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Tandem reaction to 3-(2-quinolyl) chromones from ynones and quinoline *N*-oxides under transition metal- and additive-free conditions

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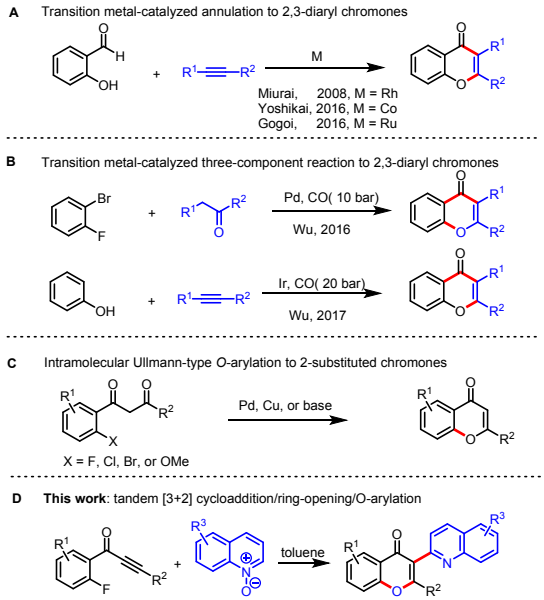
A novel method to synthesis of 3-(2-quinolyl) chromones *through* a tandem [3+2] cycloaddition/ring-opening/*O*-arylation from ynones and quinoline *N*-oxides has been developed. This protocol proceeds under transition metal- and additive-free conditions and can be amplified to gram level in 91% yield. 3-(1-isoquinolyl) and 3-(2-pyridyl) chromones are also successfully synthesized using isoquinoline and pyridine *N*-oxides under basic conditions. Various heteroarene-contaning chromones were afforded in 30-98% yields, which are difficult to be obtained and are compounds of interest in pharmaceutical chemistry and chemical biology.

Chromones are widely distributed in nature, and are used as bactericides, antioxidants, and drugs due to their remarkable biological properties.[1] The increasing incidences of tumor, malarial, bronchial, and pneumonia diseases have stimulated the preparation of chromone-based drugs.[2] Although multitudinous synthetic protocols have been developed for the synthesis of chromones,[3,4] there are few methods to access the 3-aryl chromones, which are of vital importance because they possess increased biological activities.[5] The palladium-catalyzed Suzuki and Stille couplings of 3-iodochromones with aryl boronic acids or aryl stannanes are the commonly used methods for the synthesis of 3-aryl chromones.[6,7] The preparing of nucleophilic coupling partners such as heteroaryl boronic acids and stannanes is challenging. The oxidative [4+2] cycloaddition of salicylaldehydes and internal alkynes using Rh,[8a] Co, [8b] Ru,[8c] represents an attractive route to 2,3-diaryl chromones (Scheme 1A). Recently, Wu and co-workers reported the transition metal-catalyzed three-component reactions for the assembly of 2,3-diaryl chromones (Scheme 1B).[9] However, those synthetic methods are not transferable to heteroaryl substituted substrates, probably due to the strong coordinative properties of heteroarenes.



Scheme 1 Methods for the synthesis of 3-(hetero)aryl chromone derivatives

In the past decade, the intramolecular *O*-arylation through transition metal-catalyzed Ullmann reaction[10] or base-promoted nucleophilic aromatic substitution (S_NAr)[11] have been well developed to access 2-substituted chromones (Scheme 1C). However, transition-metals or strong bases are commonly required. Thus, the development of new transition metal- and additive-free synthetic method that addresses the aforementioned shortcoming would therefore offer new opportunities to incorporate heteroaryl chromones into drug candidates.

Recently, we have discovered a base-promoted Michael addition/Smiles rearrangement/*N*-arylation cascade reaction for the synthesis of 1,2,3-trisubstituted 4-quinolones from *ortho*-holagenphenyl ynones.[12a] In our sustaining interest in ynones chemistry,[12] herein, we report a novel and efficient method for the synthesis of 3-heteroaryl chromones through

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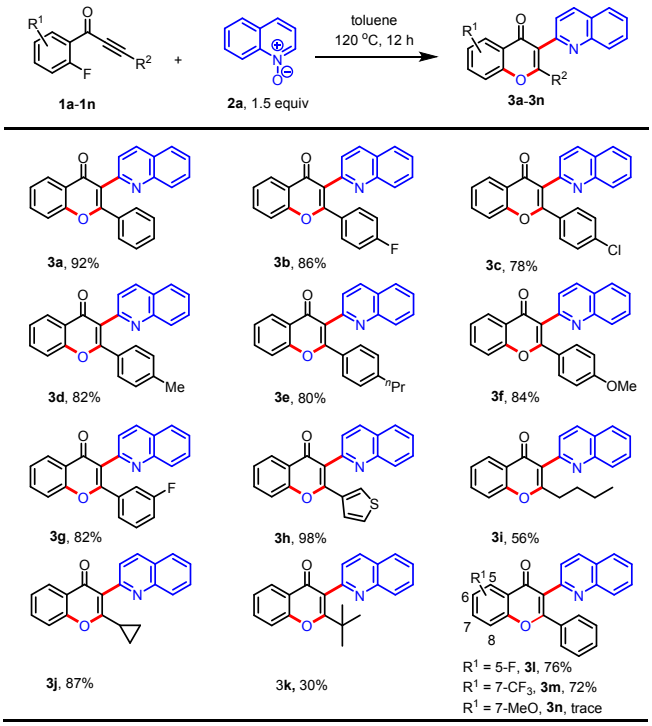
tandem [3+2] cycloaddition/ring-opening/*O*-arylation reaction from easily obtained ynones and heteroarene *N*-oxides (Scheme 1D).[13] While this work was under review, an elegant work was reported by Wang, in which 3-(2-quinolyl) chromones were synthesized *via* acid-mediated cascade reaction of quinoline *N*-oxides with *ortho*-hydroxyphenyl ynones.[14]

Our study was initiated by employing 1-(2-fluorophenyl)-3-phenylprop-2-yn-1-one **1a** and quinoline *N*-oxide **2a** as the model substrates to screen the reaction parameters. The reaction was conducted using **1a** (0.1 mmol), **2a** (0.15 mmol), and DMF (0.5 mL) at 120 °C under air for 12 h to afford the desired chromone product **3a** in 90% yield. The effect of the solvent was subsequently investigated, and other solvents, such as CH_3CN, *tert*-butanol, DCE, and 1,4-dioxane, all could give **3a** in good yields. 92% yield of **3a** could be obtained using toluene, and no product was observed when water was used as solvent. Then, the optimal conditions were identified as **1a** (0.1 mmol), **2a** (0.15 mmol), and toluene (0.5 mL) at 120 °C under air for 12 h.

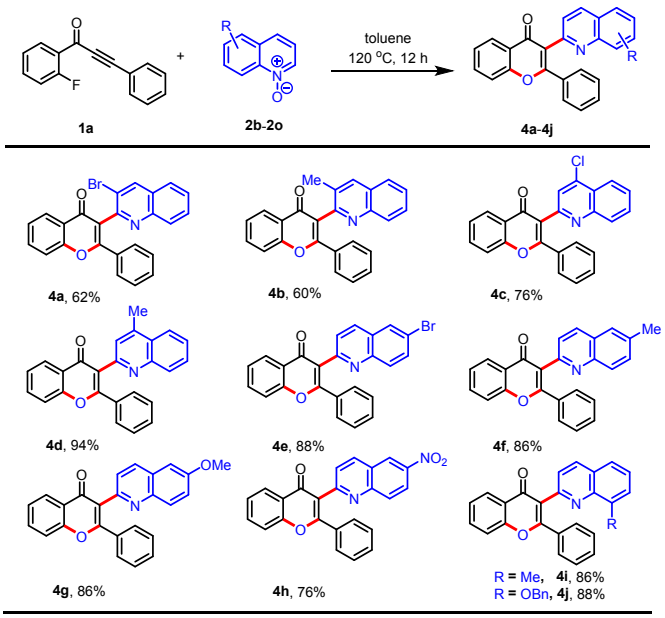
With the optimized protocols in hand, we firstly investigated the scope of ynones (Scheme 2). Having proved the perfect matching of this reaction system with a range of ynone derivatives, the desired chromone products were afforded in 30%-98% yields (**3a**–**k**). Ynones possessing halogens on R^2 could furnish the corresponding chromone derivatives (**3b**) and (**3c**) in good yields (86% and 78%). In addition, the electron-donating groups (methyl, *n*-propyl, and methoxyl) on R^2 for the corresponding ynones could also afford the target products in 82%, 80%, and 84% yields, respectively (**3d, 3e**, and **3f**). Similarly, *meta*-fluoro substituted substrate also could afford the desired product in 82% yield (**3g**). On the other hand, the reaction was conducted by using heteroarene-substituted



Scheme 2 Scope of the ynones

ynone, an excellent yield of product was obtained (**3h**, 98%). These results indicated that the reactivity was not sensitive to the electronic properties of R^2. Importantly, the ynone with *n*-butyl and cyclopropyl groups could give the products in 56% and 87% yields, respectively (**3i** and **3j**). The target product was afforded in a poor yield (**3k**, 30%), when R^2 was a *t*-butyl group, probably because of the increased steric hindrance. Remarkably, the presence of halogen (F) on the aroyl moiety of ynone was well tolerated (**3l**, 76%), which makes this reaction particularly attractive for further transformation. Ynone with an electron-withdrawing group on the aroyl moiety could also deliver the corresponding product (**3m**) in 72% yield. However, a complex mixture was obtained and the desired product (**3n**) was formed in a trace amount using ynone with an electron-donating group as substrate.

We next turned our attention to investigation of the scope of quinoline *N*-oxides for this transformation. Quinoline *N*-oxides with different functional groups were investigated under the standard reaction conditions using ynone **1a** as the coupling partner (Scheme 3). In general, quinoline *N*-oxides bearing both electron-donating substituents and electron-withdrawing substituents all could give the desired products in moderate to excellent yields (**4a**–**j**). Remarkably, halogen group (Br) and electron-donating group (methyl) at the C3-position of the quinoline *N*-oxides were well tolerable, affording the corresponding product in good yields (**4a** and **4b**, 62% and 60%), which suggested that the steric hindrance on the quinoline *N*-oxides had a significant effect. The structure of **4a** was unambiguously confirmed by single-crystal X-ray crystallography. Halogen group (Cl) on the 4-position of the quinoline ring could lead this reaction system in 76% yield (**4c**). On the other hand, the target product could be afforded in excellent 94% yield from 4-methyl quinoline *N*-oxide (**4d**). The electron-donating groups (methyl and methoxyl) at the

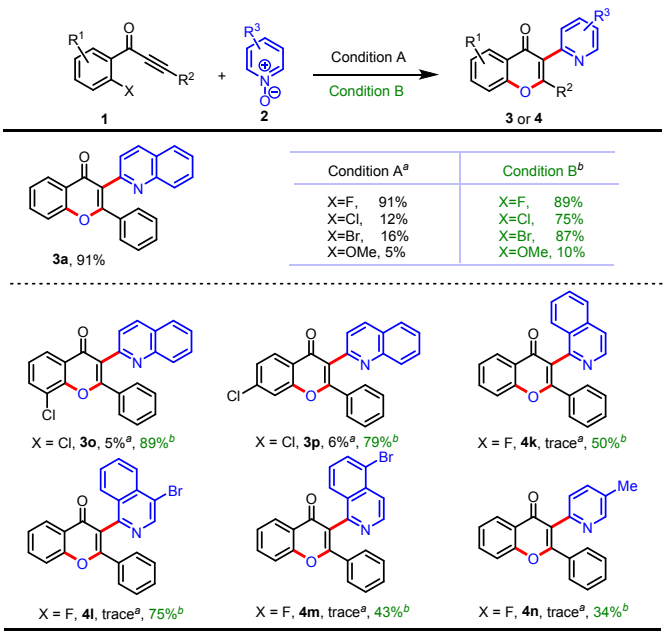


Scheme 3 Scope of the *N*-oxides.

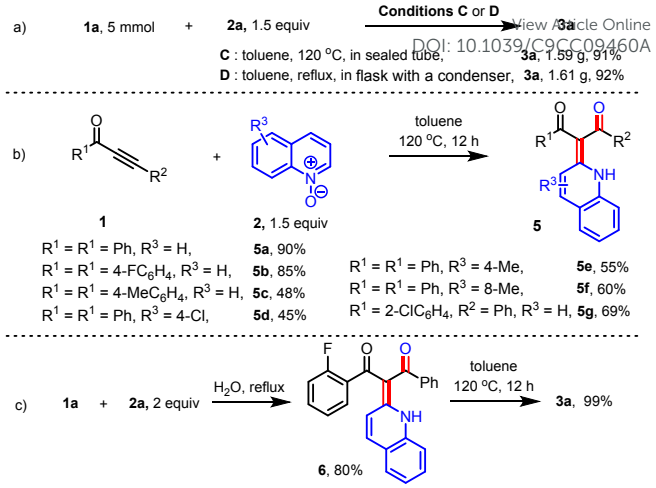
C6-position of the quinoline *N*-oxide also could afford the desired products **4f** and **4g** both in higher yield (86%), comparing to electron-withdrawing group (Br, **4e**, 88%). Introduction of a nitro group at the C6-position led to a slightly lower yield (**4h**, 76%). The methyl and benzyloxyl groups at the C8-position could afford the target products in good yields (**4i** and **4j**, 86% and 88%).

Inspired by these exciting results, we further investigated the effect of the X substituent on the aroyl moiety of the ynones (Scheme 4). However, poor yields were observed when the fluoro group was replaced by chloro, bromo, and methoxyl groups (Scheme 4, Condition A). To our delight, good yields could be obtained when the reaction was conducted under basic conditions (Scheme 4, Condition B). Subsequently, chromones **3o** and **3p** were synthesized in good yields from *ortho*-chloro aroyl ynones. In addition, the desired products could be afforded in 43-75% yields by using isoquinoline *N*-oxide as the substrates (**4k**–**m**). Significantly, the reaction also proceeded and the desired product **4n** was afforded in 34% yield by using pyridine *N*-oxide as the substrate.

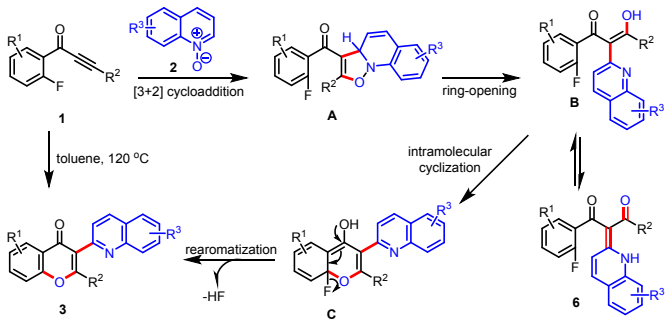
A gram-scale conversion was performed using **1a** and **2a** as substrates, and excellent isolated yields of **3a** were obtained, indicating the practicality of this method (Scheme 5a). To explore the mechanistic hypothesis, control experiments were performed. The reaction of ynones **1** and quinoline *N*-oxides **2** could give the 1,3-dione products (**5a**–**g**) in 45-90% yields under the standard conditions (Scheme 5b). Subsequently, the intermediate **6** was independently synthesized in 80% yield from ynone **1a** and quinoline *N*-oxide **2a**, and the target product **3a** was afforded in 99% yield from intermediate **6** (Scheme 5c).



Scheme 4 Scope of the ynones and *N*-oxides. [a] Condition A: **1** (0.1 mmol), **2** (0.15 mmol), toluene (0.5 mL) at 120 °C under an air atmosphere for 12 h. [b] Condition B: **1** (0.1 mmol), **2** (0.15 mmol), Na_3PO_4 (0.2 mmol), DMF (0.5 mL) at 100 °C under air atmosphere for 12 h.



Scheme5 Gram-scale reaction and control experiments.



Scheme 6 Possible reaction mechanism

On the basis of the experimental results and literature reports,[11,13] the reaction mechanism was proposed as shown in Scheme 6. Initially, the base-promoted regioselective [3+2] cycloaddition of ynone **1** and quinoline *N*-oxide **2** affords intermediate **A**. Then, a ring-opening process of intermediate **A** by N–O bond cleavage generates the key enol intermediate **B**, which then is reversibly converted to 1,3-dione **6**. Subsequently, the species **C** is formed *via* intramolecular cyclization of **B**. Finally, rearomatization of **C** by elimination of HF provided chromones **3** (Scheme 6).

In summary, we have developed a general and practical strategy for the synthesis of 2,3-disubstituted chromone derivatives through regioselective [3+2] cycloaddition, ring-opening, and *O*-arylation cascade reaction from ynones and *N*-oxides. This transition metal-free protocol can be completed in one step with construction of one C–C bond and two C–O bonds. The successful incorporation of heteroaryl groups into chromone cores makes this method highly important in drug discovery.

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Conflicts of interest

There are no conflicts to declare.

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