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Novel and Efficient Access to Flavones under Mild Conditions: Aqueous HI-Mediated Cascade Cyclization/Oxidative Radical Reaction of 2-Propynolphenols

Xian-Rong Song, [a] Ren Li, [a] Tao Yang,[a] Xi Chen,[a] Haixin Ding,[a] Qiang Xiao,*[a] and Yong-Min Liang[b]

Dedication ((optional))

Abstract: Herein we disclose a metal-free and efficient method for the direct conversion of 2-propynolphenols to biologically important flavones using aqueous HI as the promoter. This transformation was proved via 4-iodo-2*H*-chromenes intermediate, which was simultaneously converted to corresponding flavones by a C_{sp2}−I bond cleavage and a C−O bond formation under air.

Introduction

Flavonoids are important scaffolds present occurring in numerous plant secondary metabolites and natural products.[1] Such compounds exhibit latent pharmacologically and biologically activity, especially with anti-inflammatory,[2] antiestrogenic,[3] antioxidant,[4] antimicrobial,[5] cardiovascular, [6] and chemo preventative activities.[7] **Figure 1** lists several representative natural product molecules containing flavonoid skeletons. Many efforts have been made to construct flavonoids due to their significant biological activities. Until now, various methods have been established for the preparation of flavones, such as the cyclization of 1-(o-hydroxyphenyl)-1,3-diketones,[8] the cyclization of 2-chalconesphenols,[9] the cyclization of alkynones,[10] the reaction of 2-iodophenols with alkynes [11] and the oxidation reaction of flavanones.[12] Although these approaches are highly efficient and innovative, some of them have one or more disadvantages, such as low yield, long reaction times, expensive catalyst and microwave radiation. Thus, to develop an effective synthetic approach for the construction of flavones is extremely attractive and challenging.

Cascade cyclization is one of the most important and powerful tactics for constructing cyclic compounds and has attracted the attention of many chemists. [13] Recently, propargylic alcohols with two mutual activated functional groups have served as versatile synthons for the construction of various

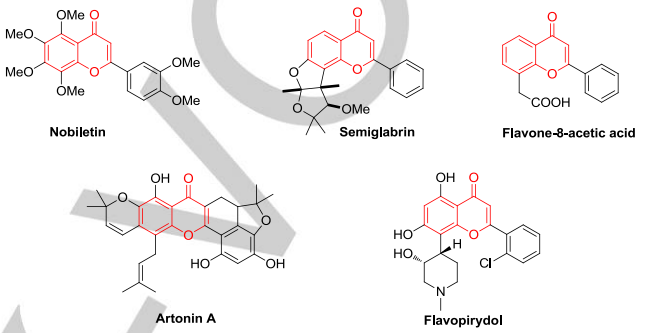
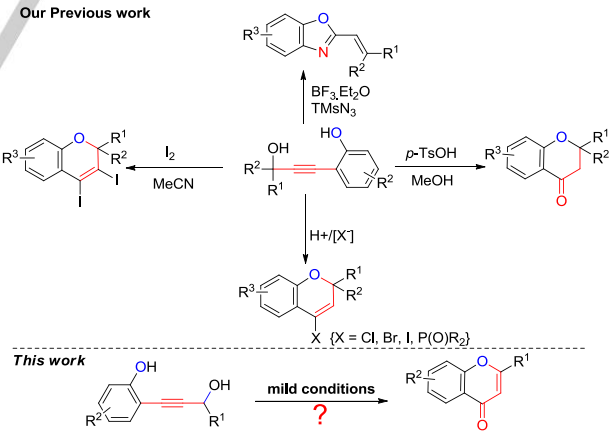


Figure 1. Representative bioactive natural products

synthetic intermediates in synthetic methodology,[14] which has made great achievements in the synthesis of carbo- and hetrocyclic compounds. Over the past few years, our group had reported numerous effective synthetic strategies for the synthesis of heterocyclic compounds by tandem cyclization of propargylic alcohols, such as 2*H*-chromenes, 4-chromanones and benzoxazoles (Scheme 1). [15]



Scheme 1. Our previous work and new strategy towards the synthesis of flavone derivatives

By taking into consideration our continuous interest in the potential reactivity of propargylic alcohols, we herein report an efficient strategy for the synthesis of flavones through Brønsted acid promoted cascade cyclization of 2-propynolphenols (Scheme 1). It is worth noting that the efficient transformation of 2-propynolphenols to flavones through C−O bond formation and C_{sp2}−I bond cleavage has rarely been reported in previous literature.[10d] Compared with the established methods, our

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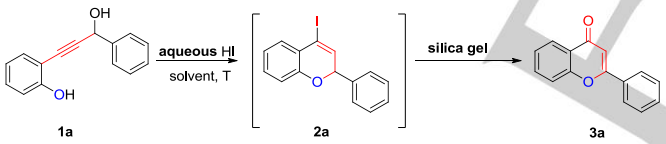
developed strategy have the advantages of atomic economy, high yield and simple operation, which provide potential possibilities for the application of this method in medicinal chemistry.

Results and Discussion

Initially, 2-propynolphenols **1a** was selected as representative substrate using aqueous HI as promoter in CH_2Cl_2 at 30 ºC to investigate this proposed transformation (Table 1). Only trace of 2-phenyl-4*H*-chromen-4-one (**3a**) was observed through TLC analysis with almost whole of 4-iodo-2*H*-chromenes (**2a**) detected after 2.0 h. **2a** was found to be extremely unstable, which could be transformed into **3a** in a test tube during column chromatography separation process, leading to the formation of **3a** in 89% yield (entry 1). The existence of the resulting **2a** was confirmed by standard ^{1}H NMR spectroscopy or TLC. So the optimization of product **3a** became the subsequent goal. Subsequently, a series of solvents was tested and no better results were obtained (entries 2-7). Furthermore, 73% yield of **3a** was isolated at ambient temperature because of the lower activity (entry 8). Further screening of the loading of aqueous HI proved that 1.5 equiv was the most effective for this transformation (entries 9-10). Afterward, 78% yield of **3a** was also obtained when HBr was used instead of HI (entry 11). However, 4-chloro-2*H*-chromene was isolated when HCl as acid promoter was used for this transformation, and no desired product **3a** was obtained (entry 12). Finally, the use of aqueous HI (1.5 equiv) in CH_2Cl_2 at 30°C was determined to be the best conditions to form 2-phenyl-4*H*-chromen-4-one.

Table 1. Optimization of the reaction for the synthesis of **3a**[a]

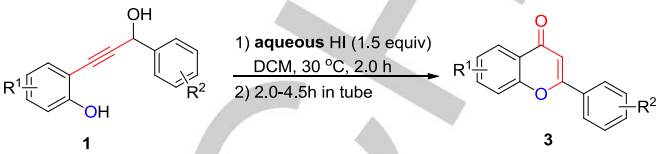


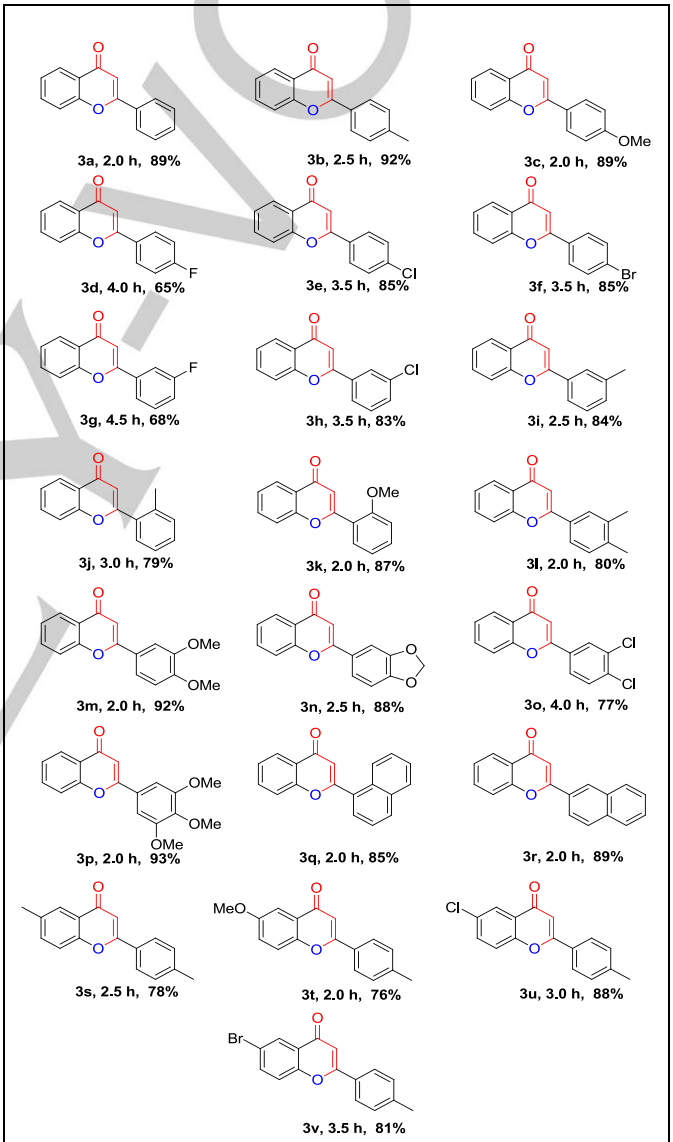
Entry	Solvent	HI (equiv)	T[ºC]	Yield[%]
1	CH_2Cl_2	1.5	30	89
2	$MeNO_2$	1.5	30	80
3	MeCN	1.5	30	78
4	DCE	1.5	30	83
5	THF	1.5	30	73
6	1,4-dioxane	1.5	30	79
7	HOAc	1.5	30	75
8[b]	CH_2Cl_2	1.5	rt	73
9	CH_2Cl_2	2.0	30	88
10	CH_2Cl_2	1.2	30	83
11[c]	CH_2Cl_2	1.5	30	84
12[d]	CH_2Cl_2	1.5	30	0

[a] Unless otherwise noted, all reactions were performed with 0.2 mmol of **1a** with aqueous HI, in solvent (2.0 mL) at 30 ºC. [b] 4.0 h. [c] HBr was used instead of HI; [d] HCl was used instead of HI.

Subsequently, various 2-propynolphenols was investigated to examine the scope of this transformation under the optimal conditions (Table 2). Generally, a number of propargylic alcohols can be successfully converted to the corresponding flavone derivatives (**3a-3s**) in good to excellent yields. Firstly, various substituted 2-propynolphenols were performed with aqueous HI to examine the electron effects of substituents. Propargylic alcohols bearing electron-rich and –poor substituents on the

Table 2. Transformation of propargylic alcohols to flavones[a]



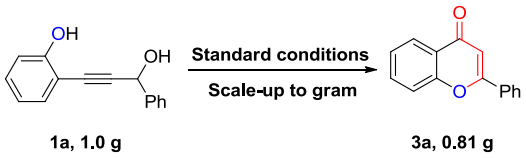


[a] Unless otherwise noted, all reactions were performed with 1 (0.2 mmol) and aqueous HI (1.5 equiv) in DCM (1.0 mL) at 30 °C for 2.0 h, and the residue was further flashed by chromatography on silica gel, which then allowed to stand for several hours in tube. Isolated yields.

aromatic ring attached to the alcohol position were compatible for this transformation, the target products were obtained in good to high yields. Various substituents, including methyl, methoxy, halogens, were tolerated at the different position of the aromatic ring. Especially, substrates with halo-substituted can proceed successfully to achieve the desired products (**3d-3h**

and **3o**), which offered an opportunity for further transformation *via* cross-coupling reactions promoting the efficient synthesis of complexes compounds. Notably, substrates with two or more substituents were also tolerated to form the desired products in good to high yields under optimal conditions (**3l-3p**). Moreover, the cascade transformation proceeds easily when the substrates with a poly-ring group, giving the target products in satisfied yields (**3q-3r**). Finally, diverse substituents such as Me, OMe, Br, and Cl at another aromatic ring could also comfortable with the optimal conditions to obtain the target products in excellent yields (**3s-3v**).

A clear merit of our established approach was that this transformation was developed through a scale-up reaction (Scheme 2); an 81% yield of desired product **3m** was obtained on the gram-scale under standard operations, which could provide a potential application value in the field of medicinal chemistry.



Scheme 2. Scale-up experiment.

To explore the reaction mechanism, the process of the reaction of 4-iodo-2-(2-methoxyphenyl)-2*H*-chromene **2k**[16] was monitored by ^{1}HNMR spectroscopy (Figure 2). The signal corresponding to the methoxy hydrogen in **3k** (**3k;** δ=3.98 in d-DMSO) appeared at 10 min after the transformation started. This signal of **3k** became strong at the end of the reaction. The consumption of **2k** and production of **3k** could be easily observed in the spectrum as the transformation proceeded. These results strongly indicated that 4-iodo-2*H*-chromene **2a** is an intermediate of this transformation. Moreover, we recorded the change process of **2k** to **3k** through the images (Figure 3). The different colours of pictures were clearly demonstrated the conversion process.

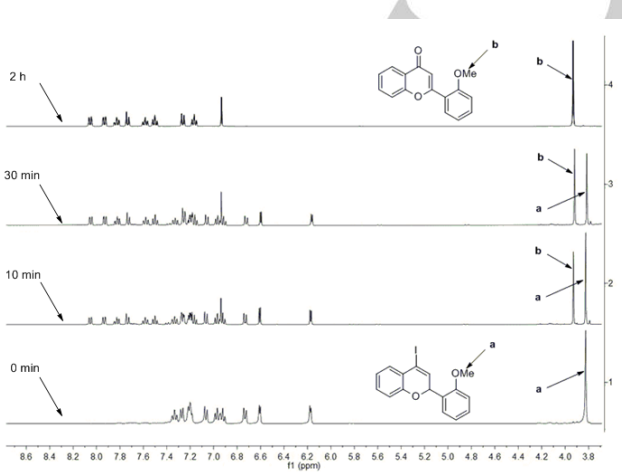


Figure 2. Reaction monitoring by NMR spectroscopy. a = methoxy group in **2k**. b = methoxy group in **3k**.

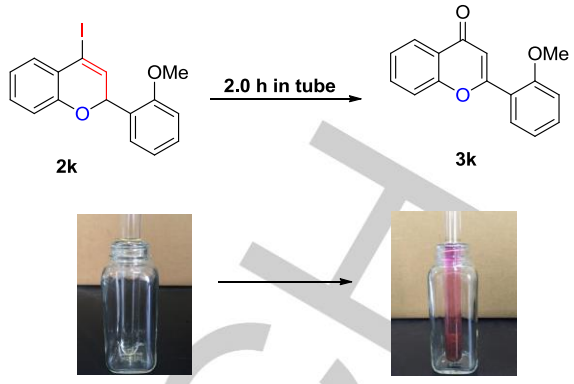
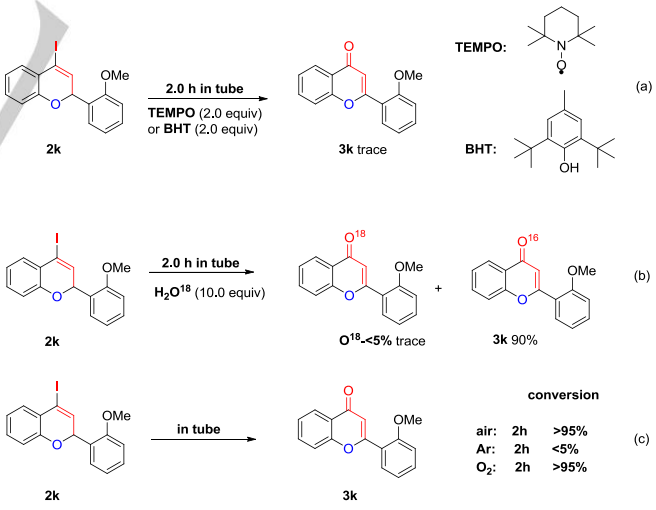


Figure 3. Reaction monitoring by precipitation phenomenon.

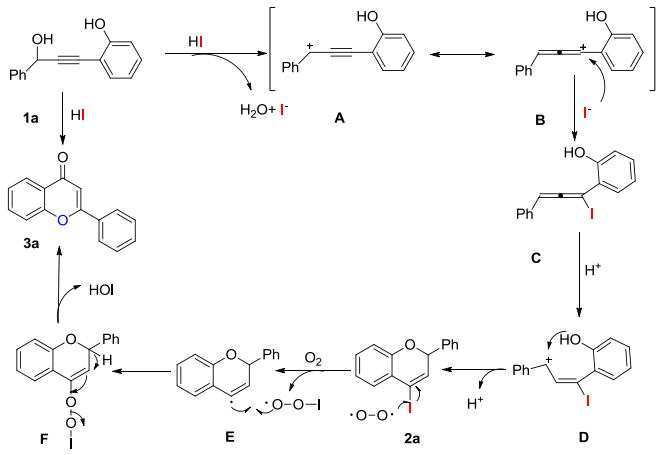
Furthermore, some experiments were performed under the controlled conditions (Scheme 3). When the radical inhibitors such as TEMPO or BHT were added to the reaction, we found that the reaction was inhibited and more than 90% of the **2k** was recovered. This result indicated that the radical intermediate may involve in this reaction (Scheme 3a). Moreover, to verity the source of oxygen atom in flavone product, H_2O^{18} (10.0 equiv) was used as additive for this reaction, only untagged product **3k** can be detected by HRMS analysis (Scheme 3b). When the reaction was performed under an air or O_2 atmosphere, over 95% of **2k** could be converted into product **3k** for 2.0 h (Scheme 3c). By contrast, a similar reaction under an argon atmosphere was difficult to be converted into product **3k**, even the reaction could not be completely transformed after 48 h (Scheme 3c). The above two results demonstrate that the oxygen atom of flavone product was probably originated from O_2.



Scheme 3. Controlled experiments.

Followed by these preliminary mechanistic studies and the previous reports,[15d],[17] a plausible mechanism of this transformation is tentatively proposed as shown in Scheme 4. The initial step involves the formation of 4-iodo-2*H*-chromene intermediate **2a** from the interaction of 2-propynolphenols **1a** with HI. Subsequently, the substitution reaction take place with oxygen radical to give vinyl radical **E**, which can be successfully

captured by peroxy radical giving intermediate **F**. Finally, the product **3a** was obtained through the elimination of HOI.



Scheme 4. Proposed mechanism

Conclusions

In conclusion, we have disclosed a cascade cyclization/oxidative radical reaction of propynols in aqueous HI-air system to construct flavones. Various flavones were formed with high yield and efficiency under mild conditions. These compounds exhibit latent pharmacologically and biologically activity. The interesting mechanistic aspects of this reaction have showed enough potential attraction for chemists working on alkynols and radical chemistry. These findings in this paper show significant progress in the synthesis of flavones and develop a new reaction strategy for investigation.

Experimental Section

Aqueous HI (1.5 equiv) was added to a solution of 2-propynolphenol **1a** (0.2 mmol) in DCM (2.0 mL), and the resulting mixture was stirred at 30°C in a sealed tube for 2.0 h. The residue was further flashed by chromatography on silica gel, which then allowed to stand for several hours in tube. The solution was evaporated under reduced pressure to afford the desired product **3a** in 89% yield.

Acknowledgements ((optional))

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Keywords: 2-propynolphenols • cascade cyclization • flavones • Brøsted acids •synthetic methods

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[16] For the preparation of **2k**: Aqueous HI (1.5 equiv) was added to a solution of 2-propynolphenol **1k** (0.2 mmol) in DCM (2.0 mL), and the resulting mixture was stirred at 30°C in a sealed tube for 2.0 h. The

residue was further flashed by chromatography on silica gel to obtain **2k**, which should be quickly analyzed by ^{1}HNMR spectroscopy.

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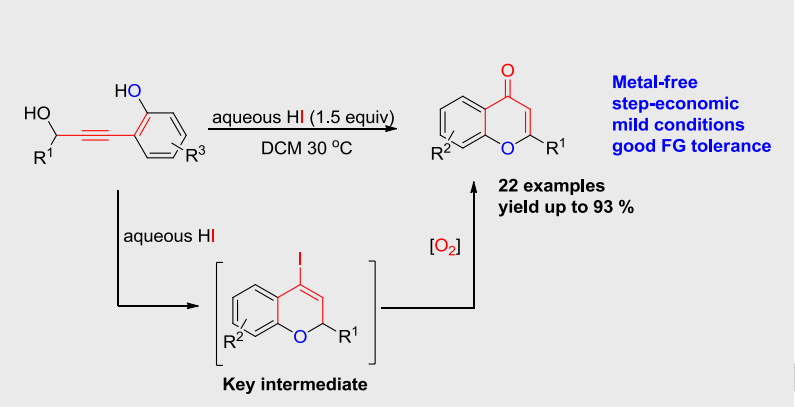

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