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Synthetic Methods

Convenient and Highly Efficient Routes to 2*H*-Chromene and 4-Chromanone Derivatives: Iodine-Promoted and *p*-Toluenesulfonic Acid Catalyzed Cascade Cyclizations of Propynols

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Abstract: A convenient strategy is presented for the easy preparation of a series of 2*H*-chromenes under mild conditions through iodocyclization of readily accessible propynols. In addition, various 4-chromanones can be synthesized through a *p*-toluenesulfonic acid catalyzed cascade cyclization with high efficiency (yields up to 99%). Our developed reaction systems are proven to have good functional-group applicability and can be scaled up to gram quantities in satisfactory yields. These systems also provide a new synthetic strategy for two types of important flavonoid skeleton without using costly and toxic metal catalysts. Additionally, the resulting halides could be further exploited in subsequent palladium-catalyzed coupling reactions, so these compounds could act as potential intermediates for the construction of some valuable drug molecules.

Introduction

2*H*-Chromene and 4-chromanone are vitally important flavonoid skeletal structures, which are found in a wide variety of natural products and pharmaceutically active molecules (Figure 1).[1] Such compounds have been identified as having antifungal, antibacterial, antiviral, anti-inflammatory, anticancer, antidepressive, antihypertensive, antidiabetic, and antioxidant activities.[2,3] They are also valuable intermediates in synthetic and material chemistry.[2h,4,5] Due to the outstanding physiological and pharmaceutical activities of these compounds, as well as their important position in synthetic chemistry, the advancing aspirations of scientists and interest in new routes to construct benzopyran and benzopyrone rings systems further stimulates studies in this area. The well-known synthetic route to 2*H*-chromenes is by the cyclization of substituted phenolic propargyl ether compounds,[6] whereas the classical methods for preparing 4-chromanones involve the condensation cyclization of carbonyl compounds with *o*-hydroxyacetophenones[5b,7] and the addition reaction to 4*H*-chromen-4-ones.[8] With the persistent efforts of many chemists, adequate evolutions have been

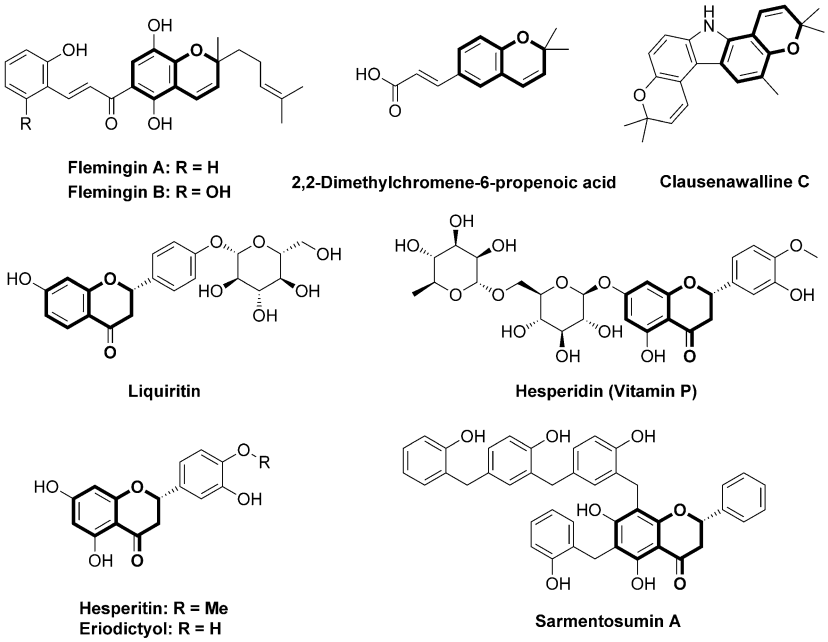

Figure 1. Representative bioactive natural products possessing 2*H*-chromene or 4-chromanone moieties.

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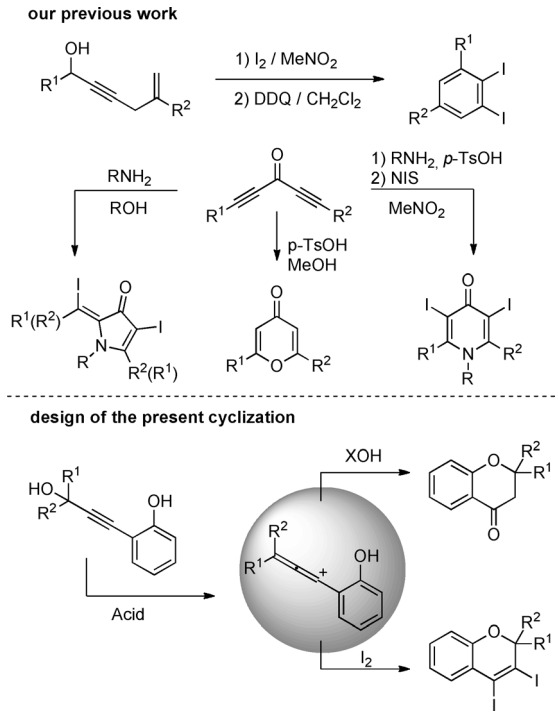
achieved on the synthesis of both types of essential molecular scaffolds.[2f–i, 3a,e,f, 9, 10] Nevertheless, the development of efficient and straightforward methods in a simple operation and under mild conditions is still fueled by the strong and growing aspiration for such processes in most areas of chemical synthesis.

It is known that the status of cascade cyclization as a powerful and ingenious strategy for the synthesis of cyclic compounds is irreplaceable. Herein, iodocyclization shows undeniable benefits in most cases, including being metal-free, having mild conditions, having the potential for further exploitation, and providing economies of time, labor, and cost,[11] whereas Brønsted acids, as budget and green catalysts, have emerged as valuable tools for the generation of carbo- and/or heterocyclic skeletons with unmatched advantages.[12] Alkynols, as interesting and important starting materials with two mutual activated functional groups, have become star molecules in synthetic methodology.[13] In the past few years, our group has successfully developed a series of efficient methods for the synthesis of carbo- and/or heterocyclic building blocks through cascade iodocyclization[11] and Brønsted acid catalyzed cyclization with various alkynols (or alkynones) as the starting materials.[14] By taking into consideration our current interest in new approaches to cyclic skeletons with atom economy, as well as the continued advancement of green chemistry, we designed an iodocyclization and a Brønsted acid catalyzed cascade cyclization for the synthesis of 2*H*-chromene and 4-chromanone derivatives by using various propynols as the substrates (Scheme 1). Herein, different products derived from the same starting materials are observed under diverse reaction systems. Relative to the traditional strategies, our developed reaction systems could be conveniently operated and avoid inert-gas protection or toxic transition-metal catalysts, which may open up a new potential application for these systems in industrial production.

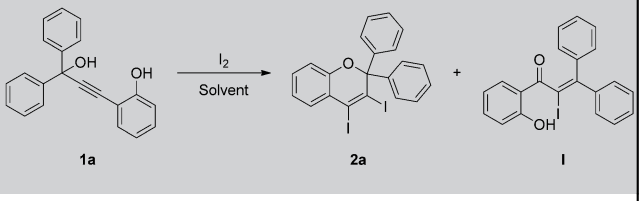


Scheme 1. Our previous work and new anticipation towards the synthesis of 2*H*-chromene and 4-chromanone derivatives. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; NIS: *N*-iodosuccinimide; *p*-TsOH: *p*-toluenesulfonic acid.

Results and Discussion

The initial exploration for the synthesis of 2*H*-chromenes was started by employing compound **1a** (0.1 mmol) as the model substrate with iodine (2.0 equiv) in MeCN (2.0 mL) at 60 °C (Table 1, entry 1). To our delight, our anticipated product, 3,4-diiodo-2,2-diphenyl-2*H*-chromene (**2a**), was isolated in 79%. However, no better results were obtained after a brief survey of various representative solvents (Table 1, entries 2–7). Lowering of the temperature led to a higher yield of 90% (Table 1 entry 8). We believe that the higher temperature was advantageous to the generation of the iodo Meyer–Schuster rearrangement by-product. Other adjustments indicated that the most appropriate amount of iodine was 1.2 equivalents, which gave 98% yield (Table 1, entries 8–10). Afterwards, 95% yield of **2a** was achieved at 0 °C due to the relatively lower activity, as expected (Table 1, entry 11). Finally, the optimal reaction conditions for producing **2a** were affirmed as the use of iodine (1.2 equiv) in MeCN (2.0 mL) at room temperature for 0.5 h (Table 1, entry 9; conditions A).

Table 1. Optimization of the iodocyclization for the synthesis of **2a**[a]



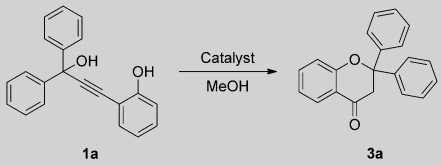
1a 2a I

Entry	Solvent	I_2 [equiv]	*T* [°C]	Yield [%][b]
1	MeCN	2.0	60	79
2	$MeNO_2$	2.0	60	45
3	1,2-DCE[c]	2.0	60	61
4	toluene	2.0	60	N.R.[d]
5	THF	2.0	60	62
6	DMSO	2.0	60	trace[e]
7	1,4-dioxane	2.0	60	trace[f]
8	MeCN	2.0	RT	90
9	**MeCN**	**1.2**	**RT**	**98**
10	MeCN	1.0	RT	93
11	MeCN	1.2	0	95

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) with I_2 in anhydrous solvent (2.0 mL) under an air atmosphere for 0.5 h. [b] Yields of isolated products. [c] 1,2-DCE: 1,2-dichloroethane. [d] N.R.: no reaction. [e] 79% of 1-(2-hydroxyphenyl)-2-iodo-3,3-diphenyl-prop-2-en-1-one was detected. [f] 71% of **1a** was recovered.

To verify our concept of the Brønsted acid catalyzed cascade cyclization for the generation of 4-chromanones, *p*-TsOH (10 mol%) was used as the catalyst to initiate a tentative inquiry in a solution of **1a** (0.1 mmol) and MeOH (2.0 mL) at room temperature. Only 36% of **3a** and 59% of 1-(2-hydroxy-

Table 2. Optimization of the cascade cyclization for the synthesis of **3a**[a]



Entry	Catalyst [mol%][b]	T [°C]	Yield [%][c]
1	*p*-TsOH [10]	RT	36[d]
2	*p*-TsOH [10]	80	92
3	TfOH [10]	80	92
4	MsOH [10]	80	89
5	TFA [10]	80	83
6	HI [10][e]	80	76
7	$H_2C_2O_4{\cdot}2H_2O$ [10]	80	61
8	$Sc(OTf)_3$ [10]	80	88
9	$Bi(OTf)_3$ [10]	80	91
10	$Zn(OTf)_2$ [10]	80	72
11	$FeCl_3$ [10]	80	89
12	*p*-TsOH [10]	70	99
13	*p*-TsOH [10]	60	88[f]
14	***p*-TsOH [5]**	**70**	**99**
15	*p*-TsOH [2]	70	93

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) with Brønsted or Lewis acids in methanol (2.0 mL) under an air atmosphere for 4.0 h. [b] *p*-TsOH: *p*-toluenesulfonic acid; TfOH: trifluoromethanesulfonic acid; MsOH: methylsulfonic acid; TFA: trifluoroacetic acid; OTf: trifluoromethanesulfonate. [c] Yields of isolated products. [d] 59% of the intermediate 1-(2-hydroxyphenyl)-3,3-diphenylprop-2-en-1-one was detected after 48.0 h. [e] An aqueous solution of 45% HI was used. [f] 12% of intermediate was detected.

phenyl)-3,3-diphenylprop-2-en-1-one (intermediate **F** in Scheme 5) without further cyclization came under observation (Table 2, entry 1). Therefore, the temperature was raised to 80 °C to facilitate the cyclization process, which gave an excellent yield of 92% (Table 2, entry 2). After subsequent optimization experiments with a series of Brønsted and Lewis acids, TfOH and $Bi(OTf)_3$ were found to be the best two and gave similar satisfactory yields (Table 2, entries 3–11). Given the operational convenience and the demand for green chemistry, *p*-TsOH was finalized as the most efficient and outstanding catalyst. Ultimately, the followed screening of the reaction temperature and catalyst loading (Table 2, entries 12–15) settled the optimal conditions for the generation of **3a** as the addition of *p*-TsOH (5 mol%) to a solution of **1a** (0.1 mmol) and MeOH (2.0 mL) at 70 °C for 4.0 h (Table 2, entry 14; conditions B).

A series of substituted alkynol substrates, including tertiary (**1a**–**1t**, and **1z**) and secondary propynols (**1u**–**1y**), were prepared to investigate the scope of the cascade iodocyclization. The corresponding 2*H*-chromene derivatives **2a**–**2y**, **2a′** and **2a″** were obtained in moderate to excellent yields under conditions A (Table 3). The structure of **2s** was confirmed by X-ray crystal structure analysis (Figure 2).[15] The influence of substituent electronic effects on the reaction made little difference for substituents R^1 and R^2; in general, tertiary propynols with two aryl groups gave good yields (**2a**–**2r**), whereas decreased yields were observed with secondary propynols (**2u**–**2y**). We believe that two aryl groups would be much more effective for the stability of intermediates **A** and **B** (see Scheme 5). Furthermore, substrates bearing alkyl groups worked passably for this transformation (**2s** and **2t**). Despite the fact that only a trace amount of **2z**, with two *o*-methoxyphenyl groups, was observed due to the combined impact of the particularly strong electron-donating and steric effects, 52% of **2h** was still achieved with one substituent replaced by a phenyl group. In this reaction, we observed that more of the iodo Meyer–Schuster rearrangement product was generated. Notably, the transformation proceeded smoothly for the substrates with a multiple-ring group (2-naphthyl group in **1n**) or a heterocyclic group (2-thienyl group in **1o**). Substrates with diverse substituents as the R^3 group could also be converted into the corresponding products in good yields (**2p**–**2r**). The final concern was that the reaction system still worked smoothly with other iodination reagents; 89 and 77% yields of the corresponding products were obtained in the presence of ICl and IBr, respectively, which provided another diversified selectivity for further transformations through coupling reactions (**2a′** and **2a″**). The structure of **2a″** was also confirmed by X-ray crystal structure analysis (Figure 2).[15]

The diversity and applicability of the *p*-TsOH-catalyzed cascade cyclization for the synthesis of 4-chromanone derivatives were also surveyed with the same substrates. Gratifyingly,

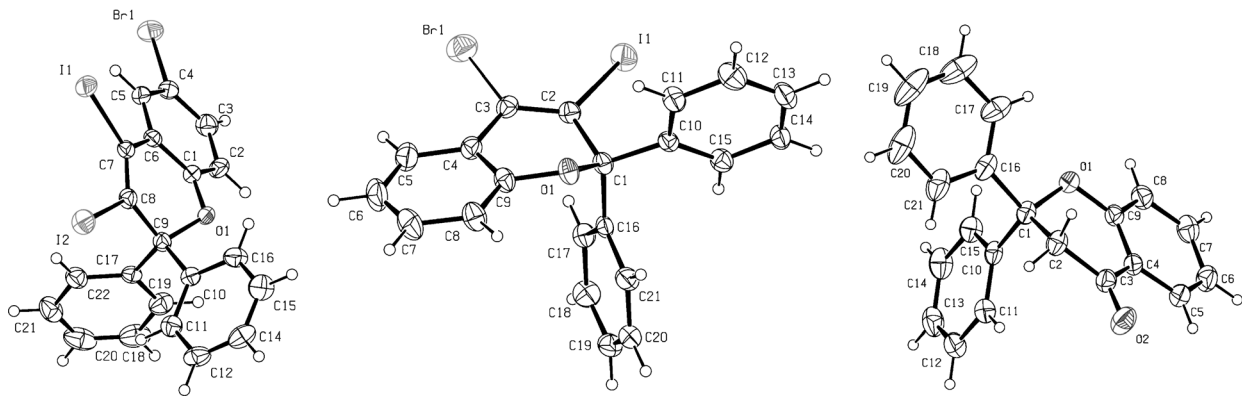
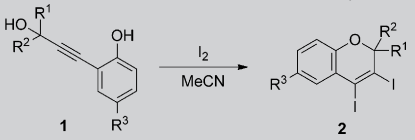
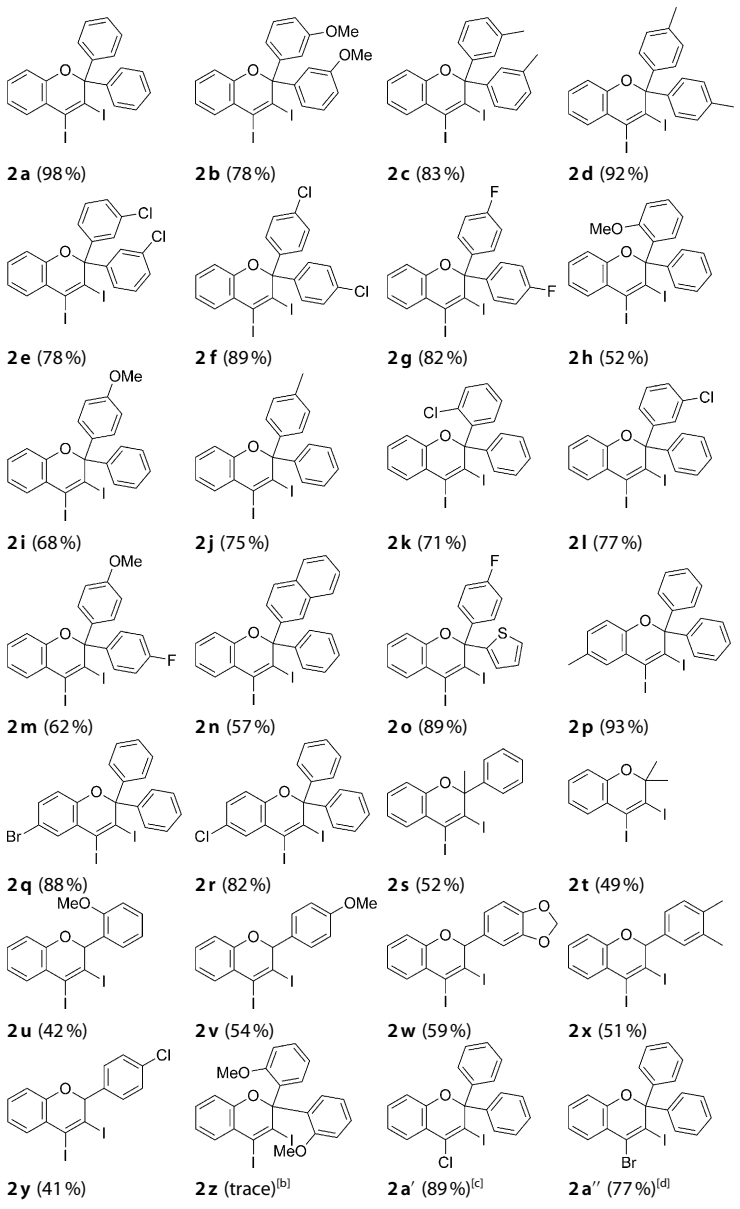


Figure 2. X-ray structures of **2s**, **2a″**, and **3a**.[15]

Table 3. Synthesis of 2*H*-chromene derivatives **2** from propynols **1**.[a]





[a] Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) with I_2 (1.2 equiv) in anhydrous MeCN (2.0 mL) under an air atmosphere at room temperature for 0.5 h. Yields are given for isolated products. [b] 85% of the iodo Meyer–Schuster rearrangement product was detected. [c] A solution of iodine chloride in dichloromethane (1 mol L^{-1}) was used instead of iodine. [d] Iodine bromide was used instead of iodine.

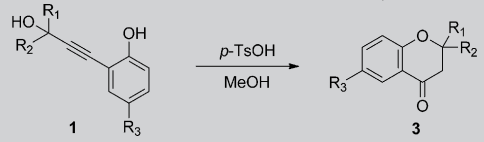
various substituted 4-chromanones were isolated in moderate to excellent yields under conditions B (Table 4). The structure of product **3a** was confirmed by X-ray crystal structural analysis (Figure 2).[15] This reaction seemed to be more distinct and sensitive to substituent electronic effects than the above iodocyclization: substrates with electron-deficient moieties on phenyl groups and unsubstituted phenyl groups as the substituents R^1 and R^2 gave excellent yields up to 99%, whereas slightly lower yields were obtained with electron-rich moieties (**3a**, **3e**–**3g**, and **3l** versus **3b**–**3d** and **3h**–**3j**). We were convinced that electron-deficient moieties on phenyl groups (R^1 and R^2) could be beneficial for the attack of the phenolic hydroxy group onto the double bond of intermediate **F** (see Scheme 5). Similarly, substrates with alkyl groups instead of aryl groups still gave acceptable yields (**3s** and **3t**). It was an unfortunate fact that substrate **1z** still worked imperfectly in this reaction system: 87% of the intermediate for **1z** was isolated without further cyclization, whereas 78% of product **3h** was obtained with an *o*-methoxyphenyl group. The reaction performed well with secondary propynols **1u**–**1y**, which gave moderate to good yields under conditions B. It is worth noting that 94% of **3n**, with the 2-naphthyl group, was isolated in this transformation. This reaction could also be performed with a 2-thienyl group as the R^1 substiuent in a high yield of 88% (**3o**). The yield of substrates with representative R^3 substituents seems to be good as well, including electron-rich (methyl-substituted, **3p**) and electron-deficient groups (chloro- and bromo-substituted, **3q** and **3r**).

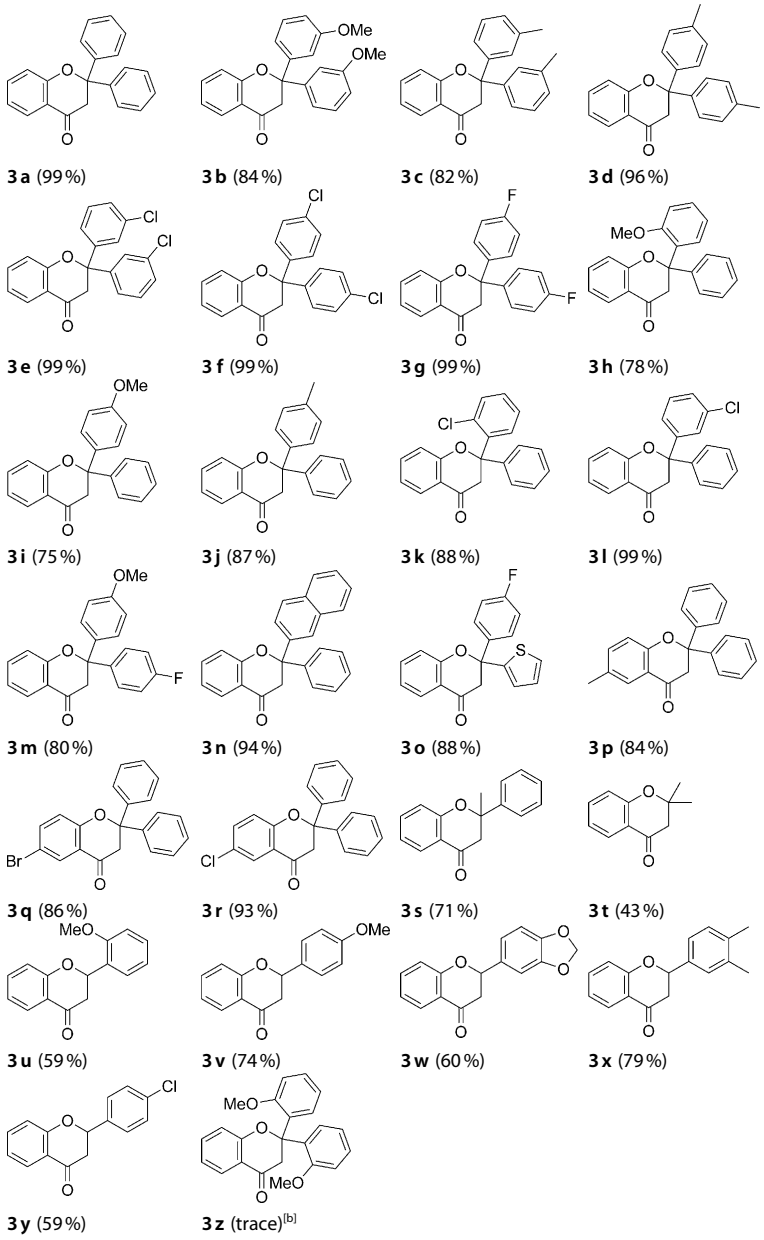
A noteworthy advantage of our methods was that both reaction systems could be scaled up to gram quantities; 89% of 3,4-diiodo-2,2-diphenyl-2*H*-chromene (**2a**) and 92% of 2,2-diphenylchroman-4-one (**3a**) were isolated on the gram scale under the respective optimal conditions, which might provide a potential application for this method in the synthetic industry (Scheme 2).

Another obvious feature of iodocyclization was that the iodosubstituted 2*H*-chromenes might be advantageous intermediates for the synthesis of some natural products through various palladium-catalyzed reactions. As an example, the Suzuki coupling of **2a** with a variety of phenylboronic acids afforded the corresponding derivatives (**2aa**–**2ae**) in good to excellent yields (Scheme 3).

In order to investigate the mechanism for both reactions, some necessary control experiments were carried out. First of all, as depicted in Table 3, with the addition of ICl or IBr, the corresponding products **2a′** and **2a″** were obtained in 89 and 77% yields, respectively. With the confirmation of the structure of **2a″** by X-ray crystal structure analysis,[15] the sources and properties of the two iodine atoms in products **2** were demonstrated unequivocally. For the *p*-TsOH-catalyzed cascade cyclization for the synthesis of 4-chromenones, compound **F** (see Scheme 5) was captured and isolated in the presence of *p*-TsOH (5 mol%) in MeOH (2.0 mL) at room temperature for 4.0 h. Interestingly, compound **F** could be isolated in the same yield even after 48.0 h (Scheme 4, eq. 1). Isolated compound **F** was then subjected to conditions B, and product

Table 4. Synthesis of 4-chromanone derivatives **3** from propynols **1**.[a]





[a] Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) with *p*-TsOH in methanol (2.0 mL) under an air atmosphere at 70 °C for 4.0 h. Yields are given for isolated products. [b] 87% of 1-(2-hydroxyphenyl)-3,3-bis(2-methoxyphenyl)prop-2-en-1-one was isolated.

3a was obtained in 92% after 4.0 h (Scheme 4, eq. 2). In addition, direct heating of the original reaction system could give product **3a** in 96% yield (Scheme 4, eq. 3). Therefore, compound **F** was determined to be the intermediate of the above reaction. Furthermore, after consulting our previous work,[14] we believe that the oxygen atom of the carbonyl group in **3a** probably might come from the initial intramolecular dehydration of substrate **1a**. To verify this assumption, heavy-oxygen water (2.0 equiv) was added to the reaction system together with the catalyst, and a mixture of ^{18}O-tagged and untagged product **3a** could be simultaneously detected by GC-MS analysis, which indicates that this transformation could go through a Meyer–Schuster rearrangement process (Scheme 4, eq. 4).

The plausible mechanisms that are consistent with the experimental results mentioned above and the precedent literature[11,16] are proposed in Scheme 5. In fact, the propargyl hydroxy group of substrate **1a** is initially activated by an iodine cation (or proton) and generates propargylic cation **A**, which would undergo a subsequent tautomerism to generate the allenic cation **B**.[11,13d,e] The attack of iodide (or water) onto **B** affords **C** (or **E**). The interaction of **C** and an iodine cation then gives iodonium cation **D**, which is attacked by the phenolic hydroxy group to produce iodo-2*H*-chromene **2a**. Intermediate **E** undergoes a keto–enol tautomerization to afford **F**.[14,16] A subsequent endo attack of the intramolecular phenolic hydroxy group onto the carbon–carbon double bond generates 4-chromanone **3a**. The attack of iodide onto **E** generates the main by-product **I**.

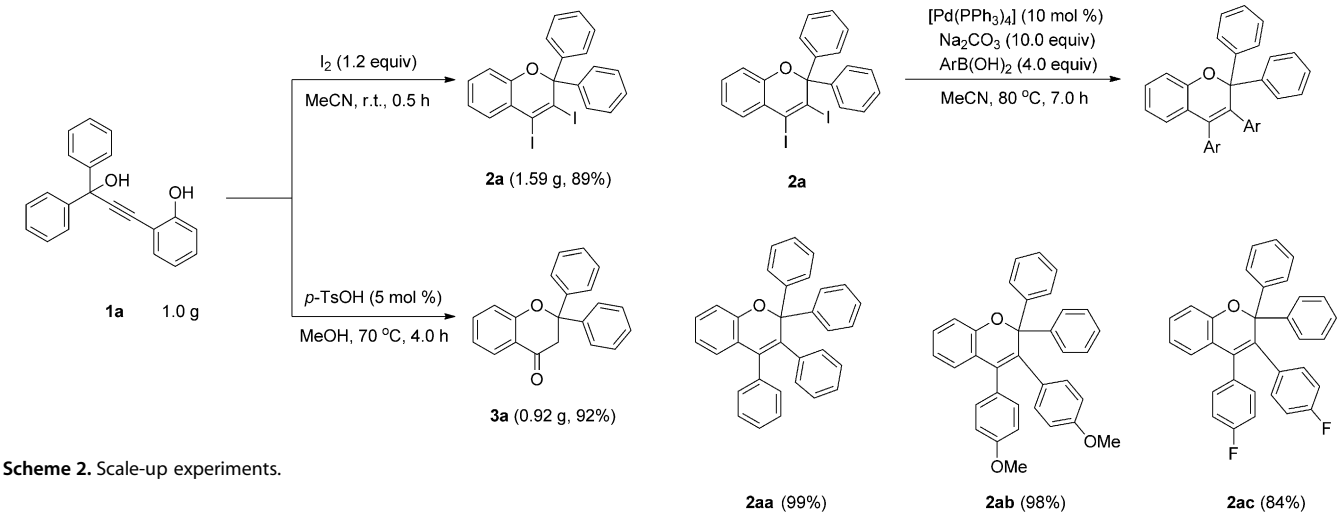
Conclusion

To sum up, we have disclosed a direct and convenient cascade iodocyclization and Brønsted acid catalyzed cascade cyclization for the synthesis of two types of important flavonoid skeletons. The respective processes enable a highly efficient protocol for preparing various 2*H*-chromenes or 4-chromanones from easily prepared propynols. As different nucleophiles, diverse reagents were employed to facilitate cyclization with excellent yields of up to 99%. Compared to transition-metal-catalyzed reactions, our developed reaction systems are equipped with obvious advantages for the continued increasing requirements of atom economy and green chemistry. In addition, the synthetic utility of both reaction systems has been demonstrated by their applicability to a wide range of propynol substrates and a large reaction scale for potential applications in industrial production.

Experimental Section

General procedure for the synthesis of product 2a

Iodine (1.2 equiv) was added to a solution of 2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)phenol (**1a**; 0.1 mmol) in anhydrous MeCN

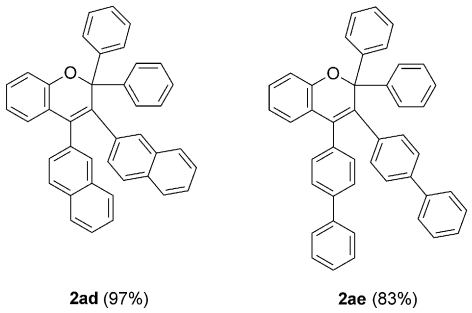


Scheme 2. Scale-up experiments.

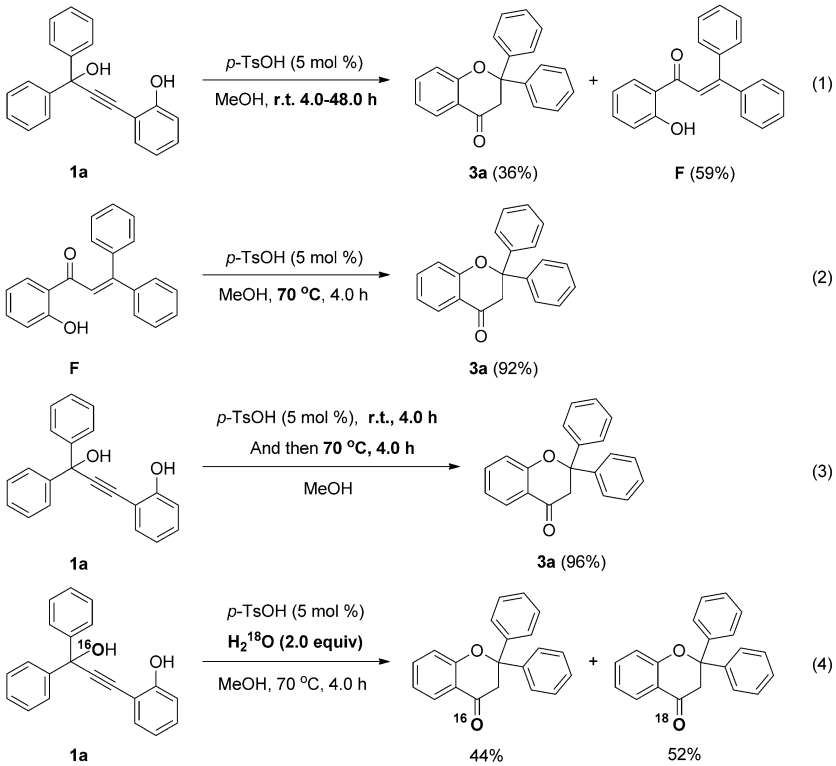
(2.0 mL), and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was then diluted with ethyl ether (2×15 mL), washed with a saturated aqueous solution of sodium thiosulfate and saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was further purified by chromatography on silica gel (petroleum ether/ethyl acetate, 30:1) to afford the product 3,4-diiodo-2,2-diphenyl-2*H*-chromene (**2a**) in 98% yield.

General procedure for the synthesis of product 3a

p-TsOH (5 mol%) was added to a solution of 2-(3-hydroxy-3,3-diphenylprop-1-yn-1-yl)phenol (**1a**; 0.1 mmol) in MeOH (2.0 mL), and the resulting mixture was stirred at 70 °C in a sealed tube for 4.0 h. The reaction mixture was then diluted with ethyl ether (2×15 mL), washed with a saturated aqueous solution of sodium bicarbonate and saturated brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was further purified by chromatography on silica gel (petroleum ether/ethyl acetate, 50:1) to afford the product 2,2-diphenylchroman-4-one (**3a**) in 99% yield.



Scheme 3. Palladium-catalyzed Suzuki coupling reactions and the products



Scheme 4. Verification experiments for the mechanisms.

Acknowledgements

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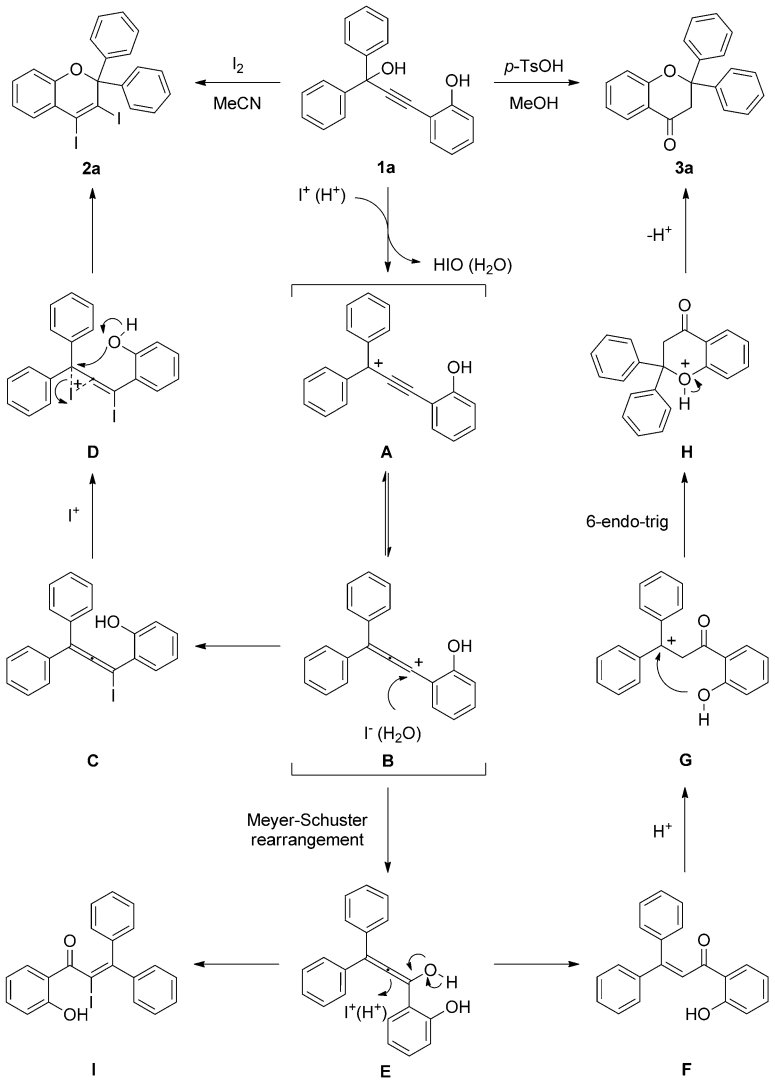

Scheme 5. Proposed mechanisms.

Keywords: Brønsted acids · cyclization · flavonoids · iodine · propynols · synthetic methods

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[15] CCDC 1030410(**2 s**), 1030411(**2 a**′′), and 1030409(**3 a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif.

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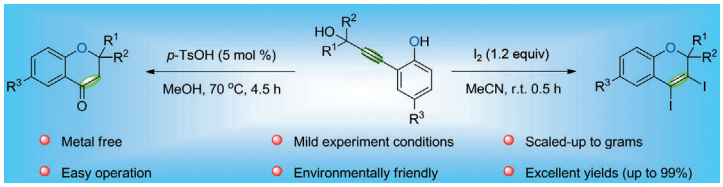

A better route: Convenient and highly efficient strategies are presented for the easy preparation of 2*H*-chromenes and 4-chromanones through iodocyclization and *p*-toluenesulfonic acid (*p*-TsOH) catalyzed cascade cyclization of readily accessible propynols (see scheme). The developed systems have good functional-group applicability, can be scaled up to gram quantities in satisfactory yields, and provide a new synthetic strategy for two types of important flavonoid skeleton without using costly and toxic metal catalysts.

Synthetic Methods

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Convenient and Highly Efficient Routes to 2*H*-Chromene and 4-Chromanone Derivatives: Iodine-Promoted and *p*-Toluenesulfonic Acid Catalyzed Cascade Cyclizations of Propynols