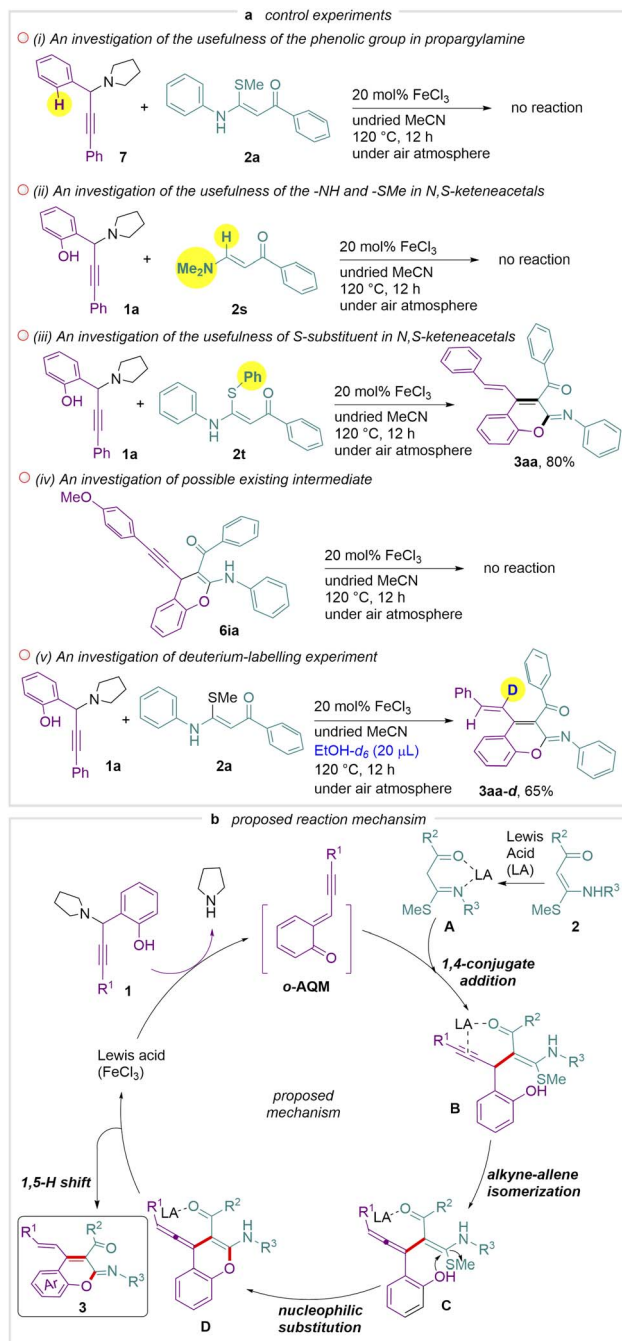
With the optimised reaction conditions, we next explored the substrate scope (Scheme 2). Given the unique feature of halogen-containing arene systems in halogen-bonding medicinal chemistry and chemical biology¹⁸ and the possibility of further functionalization using coupling technology,¹⁹ the substituents, *e.g.* –Br, –Cl and –F on the phenolic moiety and alkynyl arene moiety at the propargylic scaffold were therefore investigated. In contrast to the common Fe-catalysed coupling reaction where the halo groups would react, the present reaction system showed a halo moiety which remained intact under the stated reaction conditions (Scheme 2a, products **3ba**, **3ca**, **3ea**, **3ha** and **3qa**). In addition to halo-substituents, the steric bulky *tert*-butyl group at the *ortho*-phenolic-position of propargylamine was found to be a feasible reaction partner towards the ring-forming process (product **3ga**). Substrates with an *ortho*-hindered-substituent at the alkynyl arene moiety were also cyclised successfully to afford target iminochromenes (products **3na** and **3oa**). The alkenyl or alkyl unit located at propargylic amines furnished the products **3ra** and **3sa** in both 72% yield. Next, the reaction scope was further tested using various *N,S*-keteneacetal derivatives (Scheme 2b). The reactions were found to proceed smoothly and the functional groups of –Br and –Cl again were well tolerated (products **3ab–3ak**). Strongly electron-withdrawing –CN and –CF₃ positioned at the *para*-position of the arene moiety of **2** did not affect the annulation process (products **3ac** and **3ae**). Particularly noteworthy is that this method was found even able to accommodate *ortho*-substituted substrates, *e.g.* a chloro-substituent at the *ortho*-position of the arene moiety close to the carbonyl group and bromo-substituent at the *ortho*-position of the arene moiety near the imine group, in accessing **3ak** (78%) and **3am** (65%), respectively. These outcomes showed the suitability of this approach for further transformation of a π -extended system using an intramolecular annulation pathway.²⁰

Considering the prevalence of the 4-arylchromene skeleton in drug discovery,²¹ we attempted to conduct the reaction using arene-containing aminoalkylphenols **4** (Scheme 3a). In fact, common modular assembly of chromene, which consists of aryl units, relies on the palladium-catalysed Suzuki–Miyaura coupling of its sulfonates/bromides with arylboronic acids in which the reaction scope is often limited by the incompatibility of –Br or –Cl groups.²² Scheme 3a shows that various halogen-bearing aminophenols were tested in delivering products **5ca–5ga**. Indeed, these resulting compounds exhibit rich potential for further functionalization using well-established cross-coupling technology.²³ Product **5ga** was unambiguously confirmed by single crystal X-ray crystallography (CCDC 2184625†). Steric bulky product **5ba** was obtained in 82% yield. 4-Alkynyl-chromenes **6aq** and **6ia** were also afforded successfully (Scheme 3b). These products offer a high opportunity for further functionalization and thus allows new entities for material investigations.²⁴



Scheme 3 Substrate scope of aryl- and alkynyl-iminochromene. Reaction conditions: (a) **4** (0.3 mmol), **2a** (0.2 mmol), and FeCl₃ (20 mol%) in undried MeCN at 120 °C for 12 h. Isolated yields were reported. (b) **1a** (0.3 mmol), **2r** (0.2 mmol), and FeCl₃ (20 mol%) in dried MeCN at 120 °C for 5 h. Isolated yield was reported. (c) **1f** (0.3 mmol), **2a** (0.2 mmol), and FeCl₃ (20 mol%) in undried THF at 80 °C for 12 h. Isolated yield was reported.

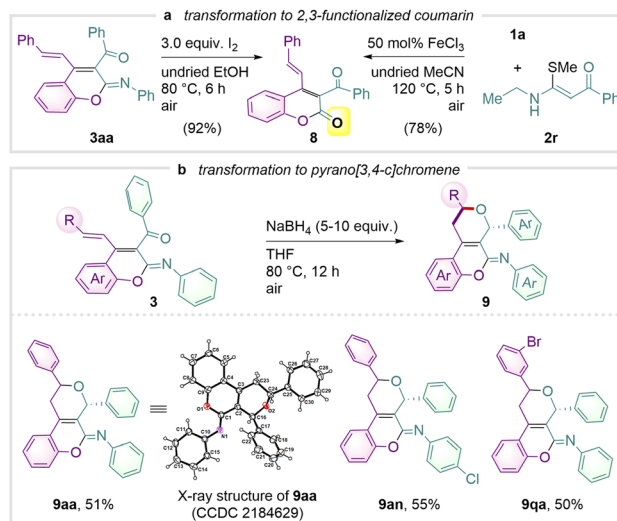
To gain more insight on this transformation, control experiments were carried out (Scheme 4a). Propargylamine **7** without a hydroxyl group did not react with **2a** which indicates that the hydroxyl group plays a crucial role in the initial stage of this reaction (Scheme 4a(i)). Further attempts of **2s** and **2t** revealed that the –NH and –S–R groups in *N,S*-keteneacetals are essential for the reaction while the latter showed that the *S*-substituent did not affect the reaction (Scheme 4a(i) to (iii)). We were intrigued that **6ia** is a probable intermediate before achieving product **3** (Scheme 4a(iv)). Yet, investigation showed that the *in situ* cyclisation does not occur. Furthermore, a deuterium-labelling experiment was performed, and compound **3aa–d** was obtained with 85% of the deuterium atoms at the alkenyl group (Scheme 4a(v)). A mechanistic proposal is illustrated in Scheme 4b. Initially, the *ortho*-alkynyl quinone methide (*o*-AQM) intermediate is formed in the presence of Lewis acid (FeCl₃), as proposed in the literature.²⁵ Meanwhile, **2** coordinates with Lewis acid to form intermediate **A** with higher nucleophilicity. Intermediate **B** is then generated *via* the 1,4-conjugate addition between intermediate **A** and *o*-AQM, followed by alkyne–allene isomerization to give the intermediate **C**. Finally, a proton transfer followed by an intramolecular nucleophilic attack of the oxygen anion of the intermediate **C** yields the intermediate **D**,²⁶ which further transforms to desired product **3** *via* 1,5-H shift and releases the Lewis acid. In order to



Scheme 4 Control experiments and proposed reaction mechanism.

further elucidate the reaction mechanism, we also carried out theoretical investigations. Detailed information is presented in ESI Fig. S4.^{†26}

To demonstrate the synthetic versatility of 2,3,4-multi-functionalized iminochromene in resembling biological frameworks²⁷ as well as photosensitive molecular assemblies,²⁸ further pursuit of organic transformations was performed to show the accomplishment of multi-functionalized coumarins (Scheme 5). An iodine-promoted hydrolysis allowed the formation of coumarin **8** in 92% yield (Scheme 5a). Alternatively, the same product was able to be obtained in 78% yield when **1a** was



Scheme 5 Applications of 2,3,4-multi-functionalized iminochromene transformation.

treated with **2r** under standard reaction conditions. A method of accessing 1,5-dihydro-2H,4H-pyrano[3,4-c]iminochromenes is also shown in Scheme 5b (products **9aa**, **9na** and **9qa**). The pyrano-embedded product **9aa** was unambiguously confirmed by single crystal X-ray crystallography (CCDC 2184629[†]).

Conclusions

In conclusion, we have succeeded in showing a simple protocol for accessing all pyranyl-moiety-substituted chromenes efficiently. This FeCl₃-catalyzed cascade reaction allows the formation of a variety of alkenyl-, aryl- or alkynyl-incorporated iminochromene skeletons with rich substitution patterns. Indeed, the present modular strategy meets the challenging demand of targeting diversified chromene structures for material and pharmaceutical investigations. Particularly noteworthy is that the -Br and -Cl groups which are often found impermissible in existing Pd-catalysed aromatic C-C or C-O bond ring-forming processes are well tolerated. This outcome should be beneficial for intended functionalization using versatile cross-coupling reactions.

Data availability

The data supporting this study are available within the article and the ESI.[†] The X-ray crystallography coordinates for structures of **3aa** (CCDC 2184624), **5ga** (CCDC 2184625), and **9aa** (CCDC 2184629) have been deposited at the Cambridge Crystallographic Data Centre.

Author contributions

F. Y. K. and X. H. conceived and supervised the project. X. H., R. L., and J. D. designed and performed the experiments. R. L. and P. Y. C. carried out the data analysis. Z. Y., K. X., and Q. T. prepared the ESI.[†] Y. S. participated in the scientific

discussions. R.-L. Z. carried out the theoretical study. X. H., P. Y. C. and F. Y. K. wrote and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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- 26 A density functional theory (DFT) calculation was further performed to elucidate the possible transformation pathways of intermediate C to D, see the ESI Computation study section for details and Fig, S4† for the DFT Gibbs energy profile of the ring-closure process.
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