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COMMUNICATION

A Cascade Claisen Rearrangement/*o*-Quinone Methide Formation/Electrocyclization Approach to 2*H*-Chromenes

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A new approach has been developed for the synthesis of 8-substituted *2H*-chromenes, featuring a novel cascade aromatic Claisen rearrangement/o-quinone methide formation/6π-electrocyclization. This new method was demonstrated with 28 examples tolerating different substitution at alkenes, allylic and aromatic ring and with total syntheses of three *2H*-chromene natural products.

2*H*-chromenes (2*H*-1-benzopyrans) are very important structural units of and building blocks for many pharmaceutically significant compounds and biologically active natural products[1] (Figure 1). They have attracted great interest in the field of organic synthesis to develop new and improved synthetic methods.[2] Among all the methods of the myriad, 6π-electrocyclization[3] (6π-EC) involving *ortho*-quinone methide (*o*-QM) intermediates provides a rapid access to the privileged functionalized 2*H*-chromenes.[4] The *in situ* generation of the non-isolable reactive *o*-QMs is key to this process and can be promoted by various methods such as thermolysis, oxidation, acid- or base-promoted β-elimination, and photolysis.[5]

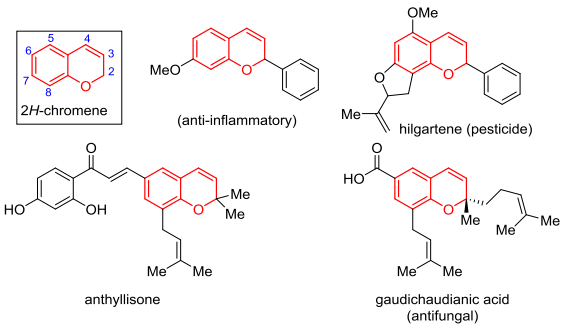
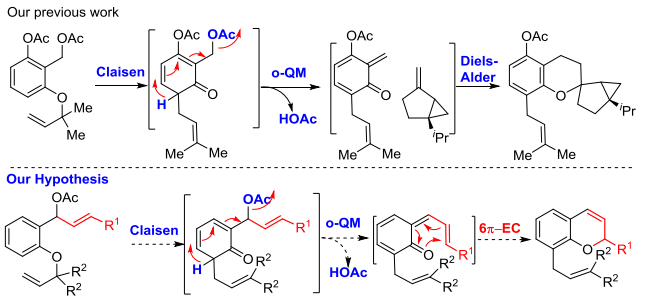


Figure 1. Selected compounds containing 2*H*-chromene motif.

All these methods share a common feature: loss of small molecules ("H-H", H_2O, MeOH, HOAc, HNR_2, *etc.*) to *in-situ* generate *o*-QMs. We conceived that if the loss of these small molecules could not only generate *in-situ* *o*-QMs for subsequent 6π-EC but also form a new C-C bond, a new cascade approach involving one C-C bond and one C-O bond formations might be developed to provide the 2*H*-chromenes with aromatic substitutions.

Recently, we reported a new cascade reaction for the synthesis of spirooliganones A and B.[6] The key cascade process was believed to involve aromatic Claisen rearrangement, *in situ* generation of *o*-QM intermediate via 1,6-elimination of HOAc and intermolecular hetero-Diels-Alder reaction[7] (Scheme 1). We hypothesized that if an alkenyl group was pre-installed, a new cascade involving Claisen rearrangement/*o*-QM formation/6π-electrocyclization would deliver 2*H*-chromenes with a variety of substitution at C2 and the versatile allyl substitution at C8, which have rarely been addressed by prior synthetic methodologies. Importantly, if this idea works, it not only constitutes a new synthetic method for the important 8-substituted 2*H*-chromenes (*eg.* anthyllisone[8] and gaudichaudianic acid,[9] Figure 1), but also provides experimental evidence that supports our previously reported mechanistic hypothesis of the cascade process. Herein, we describe the development of this new cascade process for the synthesis of 8-substituted 2*H*-chromenes and its application to total synthesis of three 8-substituted 2*H*-chromene natural products.



Scheme 1. Our Hypothesis of Cascade Approach to 2*H*-Chromenes

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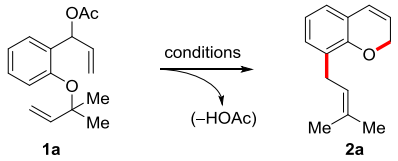
Our studies began with examination of the heating conditions to initiate the proposed cascade process using compound **1a** as the model substrate (the synthesis of **1a** was provided in ESI). A survey of different solvents was firstly conducted and both xylene and 1,2-dichlorobenzene (DCB) were found to be suitable (entries 1-4), probably owing to their high boiling points required for the thermo-promoted reaction. The concentration had a slight influence on the reaction yield (entries 5-7) and 0.02 M in xylene would give the highest yield (86%) and will be used in subsequent studies. Finally, we attempted to add a base to alleviate the acidity of the reaction (the acetic acid generated stoichiometrically might limit the substrate scope and potential applications) and accelerate the elimination of HOAc. Surprisingly, we found that either organic or inorganic base was detrimental to the reaction (entries 8-10). In addition, all Lewis acids as possible catalysts to lower the reaction temperature were found to result in decomposition (entries 11-15).

Table 1. Optimization of the cascade reaction of **1a** to 2*H*-chromene (**2a**)[a]



1a **2a**

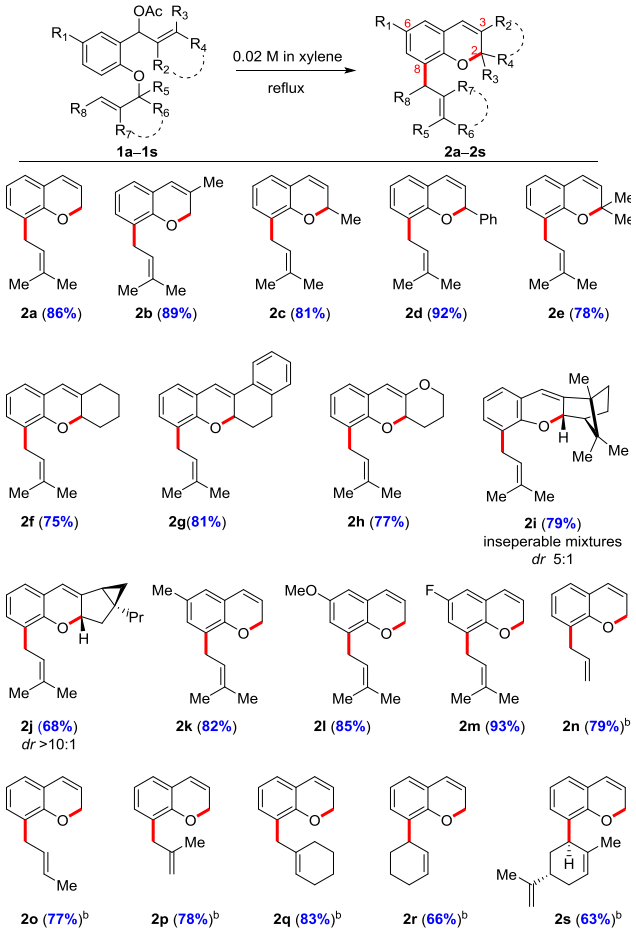
entry	conditions	yield (%)[b]
1	0.05 M, benzene, reflux	trace
2	0.05 M, toluene, reflux	15
3	0.05 M, 1,2-dichlorobenzene, reflux	80
4	0.05 M, xylene, reflux	83
5	0.1 M, xylene, reflux	76
6	0.02 M, xylene, reflux	86
7	0.01 M, xylene, reflux	84
8	0.02 M, xylene, reflux, 2 eq. $NaHCO_3$	-[c]
9	0.02 M, xylene, reflux, 2 eq. py.	-[c]
10	0.02 M, xylene, reflux, 2 eq. 2,6-lutidine	-[c]
11	0.02 M, benzene, rt → reflux, 0.2 eq. AgOTf	-[c]
12	0.02 M, benzene, rt → reflux, 0.2 eq. $SnCl_4$	-[c]
13	0.02 M, benzene, rt → reflux, 0.2 eq. $TiCl_4$	-[c]
14	0.02 M, benzene, rt → reflux, 0.2 eq. BF_3-Et_2O	-[c]
15	0.02 M, benzene, rt → reflux, 0.2 eq. $Sc(OTf)_3$	-[c]

Note: [a] Reaction conditions: **1a** (0.2 mmol), solvent, nitrogen atmosphere, 30 min. [b] Isolated yields based on **1a**. [c] Decomposition.

With the optimized conditions in hand, the substrate scope was then examined and presented in Table 2. A series of substrates (**1a—1s**) were prepared by using the modified literature protocols.[10] Notably, some substrates (acetates) were unstable for purification by flash chromatography on silica gel and would decompose completely overnight even when stored in the refrigerator.In such cases, the corresponding acetates were freshly prepared and used for the cascade reactions (see ESI for details).

As depicted in Table 2, C2- (and C3-) substituted 2*H*-chromenes (**2b–2j**) could be efficiently prepared by using the cascade reaction from **1b–1j** bearing different substituents (R_2, R_3, and R_4) on the $\Delta^{2,3}$ alkene in 68-92% yields. Interestingly, the cascade reaction of the substrates containing a cyclic $\Delta^{2,3}$ alkene (**1f–1j**) afforded polycyclic 2*H*-chromenes (**2f–2j**) in good yields with good to excellent diastereoselectivies (**2i** and **2j**). The relative stereochemistry was established either by 2D NOESY or nuclear Overhauser enhancement (NOE) experiments. Notably, the relatively sensitive enol ether and cyclopropane mioety (**2h** and **2j**) survived in our cascade protocol. The electron-rich and electron-withdrawing substituents (R_1) on the aromatic ring had little effect on the reaction yields, delivering the corresponding 2*H*-chromenes (**2k–2m**) in good to excellent yields.

Table 2. Substrate scope of the cascade reaction to 2*H*-chromenes



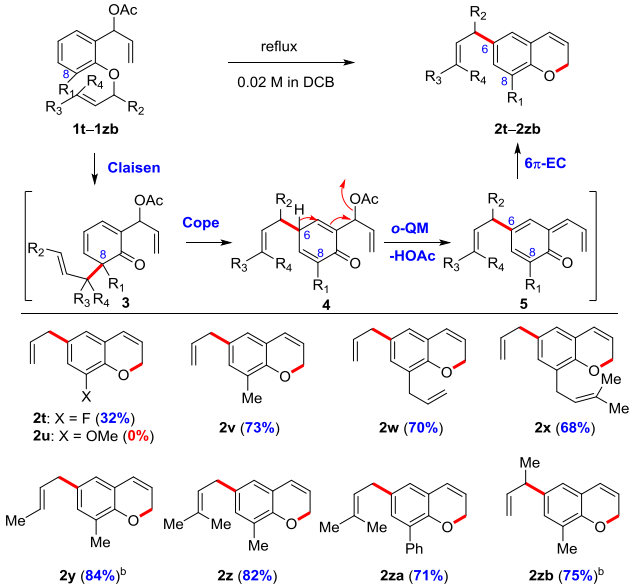
[a]Reaction conditions: **1** (0.2 mmol), xylene (10 mL), nitrogen atmosphere, reflux, 30 min. Isolated yields are shown. [b]1,2-dichlorobenzene as the solvent.

The R_5–R_7 substitution on the allyl groups did not erose the cascade reaction yields of 2*H*-chromenes (**2a**, **2n–2q**). However, lower yields were observed when R_8 was not hydrogen (**2r–2s**), which might be attributed to the negative steric effect on Claisen rearrangement. It was noted that **2s** was generated in a stereospecific fashion, consistent with the high stereocontrol of Claisen rearrangement.[11] The alkene geometry of **2o** was determined by the large coupling

constant of the *trans*-alkene protons, while the relative stereochemistry of **2s** was assigned by NOE experiments.

In order to further expand the substrate scope and provide an expedite access to aromatic C6 substituted 2*H*-chromenes, we hypothesize that if there was a non-hydrogen substituent at C8, the *para* Claisen rearrangement[11] (or Claisen-Cope rearrangement) might occur and the subsequent 1,4-elimination of HOAc would generate the requisite *o*-QM for the 6π-electrocyclization, providing otherwise poorly accessible 2*H*-chromenes with substitutions at both C6 and C8. To test this idea, we synthesized a small series of substrates (**1t**—**1zb**) with C8 substitution and examine the cascade process. It was found that the nature of the C8 substituent would have a significant influence on the reaction. For example, the cascade reaction of compounds **1t** and **1u** with fluoride and methoxy at C8 gave **2t** and **2u** in 32% and 0% yield, respectively, while substrates (**1v**—**1zb**) with the carbon-based substituents

Scheme 2. New cascade involving *para*-Claisen rearrangement/*o*-quinone methide formation/6π-electrocyclization.

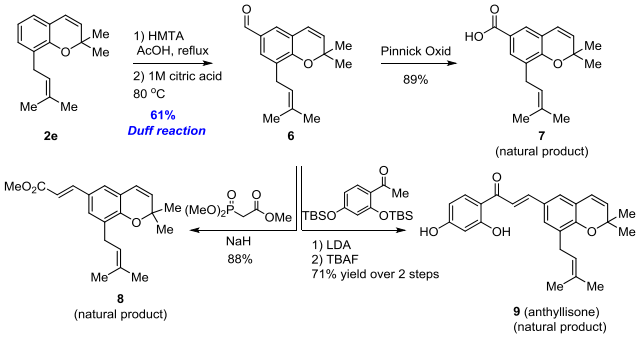


[a] Reaction conditions: **1** (0.2 mmol), 1,2-dichlorobenzene (DCB, 10 mL), nitrogen atmosphere, reflux, 30 min; isolated yields are shown. [b] Containing inseparable impurities.

(methyl, allyl and phenyl) at C8 underwent smoothly the cascade reaction in *2H*-chromenes (**2v**—**2zb**) with excellent yields. It was noteworthy that **2x** exhibited abnormal chemoselectivity because the allyl group, not the pre-installed prenyl group at C8, participated the second Cope rearrangement (**3** → **4**). This was unusual to our mechanistic understanding. In addition, the *para*-Claisen rearrangement was stereospecific as evidenced by the formation of **2y**—**2zb** from the corresponding substrates with *E*-crotyl group (**1y**), prenyl group (**1z**, **1za**) and even 1-methyl allyl group (**1zb**). Note: *ca.* 10% unidentified impurities could not be separated from **2y** and **2zb**, although many efforts had been made.

Finally, we would like to demonstrate the utility of this new cascade process by the total syntheses of three 2*H*-chromene-containing natural proudcts **7**–**9**. Natural product 2*H*-chromene **7** was isolated in 1993 from *Piper aduncum* and exhibited antimicrobial and molluscicidal activities;[12] while **8** was obtained from the aerial parts of *Werneria stuebelii.*[13] Total synthesis of **8** was elegantly achieved by Stratakis and co-workers in 2011.[2o] Anthyllisone (**9**) was isolated in 1996 from *Anthyllis hermanniae*[8] and Jun reported the total synthesis of anthyllisone in 2016. Interestingly, Jun and co-workers found that **9** showed potent *anti*-inflammatory activity without cytotoxicity.[14] The potent and promising biological acivities of these *2H*-chromene natural products prompted us to undertake their total synthesis (Scheme 3). Herein, we proposed a collective synthesis of **7**–**9** from a common intermediate **2e**, which was obtained by our new cascade approach on a 2.0 mmol scale with comparable 71% yield. Initial attempt to formylation of **2e** by Vilsmeier-Haack reaction proved fruitless, probably due to the strong acidic condition. Pleasingly, Duff reaction of **2e** in acetic acid[15] gave the desired aldehyde **6** in 61% yield. Noteworthy was that milder acid (citric acid) should be used instead of sulfuric acid to avoid decomposition.

Scheme 3. Total syntheses of 8-substituted 2*H*-chromene-containing natural products



Pinnick oxidation[16] of **6** completed the total synthesis of **7** in 89% yield. Alternatively, Horner-Wadsworth-Emmons olefination of **6** furnished **8** in 88% yield. The total synthesis of anthyllisone (**9**) was accomplished by two highly yielding steps: lithium diisopropylamide (LDA)-mediated Claisen-Schmidt condensation and TBAF desilylation. All spectroscopic data for our synthetic samples were in well agreement with those reported for the corresponding natural products.[10]

In summary, we have developed a new cascade strategy for the syntheses of substituted 2*H*-chromenes with high efficiency, featuring aromatic Claisen rearrangement, *o*-quinone methide formation and 6π-electrocyclizaiton. The strategy substantiated by 28 examples is amenable to a broad range of substrate scope tolerating different substitution. In particular, new cascade reaction involving *para*-Claisen rearrangement, *o*-quinone methide formation and 6π-electrocyclizaiton allows for an expedite access to 2*H*-chromenes with substitutions at C6. It is expected that this new approach can be extended to the efficient preparation of 2*H*-chromenes with substitutions at C2, C3, C6 and C8. Moreover, this synthetic strategy was successfully applied in the concise collective synthesis of natural products. Further exploration of the strategy for the total syntheses of other 2*H*-chromene-containing natural products is ongoing in our laboratory.

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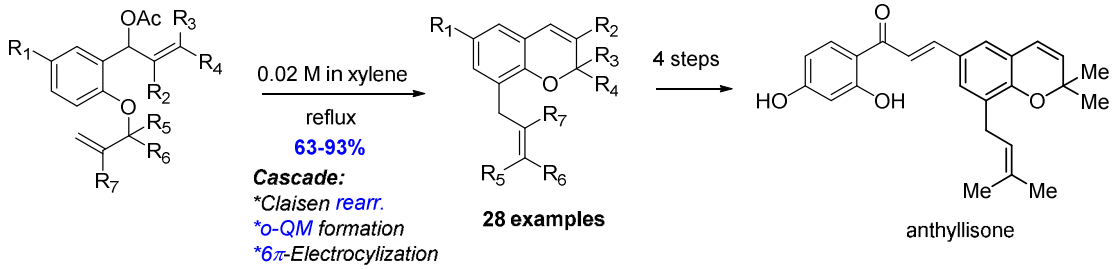

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