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# Iodine-mediated formal [3 + 2] annulation for synthesis of furocoumarin from oxime esters†

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A novel synthesis of furocoumarins was developed by a reaction between oxime esters and 4-hydroxycoumarins. The reaction was proposed to undergo radical mechanism mediated by iodine, a cheap and common laboratory reagent. Mechanistic studies showed the key for the successful transformation was the presence of α-iodoimine intermediate which facilitated the ring-closing step. The developed conditions produced good functional group tolerance with a wide range of high-profile furocoumarin product. The potential for this strategy to be applied in other syntheses of heterocyclic compounds is highly achievable.



## 1. Introduction

Heterocyclic compounds play crucial roles in the pharmaceutical industry because of their presence in substantial amount of drugs.[1] In addition to offering protein binding functional groups, heterocycles also affect favorably drugs' solubility and their pharmacokinetic properties. Among the important heterocyclic compounds, furocoumarins have been commonly targeted due to their remarkable potential biological activities (Fig. 1).[2,3] They have been demonstrating anti-bacteria, anti-viruses (including HIV), anti-cancer, and inhibitory hyperplasia activities.[4] Furthermore, furocoumarins also showed potential applications in photosensitive medications, pesticides and molecular biology.[5] In this report, we described the first metal-free formal [3 + 2] annulation between two versatile synthetic building blocks, oxime esters and 4-hydroxylcoumarine, to synthesize these important heterocyclic compounds.

Approaches for furocoumarin synthesis varied but extensively were integrated with 4-hydroxycoumarin starting materials. These 4-hydroxycoumarin substrates are known as adaptable synthons in the synthesis of countless heterocycles,[6] such as pyrazolinones,[7] 1,2-benzisoxazones,[8] quinoline.[9] For the generation of furocoumarin, 4-hydroxycoumarin would frequently be under the catalysis of metal salts, for instance, Ce(IV),[10] Ru(II),[11] Cu(II),[12] multicopper oxidase[13] or it could be in a multi-components reaction, mostly with benzaldehyde and isocyanide.[14] The disadvantages of these methods are the employment of toxic metals and increasing complexity of the reaction that would be using multiple chemicals in a single procedure. Therefore, a simpler, non-metal catalyzed protocol to generate these valuable furocoumarins is much needed. With that standpoint, we found out that oxime esters are well-suitable reagents in developing a new synthetic methodology which is metal-free, rapid and from universal starting materials.

The oxime ester compounds are widely employed in organic synthesis because they are readily accessable from oximes and acid chlorides or anhydrides.[15] The N–O σ bond of oxime esters with an average energy of ~57 kcal mol$^{-1}$ causes this bond quite unstable. And because of the susceptible cleavage of the N–O bond by active metals, the oxime esters are frequently utilized in transition metal catalyzed transformation.[16] However, there are still elegant studies which can convert these hydroxy amine

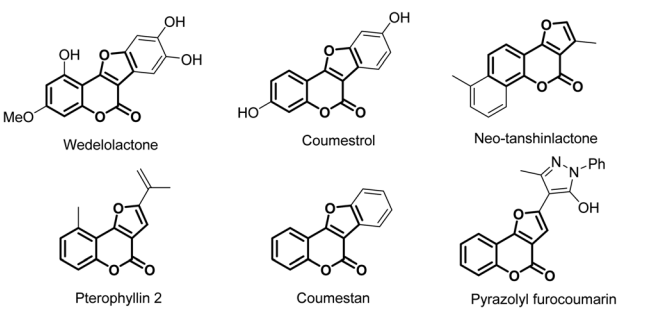


Fig. 1 Selected examples of furocoumarin derivatives.

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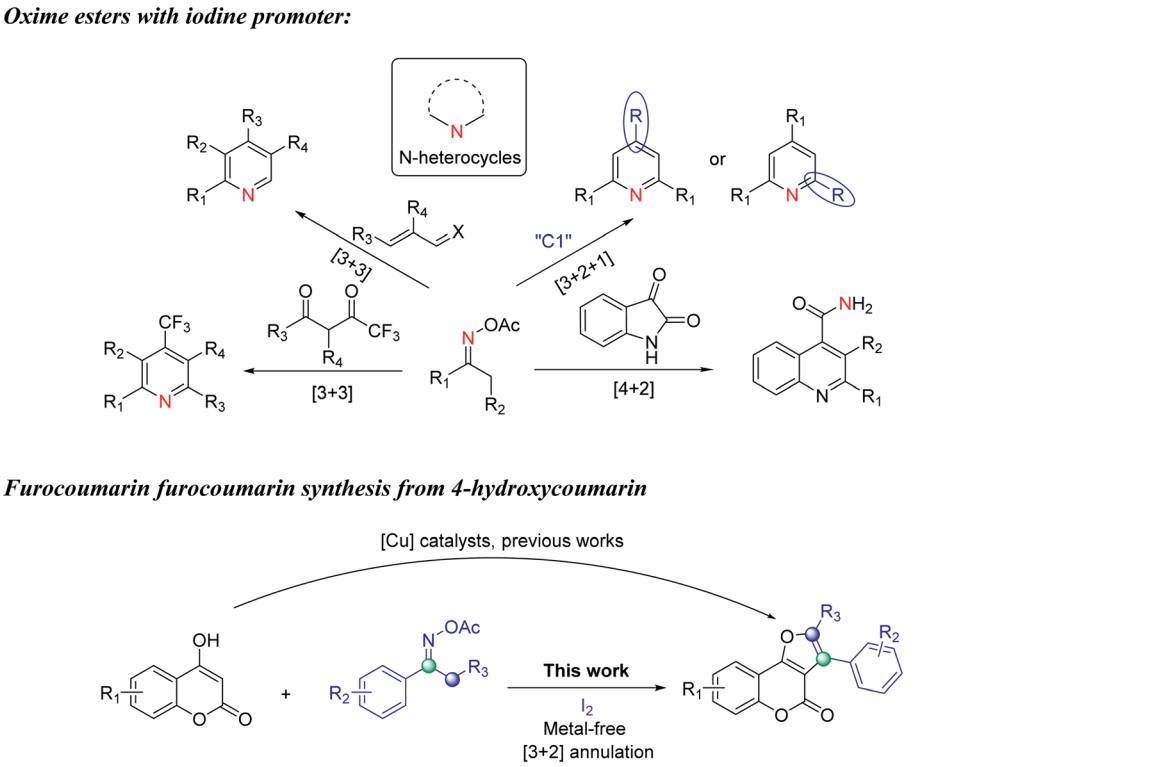
derivatives into higher value products in a transition metal-free fashion. For example, in 2016, Huang and coworkers reported the metal-free synthesis of polysubstituted pyridines from ketoximes and acroleins (Scheme 1a).[17] In this dedicated research, iodine and trimethylamine were used to facilitate the [3 + 3] reaction to form pyridine products with high chemoselectivity and wide tolerance of functional groups. The reaction was suggested to undergo a radical pathway initiated by single electron transfer from iodine to oxime substrates. Huang later found out that $NH_4I$ when incorporated with either $Et_3N$ or $Na_2S_2O_4$ could also be used to generate imine radical intermediates in the reactions with 1,3-diketone and provided diversified polysubstituted pyridines (Scheme 1a and b).[18,19] Besides, Gao developed $I_2$-catalyzed condensation of ketoxime acetates with $Et_3N$[20a] or aldehydes[20b] as the C1 source through formal [3 + 2 + 1] annulation to give structurally symmetrical pyridines or 2,4-diarylpyridines (Scheme 1c). In another research based on the transamidation of isatins, Gao and coworkers[20c] otherwise have demonstrated an efficient quinoline-4-carboxamide formation using the same substrate ketoxime acetates (Scheme 1d). Herein we envisioned that the oxime esters will practically achieve the formation of other heterocycles when cooperated with different organic moieties and with specifically 4-hydroxycoumarin to potentially form furocoumarin products.

## 2. Experimental

In a general procedure, 4-hydroxycoumarin (0.1 mmol, 16.2 mg), iodine (0.05 mmol, 12.7 mg) and mesitylene (2.0 mL) were added into the 8 mL vial containing a stirring bar. The reaction mixture was tightly sealed and heated at 140 °C in 12 hours. After completion, the reaction mixture was cooled down to room temperature and diphenylether (0.1 mmol, 17 mg) was added as internal standard. Subsequently, the resulting mixture was extracted with DCM : $H_2O$ (3 : 1) and the organic layer was collected and dried by using anhydrous $Na_2SO_4$ and then recrystallized in ethylacetate to afford desired product.

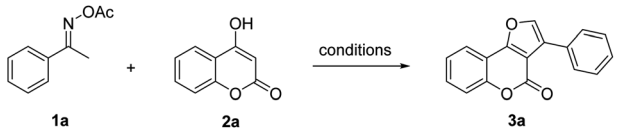
## 3. Results and discussion

Our investigation of the heterocycles synthesis started with the reaction of *O*-acetyl ketoxime **1** and 4-hydroxycoumarin **2a** (Table 1). To our surprise, furocoumarin **3a** was obtained in a small amount with DMSO as solvent at 120 °C without the need of any additives, giving very first signal that our reaction may follow different pathways rather than previous proposed mechanism (Table 1, entry 1). The structure of furocoumarin **3a** was precisely confirmed by X-ray crystallography on its single crystal (Fig. 2, CCDC number is 2026801). Furthermore, other solvents, ranging from non-polar to polar, generated products with different results (Table 1, entries 1–8). Generally, solvents such as DMF DMSO which are known to consume a big portion of the iodine radical *via* radical-mediated reactions provided the desired product in low yields.[21] Ethereal solvents were also tested and only moderate yields were achieved presumably due to the α-hydrogen abstraction of these solvents with radicals.[22] Non-polar aromatic solvents which are quite inert to radical reagents afforded higher efficiency and optimal results, 58%, were obtained in mesitylene. Other sources of iodine were also




Scheme 1 Previous works of oxime esters with iodine and furocoumarin synthesis from 4-hydroxycoumarin.

Table 1 Optimization of reaction conditions[a]




| Entry | Catalyst | Solvent | Temp. (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $I_2$ | DMSO | 120 | 8 |
| 2 | $I_2$ | DMF | 120 | 14 |
| 3 | $I_2$ | 1,4-Dioxane | 120 | 21 |
| 4 | $I_2$ | Dibutyl ether | 120 | 26 |
| 5 | $I_2$ | PhCl | 120 | 39 |
| 6 | $I_2$ | Toluene | 120 | 32 |
| 7 | $I_2$ | Xylene | 120 | 53 |
| 8 | $I_2$ | Mesitylene | 120 | 58 |
| 9 | KI | Mesitylene | 120 | 26 |
| 10 | $NH_4I$ | Mesitylene | 120 | 30 |
| 11 | $I_2O_5$ | Mesitylene | 120 | Trace |
| 12 | — | Mesitylene | 120 | ND |
| 13 | $I_2$ | Mesitylene | 80 | 44 |
| **14** | **$I_2$** | **Mesitylene** | **140** | **87** |
| 15[c] | $I_2$ | Mesitylene | 140 | 67 |
| 16[d] | $I_2$ | Mesitylene | 140 | 46 |
| 17 | $I_2$ | Mesitylene | 160 | 86 |

[a] Reaction condition: **1a** (0.15 mmol), **2a** (0.3 mmol), $I_2$ promoter (50 mol%) in solvent (1.5 mL) at *T* °C under Ar for 2 h. [b] GC yield. [c] The reaction was run under $O_2$. [d] Open air conditions.

tested, with inorganic salts KI and $NH_4I$ gave comparably low yield of product formation, 26% and 30% yield, respectively (entries 9 and 10), while $I_2O_5$ provided only trace amount of the product (entry 11). In absence of $I_2$, no fucocoumarin was observed, which showed the crucial role of the iodine promoter in this reaction (entry 12).

We next turned our attention to the effects of temperature on the reaction outcome (entries 13, 14, 17). The increase of temperature greatly facilitated product formation by speeding up the reaction rate. Among the examined temperatures, we observed that the starting material was consumed quickly at 140 °C and provided the product with highest yield, 87%. Furthermore, running reaction in different atmospheres also led to various results. In comparison with the reaction under argon, only moderate amount of **3a** was observed when the reaction was carried out under pure oxygen or air atmosphere, with 67% and 46% yield, accordingly. Apparently, other gases, especially oxygen, and moisture have momentous effects on the product formation.

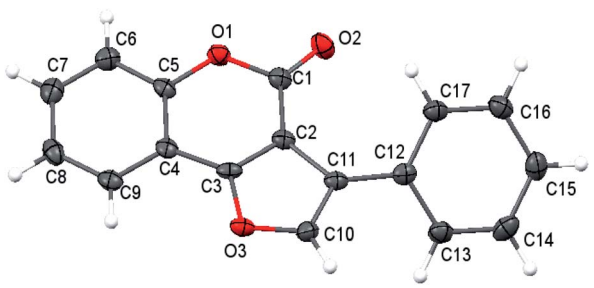
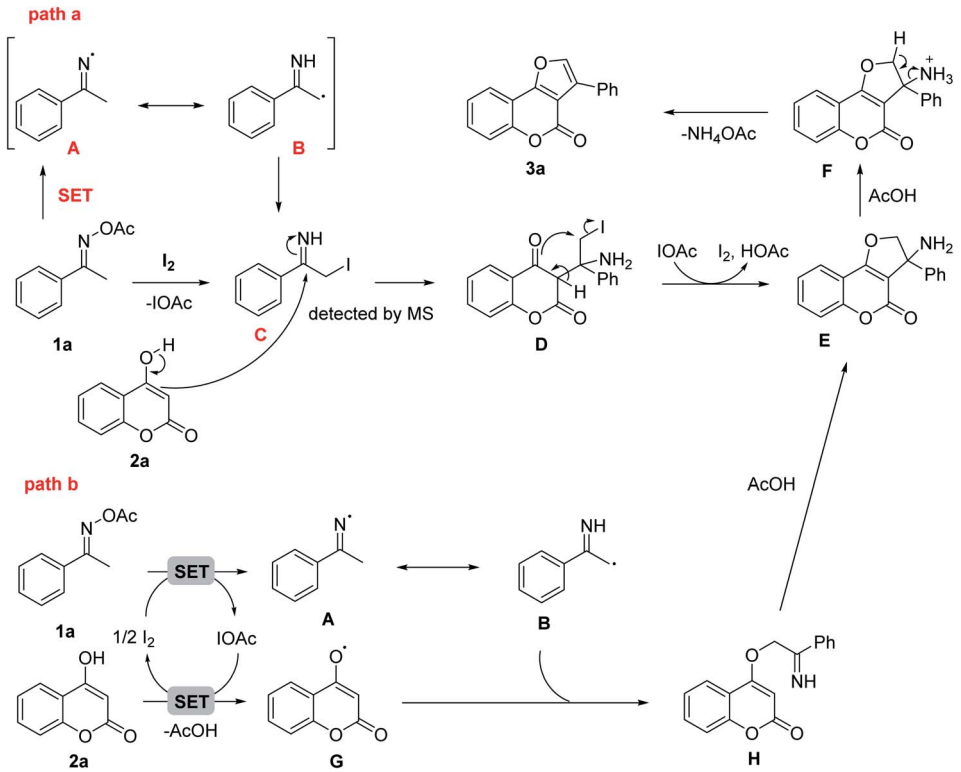



Fig. 2 Crystal structure of **3a**.

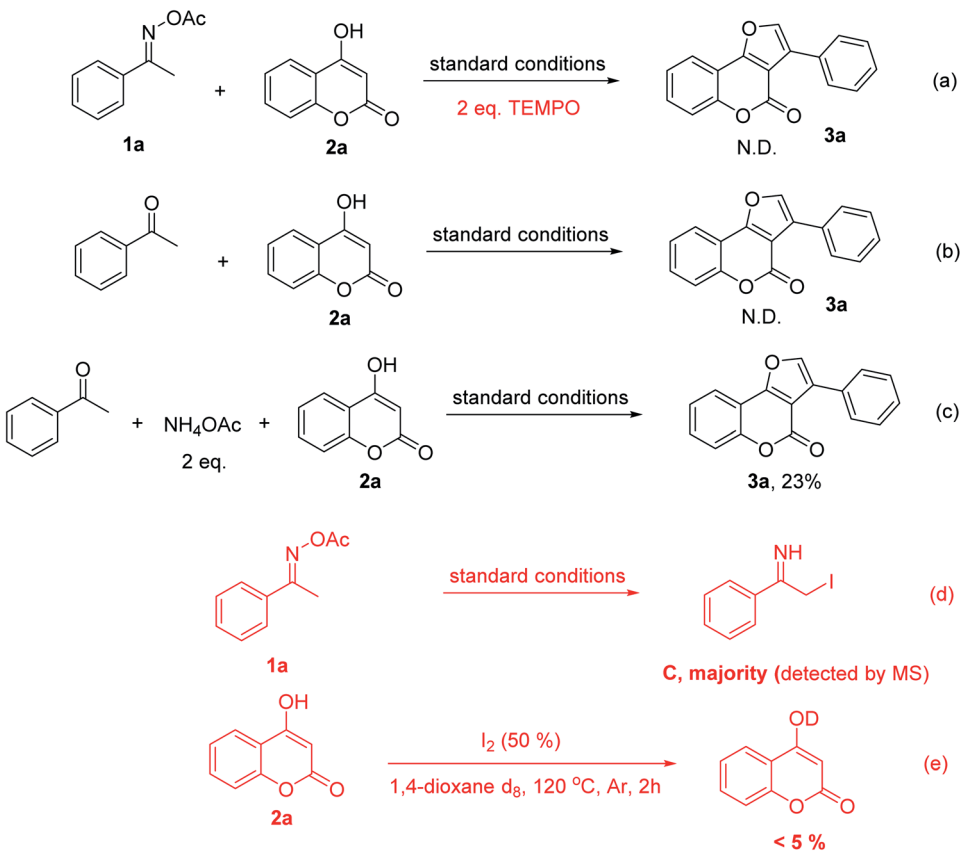
The reason of diminished product formation under air or oxygen may be due to the presence of radicals over the course of the reaction. Based on previously known iodine mediated reaction with oxime esters, a plausible mechanism was outlined in Scheme 2. The reaction started with the reduction of acetyl oxime ester **1a** by iodine to form the imino-radical **A** which could be in resonance with α-carbon radical imine **B**. After incorporated with another iodine radical, **B** was converted to α-iodoimine intermediate **C** which could be detected by mass spectroscopy (path a). The nucleophilic attack of the enol-carbon on 4-hydroxycoumarin **2a** to the imino carbon of **C** then generated iodoamine **D**. Upon electrophilic *O*-alkylation attack of ketone group on the iodocarbon with the IOAc to $I_2$ promoter recovery, the dihydrofuranocoumarine **E** was formed and accomplished the formal [3 + 2] annulation step. The intermediate **E** under acidic catalysis would then undergo olefin formation *via* elimination of the ammonium group to furnish final furocoumarin product. In addition, the intermediate **E** could be formed through the intramolecular nucleophilic cyclization of **H** which was provided by the radical coupling reaction of **B** and **G** (path b). The enolic oxygen radical **G** was generated from **2a** with [$I^+$] species as the oxidant *via* a single-electron-transfer (SET) process.

Our discovery was highly interesting because the nitrogen of oxime normally participates in the ring formation to generate *N*-containing heteocycles and the α-keto carbon of the oxime esters often plays as a nucleophile in nucleophilic attacks; however, this has not been observed in our case. To evaluate the feasibility of our proposed mechanism, we conducted mechanistic studies in which several control experiments were performed. Firstly, TEMPO was introduced to the reaction mixtures in addition to all other reagents to confirm a radical involment. The reaction was indeed completely suppressed without any trace of the furocoumarin **3a** (Scheme 3a). This result supported the proposed radical process *via* SET process. Secondly, no formation of **3a** was also observed when acetophenone was used instead of *O*-acetyl ketoxime starting material (Scheme 3b). The oxime undoubtedly played a key role as a radical component and a strong electrophilic partner in the reaction condition. The ketone, on the other hand, was unlikely to be electrophilic enough for the nucleophilic attack from 4-hydroxycoumarin. This turned out to be an appropriate rational when we used two equivalents of ammonium acetate together with acetophenone which could generate the imine *in situ*, **3a** was isolated in 23% yield (Scheme 3c). The last puzzle in our proposed mechanism was **C** detected by mass spectroscopy. The iodoimine **C** may be the key intermediate for this methodology since the iodo-substitution has made the α-carbon of the amino group become more electrophilic and facilitated the ring closure approach from keto-oxygen of the coumarin ring.[23] This was consistent with the results of reactions in the absence of 4-hydroxycoumarin (Scheme 3d). Interestingly, reaction path b is likely to be not favorable as shown in Scheme 3e. Particularly, reactions of 4-hydroxycoumarin in deuterated 1,4-dioxane



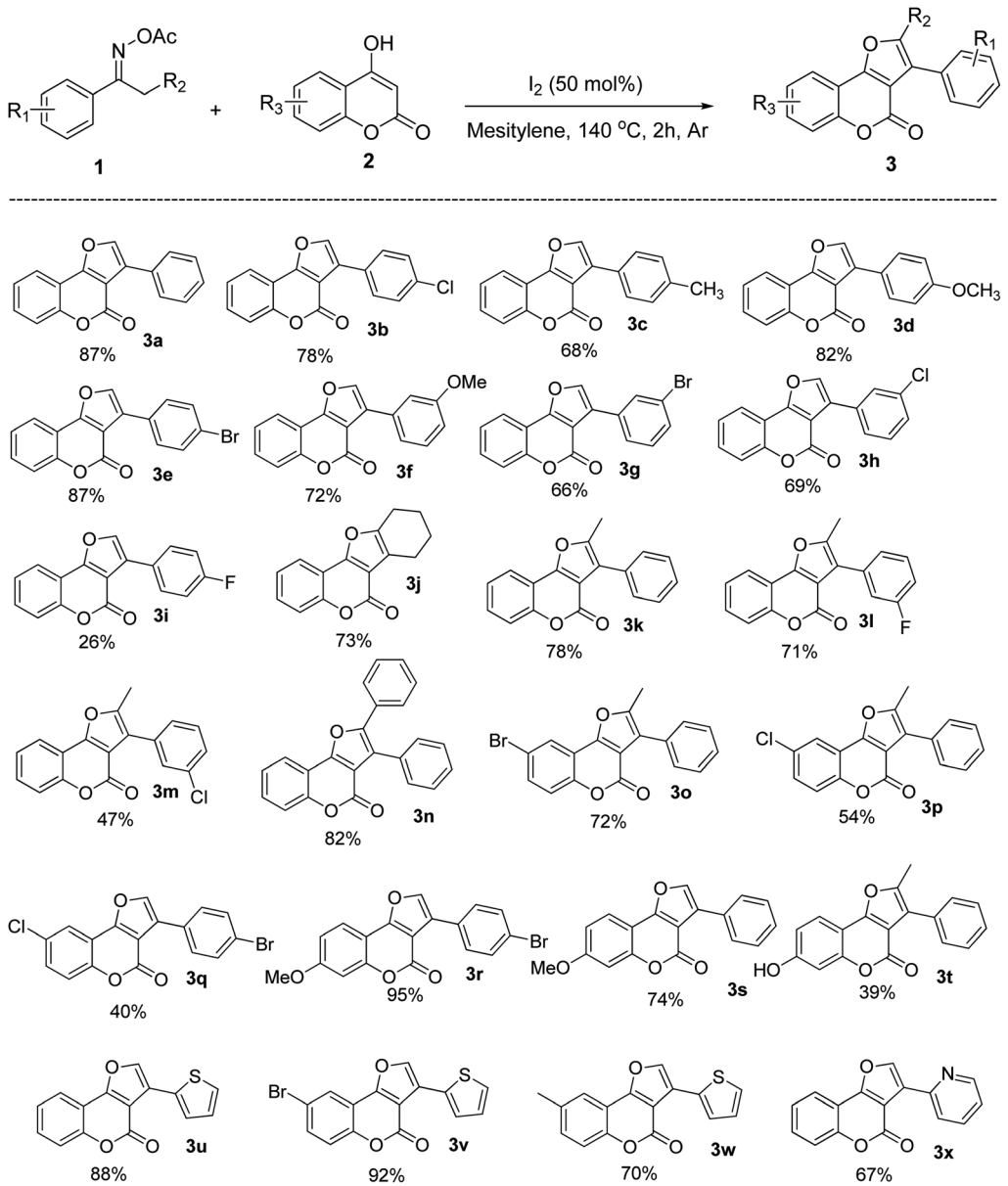

Scheme 2 Plausible mechanism of the reaction.




Scheme 3 Control experiments.

resulted in less than 5% of H/D exchange. It was reported that hydrogen abstraction of ethers by free radicals in liquid phase was significant.[24] However, more further mechanistic experiments are still needed to confirm the reaction path.

After investigating the reaction mechanism, we directed our effort to explore the generality and scope of this versatile $I_2$-triggered formal [3 + 2] annulation using optimized conditions. To our expectation, the reaction had a very broad substrate scope in regard to both substituted 4-hydroxycoumarin and oxime esters. Specifically, the reaction of 4-hydroxycoumarin with a wide range of acetophenone oximes afforded aromatic-substituted furocoumarins (**3a–3h**) in moderate to excellent yields. Both electron-donating and electron-withdrawing groups were well tolerated. Changing the positions of substituents on the benzene ring is possible, the products were still generated effectively, from 66% to 87% yield. The *p*-fluorophenyl substrate, however, worked sluggishly with only 26% yield of the product formation (**3i**). Interestingly, cyclohexanone also tolerable in reaction conditions, afforded furocoumarin **3j** in 73% yield. This showed that the method is not limited to only aromatic ketoximes. Moreover, the reaction surprisingly worked well with more steric oxime esters. When different propiophenone acetyloximes reacted with 4-hydroxycoumarin **1**, disubstituted furocoumarins (**3k–3m**) were produced from moderate to high yields. In fact, steric hindrance did not expose any barrier for the product formation, with diphenylfurocoumarin **3n** could be obtained in very good yield (82%). With regard to 4-hydroxycoumarin scope, it was realized that the electronic




Scheme 4 Substrates scope of the reaction.[a] [a]Reaction condition: **1** (0.15 mmol), **2** (0.3 mmol), $I_2$ (50 mol%) in mesitylene (1.5 mL) at 140 °C under Ar for 2 h.

nature of substituents has a certain effect on the reaction outcome. The halogenated electron-deficient substrates tend to give products with lower yield than the methoxy electron-rich substrates (compared to **3o–3p** and **3r–3s**). Especially, when both 4-hydroxycoumarin and acetophenone oxime bearing the electron-withdrawing groups, the furocoumarin was obtained with only 40% yield (product **3q**). Similarly, product **3t** with a free-hydroxyl group was also isolated in 39% yield. Nevertheless, although obtained in low yield, this product shows that a protected functional group was not necessary for a successful product generation. This also indicates that the radical scavenging property of free hydroxy groups did not totally suppress product formation in the current reaction conditions (Scheme 4).

Finally, the heteroaromatic substrates were well-tolerated in this $I_2$-promoted formal [3 + 2] annulation. The furocoumarins carrying thiophenyl groups (**3u–3w**) and pyridinyl groups (**3x**) were obtained in high to excellent yields. Since heteroatoms usually coordinate with metals and make the metal-catalyzed reaction proceed sluggishly,[25] these results demonstrate the superior of our method compared to those with metal catalysts and heterocyclic substrates.

## 4. Conclusions

In conclusion, we have successfully developed an $I_2$-mediated formal [3 + 2] annulation between two highly versatile starting materials, 4-hydroxycoumarin and acetyl oxime esters. The obtained furocoumarin products were highly applicable due to their potential biological activities. Our reaction was proposed through a radical mechanism which was supported by control experiments and observed intermediates. The ability of iodine to activate the N–O bond of the oximes and form a α-iodoimine intermediate was considered decisive for the ring-closing step which established the furano moiety of furocoumarins. This study also assisted our future protocols to employment of more steric and functional groups tolerance. We are in the process of exploring this efficient iodine catalyst system in the formation of other bioactive heterocycles.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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