Redox-neutral and metal-free synthesis of 3-(arylmethyl) chroman-4-ones via visible-light-driven alkene acylarylation

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A metal- and aldehyde-free visible-light-driven photoredox-neutral alkene acylarylation with readily available cyanoarenes is described. A variety of 3-(arylmethyl)chroman-4-ones (i.e., homoisoflavonoids) and analogs are efficiently synthesized with good functional group tolerance. This mild protocol relies on a phosphoranyl radical-mediated acyl radical-initiated cyclization and selective radical-radical coupling sequence, and is also further highlighted by subsequent derivatization to chromone and 2H-chromene as well as its application in the three-component alkene acylarylation.

KEYWORDS
chroman-4-one, 3-(arylmethyl)chroman-4-ones, phosphoranyl radical, acyl radical, radical-radical coupling

Introduction

Chroman-4-one scaffolds, a class of important oxygen-containing structural motifs, are ubiquitous in a plethora of natural products, drug candidates, and biologically active molecules (Albrecht et al., 2005; Nibbs and Scheidt, 2011; Friden-Saxin et al., 2012; Lee et al., 2014; Seifert et al., 2014; Emami and Ganbarimasir, 2015; Kumar et al., 2017; Mayuri et al., 2017). In the past years, the radical-initiated cascade cyclization strategy has attracted great attention for the construction of chroman-4-one scaffold and other (hetero)cyclic frameworks (Zhao et al., 2016; Yang et al., 2017; Hu et al., 2018a; Hu et al., 2018b; Liu et al., 2019; Sheng et al., 2019; Xiao et al., 2019; Zhou et al., 2019a; Das et al., 2020; Han et al., 2020; Huang et al., 2020; Liu et al., 2020; Mei et al., 2020; Xiong et al., 2020; Diana et al., 2021). Particularly, the photocatalytic radical-initiated cascade cyclization, including two mechanistically distinct pathways, has emerged as an elegant, green, and powerful strategy for the synthesis of such scaffold and its
derivatives. The first photocatalytic approach to diversely functionalized chroman-4-ones via various external radical-initiated cascade cyclization of o-(allyloxy) arylaldehydes is well-developed by the groups of Zhu (Lu et al., 2017; Zhou et al., 2019b), Yu (Zhu et al., 2021), Xuan (He et al., 2019), and others (Zhou et al., 2019a; Huang et al., 2020; Mei et al., 2020; Liu et al., 2022) (Figure 1A). In contrast, there are only a few examples of photocatalytic internal acyl radical-initiated cascade cyclization (Jung et al., 2017; Norman et al., 2018; Stache et al., 2018; Zhou et al., 2021) (Figures 1B–D), which limits their application for the rapid assembly of structurally diverse chroman-4-ones. Recently, Hong group (Jung et al., 2017) and Wan group (Zhou et al., 2021) independently developed a visible-light-driven radical cyclization/epoxidation of o-(allyloxy)arylaldehydes toward spiroepoxy chroman-4-one scaffolds using Ru (bpy)3Cl2 or organoselenium as photocatalyst and tert-butyl hydroperoxide (TBHP) as oxidant (Figure 1B). In 2018, McErlean group (Norman et al., 2018) disclosed a photoredox-catalyzed indirect acyl radical generation from relatively stable Crich-type thioesters generated in a single step with carboxylic acid starting materials, followed by intramolecular alkene addition/cyclization to give various cyclic ketones including chroman-4-one scaffold (Figure 1C). However, these existing strategies are solely based on the elaboration of uneasy available o-(allyloxy)arylaldehydes (almost all) or carboxylic acid thioesters (only one) and also suffer from one or more drawbacks such as excess amounts of oxidants, limited structural diversity, and lack of functionality tolerance. Therefore, the development of alternative and efficient approaches to access diversely functionalized chroman-4-one and related cyclic ketone analogs via photocatalytic internal acyl radical-initiated cascade cyclization using accessible starting materials should be highly desirable.

Carboxylic acids as starting materials are not only abundant, generally stable, and readily accessible in great structural diversity, and have also drawn much attention for their application as versatile radical precursors such as alkyl, aryl, carboxylic, and particularly acyl radicals (Mandal et al., 2018; Wang et al., 2019; Hu et al., 2020b; Chan et al., 2022; Kictatte et al., 2022; Yan et al., 2022). Recently, an elegant strategy that combines photoredox catalysis and phosphoranyl radical-mediated deoxygenation makes it possible to form acyl radicals from carboxylic acids, providing streamlined access to structurally diverse ketones (Zhang et al., 2017; Stache et al., 2018). However, to the best of our knowledge, there are not only a few reports on the application of this powerful strategy to intermolecular and intramolecular alkene acylations including ipso-acylation (Li et al., 2022b), defluorinative acylation (Guo et al., 2020), and hydro-acylation (one example of hydro-acylation: one compound chroman-4-one using expensive iridium-based photocatalyst, Figure 1D) (Stache et al., 2018; Zhang et al., 2018; Martinez Alvarado et al., 2019; Merkens et al., 2021), but also no report on alkene difunctionalizations (especially carbon-acylation) with this strategy to date. Inspired by these work and seminal pioneering reports on the photoredox-catalyzed radical-type ipso-functionalizations of electron-deficient cyanomare derivatives (Betori and Scheidt, 2019; Vorob’ev, 2019; Zhong et al., 2020; Zhou et al., 2020; Shen et al., 2021; Tong et al., 2021; Georgiou et al., 2022), we envisaged whether the radical relay strategy of the phosphoranyl radical-mediated acyl radical-initiated cascade cyclization from alkene-tethered carboxylic acids and subsequent
radical-radical coupling process could enable the rapid construction of 3-(arylmethyl)chroman-4-ones, which are one of the core frameworks in a variety of homoisoavonoids with various biological activities (Eggler et al., 1991; Desideri et al., 1997; Eggler et al., 1997; Tait et al., 2006; Basavarajappa et al., 2015). Herein, we report an efficient and practical approach for the metal-, oxidant-, and aldehyde-free synthesis of 3-(arylmethyl)chroman-4-ones and other cyclic ketone analogs via visible light-driven photoredox-neutral alkene acylation (being a class of alkene carbon-acylation, Figure 1E).

**Results and discussion**

To corroborate this hypothesis, we initially selected a model reaction of alkenoic acid 1a and 4-cyanopyridine 2a to explore...
the reaction conditions under 30 W blue LED irradiation at room temperature (Table 1). To our delight, the desired 3-
(pyridylmethyl)chroman-4-one 3aa could be obtained in 75%
yield by using 3DPAFIPN as a metal-free photocatalyst (entry 1).
In light of the fact that the excited state 3DPAFIPN [E1/2 (PC*
/PC−) = +1.09 V vs. SCE] is a strong oxidant (Speckmeier et al.,
2018), single electron transfer (SET) could occur from P (p-tol),
(E1/2 ox = +1.03 V vs. SCE, Supplementary Figure S3) to
3DPAFIPN. Additionally, the presence of alkenoic acid 1a
shifted the reductive potential of 2a from −1.81 V vs. SCE
to −1.33 V vs. SCE (Supplementary Figure S4), thus enabling
SET between the reduced 3DPAFIPN− [E1/2 (PC/PCred) = −1.59 V vs. SCE] and 2a to complete the
photocatalytic cycle without any aid of external reductant and
oxidant. Next, decreasing the loading of the photosensitizer from
2 mol% to 1 mol% or 0.5 mol% obtained a slightly decreasing
yield (entry 1). Other organic photosensitizers such as
3DPA2FBN with suitable oxidative-reductive potential
(Speckmeier et al., 2018) could also afford the desired
chroman-4-one in good yields, while using 4CzIPN
(Speckmeier et al., 2018) led to no desired product (entries
2–3). Furthermore, other electron-rich trivalent phosphorus
compounds could also be used as the phosphorus source in
this deoxygenative transformation (entries 4–8), whereas using
relatively electron-deficient ones instead of P (p-tol), led to poor
efficiency (entries 9–11). Then, the screening of solvents
demonstrated that these photocatalytic reactions performed in
CH2Cl2 or DCE also resulted in synthetically useful yields, while
other solvents such as DMF, DMSO, and THF gave no desired
product (entries 12–14). Further control experiments performed
in the absence of light, photocatalyst, or phosphine failed to give
the desired chroman-4-one, thus emphasizing their crucial role
in this photocatalytic acylationlation (entry 15).

With the optimized reaction conditions in hand, we
investigated the scope and limitations of this reaction using a
variety of alkenoic acids (Figure 2). It was worth mentioning that

FIGURE 2
Scope of alkenoic acids. Reaction conditions: 1 (0.3 mmol), 2a (0.45 mmol), 3DPAFIPN (2 mol%), P (p-tol)3 (0.6 mmol), MeCN (6 ml), 30 W blue
LEDs, argon atmosphere, r.t., 24 h. The isolated yield is based on 1. Isolated yield in parentheses is obtained on a 1.0 mmol scale.
FIGURE 3
Scope of cyano (hetero)arenes. Reaction conditions: 1 (0.3 mmol), 2 (0.45 mmol), 3DPAFIPN (2 mol%), P(p-tol)_3 (0.6 mmol), MeCN (6 ml), 30 W blue LEDs, argon atmosphere, r.t., 24 h. The isolated yield is based on 1.

FIGURE 4
Product derivatization (A) and three-component alkene acylarylation (B). Reaction conditions: (a) I_2, DMSO, reflux 2 h; (b) I_2, DMSO, reflux 2 h; (c) 30% H_2O_2, K_2CO_3, DMSO, 0°C to r.t., 24 h; (d) 2,6-di-tert-butylpyridine, Tf_2O, CH_2Cl_2, 0°C to r.t., 5 h; Pd(PPh_3)_4, p-tolyliboronic acid, DIPEA, NMP, 170°C, 10 min.
this photocatalytic reaction could be run on a 1.0 mmol scale to provide the target product 3aa in 67% yield. Firstly, we examined the effect of the aromatic moiety of the substrate alkenoic acid. It was found that the electron-donating group (Me, OMe) and electron-withdrawing groups (F, Cl, Br, CF₃) at the para- and mata-position with respect to the carboxylic acid were well compatible with this transformation and the corresponding chroman-4-ones were obtained with satisfactory yields (3ba–3ia). The structure of 3ga was confirmed by X-ray diffraction analysis (CCDC 2192065). Moreover, the ortho-F substituted alkenoic acid was also employed in this transformation, providing the desired chroman-4-one 3ja albeit in a relatively low yield. Then, we investigated the scope of the alken moiety of the substrate alkenoic acid. 1,2-Disubstituted nonterminal alkenoic acid with a phenyl group at the terminal carbon participated well in such acylarylation to give the expected product 3ka, while one with an alkyl group was transformed into the compound 3la with a low yield. And 1,1-disubstituted or mono-substituted terminal alkenoic acid could also be subjected to this transformation, affording the corresponding chroman-4-ones (3ma–3oa) albeit with diminished yields. Interestingly, replacing the oxygen atom at the ortho-position with respect to the carboxylic acid by an atom of sulphur, nitrogen, or carbon favored the photocatalytic acylation, leading to the corresponding chroman-4-one analogs such as thiocroman-4-one 3pa, dihydroquinolin-4(1H)-one 3qa, and dihydronaphthalen-1(2H)-one 3ra. Additionally, N-((homo)allyl)indole-2-carboxylic acids were proved to be suitable heteroaromatic substrates for this photocatalytic process and gave the architecturally intriguing and valuable tricyclic ketone framework including 1H-pyrrolo[1,2-a]indol-1-one (3sa) and pyrido[1,2-a]indol-9(6H)-one (3ta) in comparable yields. These experimental outcomes fully highlighted the synthetic potential to construct structurally complex ketone-containing (hetero)cycles. However, pyridyl-substituted alkenoic acid 1u and acyclic aliphatic alkenoic acid 1v could be not suitable for this alkene acylation.

To further explore the synthetic potential of our methodology, we then investigated differently substituted cyanoarene partners in this photocatalytic acylarylation.
out as shown in Figure 5A. When three equivalents of the radical scavenger TEMPO or the electron-transfer scavenger p-dinitrobenzene (DNB) were added under standard conditions, no product was observed and the corresponding TEMPO-adduct (TEMPO-1a) was detected by ESI-HRMS analysis. Additionally, when the model reaction was performed with an external radical-trapping reagent 1,1-diphenylethylene (DPE), the formation of the desired chroman-4-one 3aa was significantly inhibited and the corresponding radical-trapping product 3aa′ was also detected by ESI-HRMS analysis. Taken together, these results indicate that a radical/SET-based pathway might be involved in our photocatalytic acylarylation.

Based on the above experimental results and previous reports (Jiang et al., 2019; Hu et al., 2020a; Clarke et al., 2020; Nicastri et al., 2020; Pan et al., 2020; Rossi-Ashton et al., 2020; Zhao et al., 2020; Zhou et al., 2020; Tong et al., 2021), a plausible mechanistic pathway for this photocatalytic acylarylation is proposed as described in Figure 5B. Under the blue LED irradiation, the photocatalyst 3DPAFIPN was initially raised to the excited state *3DPAFIPN, which was reductively quenched by P (p-tol)2 to form the strongly reducing 3DPAFIPN∗ and phosphine radical cation. Subsequently, the phosphine radical cation recombined with the carboxylate anion of 1a to produce the phosphoranyl radical intermediate A, which underwent a facile β-scission to form acyl radical B and tri-p-tolylphosphine oxide. Then, the resulting radical B proceeded via intramolecular 6-exo-trig cyclization with the alkenyl moiety to provide alkyl radical C. Meanwhile, SET between the reduced 3DPAFIPN∗ and 2a·H∗ gave a persistent arene radical D and regenerated 3DPAFIPN. Finally, the alkyl radical C underwent intermolecular radical-radical coupling with radical D and sequential rearomatization via the elimination of both cyano anion and proton to achieve the corresponding chroman-4-one 3aa.

Conclusion

In summary, we have developed a novel visible-light-driven photoredox-neutral alkene acylarylation with cyanoarenes, enabling metal-, oxidant-, and aldehyde-free access to structurally diverse 3-(aryl)methylochroman-4-ones (i.e., homoisoavonoids) as well as other cyclic ketone analogs such as thiochroman-4-one, dihydroquinolin-4(1H)-one, dihydrobenzthienal-1(2H)-one, pyrrolo [1,2-α]indol-1-one, and pyrido [1,2-α]indol-9(6H)-one. Furthermore, the resulting chroman-4-ones can be scale-up synthesized and also readily parlayed into skeletally diverse and valuable compounds such as chromone and 2H-chromene. In addition, the developed powerful protocol involves phosphoranyl radical-mediated acyl radical-initiated cascade cyclization followed by radical-radical coupling with the persistent aryl radical, enabling the concomitant introduction of ketone and aromatic fragments to organic molecules.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and
accession number(s) can be found below: https://www.cdc.cdc.cam.ac.uk/structures/- CCDC 2192065.

Author contributions

QW, DY, and JW conceived and designed the study, and wrote the paper. YD, SY, MR, JL, QF, ZZ, and JB performed experiments and mechanistic studies. NH, LY, and SW analyzed the experiments. All authors contributed to the analysis and interpretation of the data.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2022.1059792/full#supplementary-material

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