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The Domino Chromone Annulation and a Transient Halogenation-Mediated C−H Alkenylation toward 3-Vinyl Chromones

Leiqing Fu, Zhongrong Xu, Jie-Ping Wan,* and Yunyun Liu*

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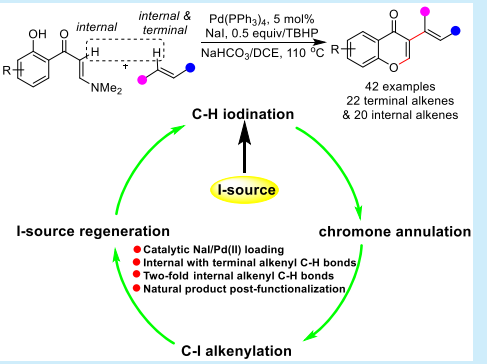
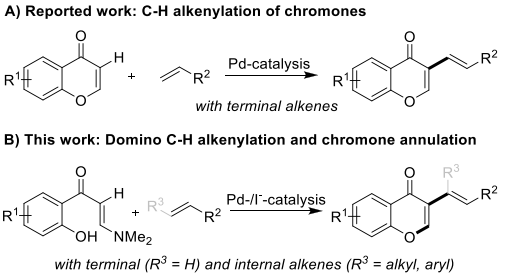
ABSTRACT: Reported in this paper is a step economical method toward the general synthesis of 3-vinyl chromones via the reactions between readily available *o*-hydroxyphenyl enaminones and various alkenes. The domino C−H alkenylation and chromone annulation of the enaminones are involved, which enables the synthesis of 3-vinyl chromone products using both terminal and internal alkenes via a key process of transient C−H halogenation.



Owing to the prevalence of the chromone ring in natural products, healthcare compounds, pharmaceuticals, and numerous other compounds with valuable applications,[1] chromone synthesis has been an issue of constant interest in organic synthesis. Over the past decade, tremendous advances have been gained in the area of diversely functionalized chromone synthesis.[2] In the early stage, direct functionalization on readily available chromones and analogous natural compounds such as flavones constitutes the main tactic for accessing chromones with increased functionalization density.[3] On the contrary, the past decade has witnessed significant progress in the synthetic methods involving chromone annulation by employing more flexible acyclic starting materials with enriched transformation pathways.[4] As one of the most successful protocols of this type, the reactions involving domino C−H functionalization and chromone annulation of *o*-hydroxyphenyl enaminones have been identified as the most reliable and versatile ones, which has been used for the synthesis of chromones containing an extraordinarily diverse C3 or C2 substitution.[5]

Interestingly, despite the important achievement of realizing the synthesis of 3-substituted chromones, a synthetic method toward 3-vinyl chromones remains largely unavailable. Besides the conventional Heck-type alkenylation employing 3-halochromones as starting materials,[6] the only hitherto systematic work on the synthesis of 3-vinyl chromones is the direct intermolecular C−H alkenylation of chromones and terminal alkenes reported by Hong and Kim (Scheme 1A).[7] Also, in several research works on Pd-catalyzed oxidative alkene−alkene coupling reactions, chromone has been used as specific alkene substrate to provide the corresponding vinyl chromone.[8] The challenges of this synthesis of 3-vinyl chromones, according to the known literature, manifest in two ways. One is the limited sources or additional synthetic preparation of chromone substrates. The other and more rigid problem is the intolerance to the reactions of internal alkenes, which hampers the diversity and application space of the vinyl chromone scaffolds. In fact, despite the splendid advances achieved in coupling alkenylation reactions, the C−H alkenylation reactions using internal alkenes remain as a severe challenge.[9] Mostly, it is those internal alkenes activated by electron-donating heteroatoms that can be used as the olefinic C−H donors in the alkenylation reaction.[10] A few intramolecular reactions involving the internal C−H bond have also

Scheme 1. Methods for the Synthesis of 3-Vinyl Chromones



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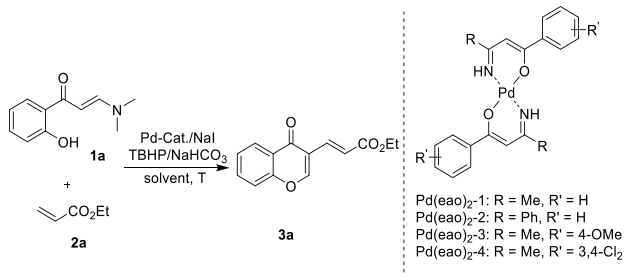
been reported.[11] The C−C bond-forming reactions involving alkenylation, on the contrary, largely rely on the utilization of prefunctionalized substrates such as organohalides and boronic acids as the reaction partners of alkenes.[12] Considering the additional labor required for the substrate functionalization and the stoichiometric halogen/boron-based waste produced in such synthetic methods, setting up new alkenylation strategies employing directly raw C−H bond donors as the reaction partners of terminal/internal alkenes is urgent.

In our long-standing efforts to develop sustainable and step economical synthetic methods using enaminones,[13] we report herein our results on the synthesis of 3-vinyl chromones via one-pot domino C−H alkenylation and chromone annulation of *o*-hydroxyphenyl enaminones in the presence of Pd and iodide catalysts. Both terminal and internal alkenes, including those derived from natural products, are well tolerated. A transient C−H iodination is utilized as the key step to enable this method toward the general synthesis of 3-vinyl chromones (Scheme 1B).

To start the work, the reaction of enaminone **1a** and ethyl acrylate **2a** was selected to screen proper conditions for the expected reaction. The Pd(II)-enaminone complex [$Pd(eao)_2$-1] previously developed in our group[14] was first used as the Pd catalyst. The reaction was comprehensively optimized with different iodo sources, oxidants, base additives, solvents, Pd catalyst species, etc. (see the Supporting Information for full data of optimization). The typical results listed in Table 1

Table 1. Typical Data for Condition Optimization[a]



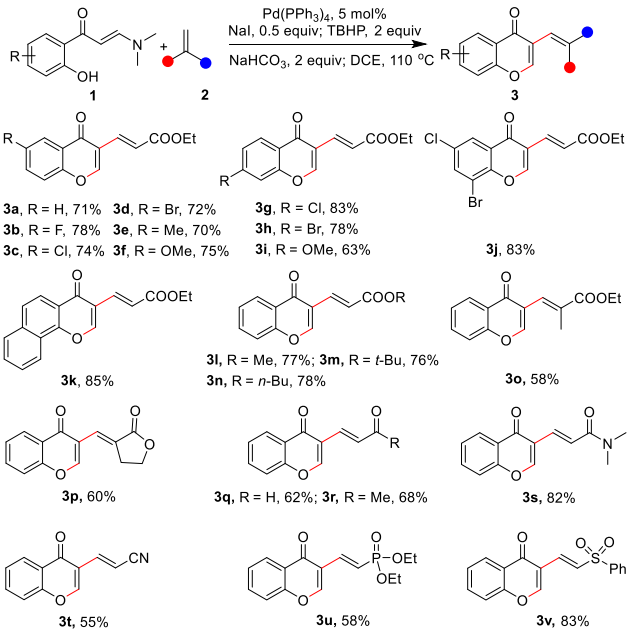
entry	solvent	catalyst	yield (%)[b]
1	DCE	$Pd(eao)_2$-1	67
2	toluene	$Pd(eao)_2$-1	38
3	dioxane	$Pd(eao)_2$-1	46
4[c]	DCE	$Pd(eao)_2$-1	63
5	DCE	$Pd(eao)_2$-2	29
6	DCE	$Pd(eao)_2$-3	47
7	DCE	$Pd(eao)_2$-4	69
8	DCE	$Pd(OAc)_2$	56
9	DCE	$PdCl_2$	52
10	DCE	$Pd(PPh_3)_4$	71

[a]General conditions: **1a** (0.3 mmol), **2a** (0.4 mmol), NaI (0.5 equiv), TBHP (2 equiv), $NaHCO_3$ (2 equiv), solvent (2 mL), Pd catalyst (5 mol %), stirred at 110 °C in a sealed tube for 24 h. [b]Yield of the isolated product based on **1a**. [c]The reaction temperature was 90 °C.

show that 1,2-dichloroethane (DCE) was the favorable medium (entries 1−3) and 110 °C was a proper temperature (entry 4) for the reaction providing **3a**. On the contrary, comparing different Pd catalysts, including different Pd(II)-enaminone complexes and commercially available $Pd(OAc)_2$, $PdCl_2$, $Pd(PPh_3)_4$, etc., indicated that $Pd(PPh_3)_4$ was among the most effective catalysts (entries 5−10). Complementarily, using NaBr as the alternative halide species gave only a trace amount of the product under the optimal conditions.

In the work of examining the synthetic scope, the reactions of enaminones **1** with terminal alkenes **2** were first conducted. When ethyl acrylate was fixed to react with different enaminone substrates, the 3-vinyl chromones containing a broad array of functional substituents, such as halogen [**3b**−**3d**, **3g**, **3h**, and **3j** (Scheme 2)], methyl [**3e** (Scheme 2)],

Scheme 2. Sope of the Synthesis of 3-Vinyl Chromones Using Terminal Alkenes[a]



[a]Isolated yields are reported.

methoxy [**3f** and **3i** (Scheme 2)], and fused aryl [**3k** (Scheme 2)] groups, were synthesized with good to excellent yields. Moreover, the terminal alkene component displayed an even more attractive scope of synthesis. The acrylates with different alkyl species [**3l**−**3n** (Scheme 2)], acylate with an additional *α*-substitution and methylene lactone [**3o** and **3p** (Scheme 2)], enal and enone [**3q** and **3r** (Scheme 2)], the vinyl amide, vinyl nitrile, vinyl phosphonate, and vinyl sulfone could all be smoothly utilized for the synthesis of the highly divergent vinyl chromones [**3s**−**3v** (Scheme 2)]. When the 1-allyl naphthalene, a nonconjugate alkene, was used to react with **1a** under the standard conditions, the formation of the corresponding 3-vinyl chromone was not observed. No expected vinyl chromone product was observed when styrene was used to react with **1a** under the standard conditions, either.

While the alkenylation transformation employing internal alkenes for the synthesis of corresponding 3-vinyl chromones was not yet available in the literature, we turned our attention to the reactions employing internal alkenes. To our delight, when internal alkenes **4** were employed to react with enaminones **1**, a broad scope of the synthesis of 3-vinyl chromones **5** was identified (Scheme 3; see the NOESY NMR data of **5a** in the Supporting Information for the assignment of the alkene configuration). Generally, the similarly diverse enaminones **1** reacted successfully with methyl 2-butenoate to provide internal alkenyl-functionalized chromones **5a**−**5j**

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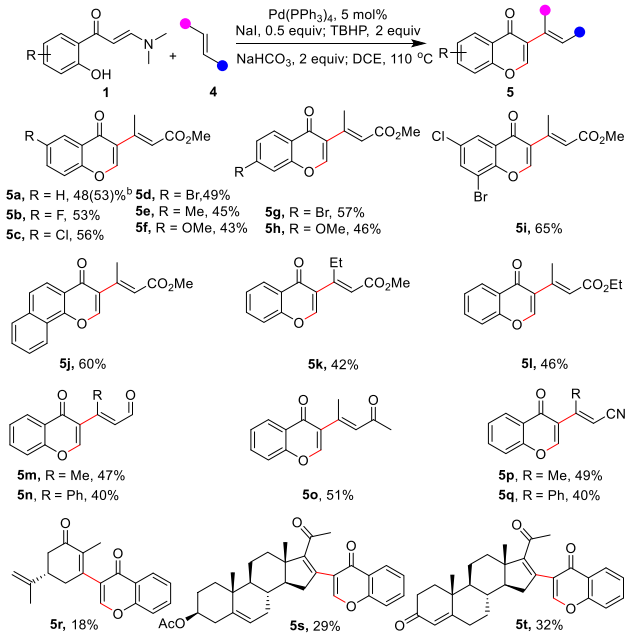
Scheme 3. Scope of the Synthesis of 3-Vinyl Chromones Using Internal Alkenes[a]



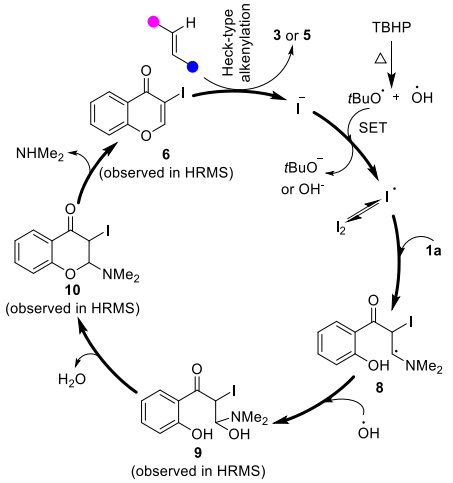
[a]Isolated yields are reported. [b]The yield in brackets was obtained by employing 1 equiv of I_2.

(Scheme 3). More interestingly, as for the internal alkene component, the high tolerance of the alkene species to the synthesis was identified. Different alkenyl esters [**5j**−**5l** (Scheme 3)], α,β-unsaturated aldehydes and ketones [**5m**−**5o** (Scheme 3)], and alkenyl nitriles [**5p** and **5q** (Scheme 3)] could all react with enaminone **1a** to afford the target products. The yields given by the reactions of the internal alkenes were lower than the product yields from the reactions of terminal alkenes. Besides the conventional alkene derivatives, the method presented here proved to be applicable for the elaboration of natural products. Several natural products featuring an internal enone structure, including Carvone, 16-dehydropregnenolone, and 16-dehydroprogesterone, could act as alkene substrates to react with enaminone **1a** to provide products **5r**−**5t**, respectively. Although these chromone-functionalized natural products were given with lower yields, the potential of the tactic in natural product postfunctionalization was guaranteed.

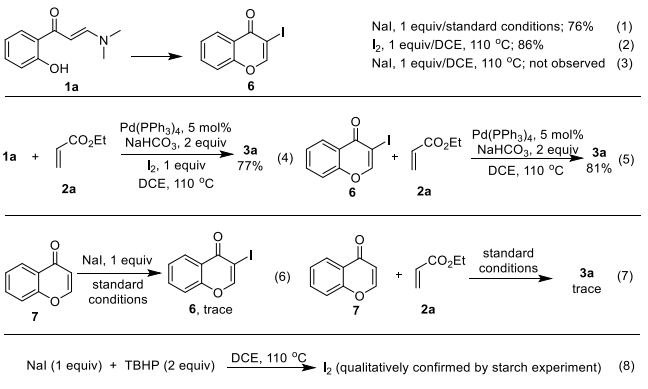
To elucidate the reaction mechanism, we performed an array of control experiments. Typically, subjecting enaminone **1a** with NaI under the standard conditions provided 3-iodochromone **6** with high yield (eq 1). A similar result was obtained by employing molecular iodine in the absence of TBHP (eq 2). In addition, employing only NaI did not give **6** (eq 3). The results presented above proved that **6** was a key intermediate in the reaction, and oxidation of the iodine anion to oxidative iodine species such as molecular iodine or iodine free radical was crucial for the generation of **6**. Subsequently, **3a** could be obtained with high yield with molecular iodine assistance, which afforded further support to the aforementioned conclusion (eq 4). When iodochromone **6** and acrylate **2a** were employed under the conditions with a Pd catalyst and a base additive, **3a** was produced with excellent yield, indicating that the Heck-type alkenylation was the other key step in the product formation (eq 5). On the contrary, directly using chromone could not react with NaI to give **6** or react with **2a** to give product **3a** (eqs 6 and 7), proving that the C−H iodination should take place before the chromone annulation. Finally, the qualitative observation of molecular iodine formation from the entry using NaI and TBHP confirmed that TBHP could oxidize the iodine anion (eq 8).

In addition, to obtain more clues and evidence, the model reaction as well as a reaction performed in neat MeOH with **1a** and molecular iodine was monitored with HRMS under an ESI model. In the course of monitoring the model reaction at 1, 2.5, and 7 h, 3-iodochromone **6** and iodinated intermediates **9** and **10**, respectively (see Scheme 4), were observed (see the

Scheme 4. Plausible Reaction Mechanism



Supporting Information). In addition, subjecting enaminone **1a** and molecular iodine in neat MeOH and room temperature stirring enabled us to observe the vicinal diiodo-functionalized intermediate analogous to species **9** (with I instead of OH). The low intensity of the HMRS signal (see the Supporting Information) indicated that this species was of low stability, and its fast transformation to featured intermediate **6** was also confirmed by the strong signal of **6** in the HRMS spectra (see the Supporting Information).



According to the clues given by control experiments (see also Table S1), the reaction mechanism based on a key transient halogenation is proposed (Scheme 4). In the presence of TBHP, the iodine anion is oxidized to iodine radical by single-electron transfer (SET). The addition of iodine radical to the C=C bond in the enaminone generates free radical intermediate **8**. The coupling of **8** with *tert*-butoxyl or hydroxyl free radical gives rise to **9**, which undergoes a

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subsequent transetherification to provide chromanone intermediate **10**. The elimination of dimethyl amine from **10** leads to the formation of 3-iodochromone **6**. Then, the Pd-catalyzed Heck-type alkenylation of the C−I bond in **10** with the alkene component yields target products **3** or **5**.

In conclusion, by a rationally designed transient C−H halogenation and subsequent alkenylation tactic, a one-step method for the synthesis of 3-vinyl chromones has been developed. Besides featuring the advantages of simple operation and easily available substrates, this work is highly attractive for its broad tolerance to the reactions of both terminal and internal alkenes, thus enabling the synthesis of 3-vinyl chromones with unprecedented high structural diversity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03548.

Experimental procedures, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Yunyun Liu − *College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P. R. China;* orcid.org/0000-0002-5553-1672; Email: chemliuyunyun@jxnu.edu.cn

Jie-Ping Wan − *College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P. R. China;* orcid.org/0000-0002-9367-8384; Email: wanjieping@jxnu.edu.cn

Authors

Leiqing Fu − *College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P. R. China; College of Chemistry and Bio-Engineering, Yichun University, Yichun, Jiangxi 336000, P. R. China*

Zhongrong Xu − *College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03548

Notes

The authors declare no competing financial interest.

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