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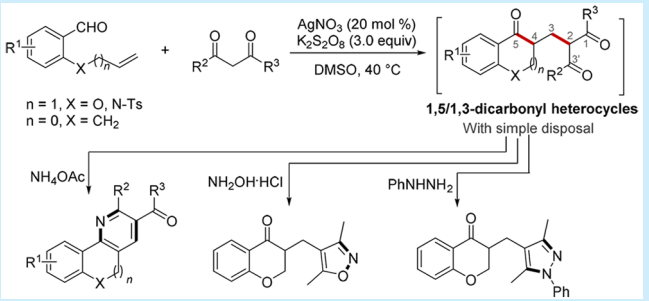
Silver-Catalyzed Radical Cascade Cyclization toward 1,5-/1,3-Dicarbonyl Heterocycles: An Atom-/Step-Economical Strategy Leading to Chromenopyridines and Isoxazole-/Pyrazole-Containing Chroman-4-Ones

Hao Hu,[†] Xiaolan Chen,*[,†,‡] Kai Sun,[†] Junchao Wang,[†] Yan Liu,[†] Hui Liu,[†] Lulu Fan,[†] Bing Yu,*[,†] Yuanqiang Sun,[†] Lingbo Qu,[†] and Yufen Zhao[†,‡]

[†]Henan Joint International Research Laboratory of Green Construction of Functional Molecules and Their Bioanalytical Applications. College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450001, China
[‡]The Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen 361005, China

Supporting Information

ABSTRACT: A novel and convenient silver-catalyzed radical cascade cyclization toward a large variety of 1,5-/1,3-dicarbonyl heterocycles containing a chroman-4-one, indanone, or 2,3-dihydroquinolin-4(1*H*)-one moiety was developed, by reacting various 2-functionalized benzaldehydes, including 2-allyloxy benzaldehydes, 2-allyl benzaldehyde, and 2-N(Ts)CH_2−CH═CH_2 substituted benzaldehyde, with 1,3-dicarbonyl compounds in the presence of $AgNO_3/K_2S_2O_8$ in one pot under mild reaction conditions. The newly obtained 1,5-/1,3-dicarbonyl-containing heterocycles were further used directly to synthesize more structurally diverse polyheterocycles, mainly including chromenopyridines as well as isoxazole- or pyrazole-containing chroman-4-ones.



Dicarbonyl compounds are a kind of indispensable building block for the synthesis of many structurally specific heterocycles. For example, 1,3-dicarbonyl compounds are essential precursors for the synthesis of isoxazole and pyrazole. 1,4-Dicarbonyl compounds are frequently used in Paal−Knorr syntheses to access furans, pyrroles, and thiophenes,[1] and 1,5-dicarbonyl compounds are often used in Paal−Knorr-like syntheses for the preparation of pyridines.[2] As shown below, chromenopyridine, a pyridine-containing polyheterocycle, is an essential structural part of diverse biologically important polyheterocycles (Figure 1), which are well-known for their pharmacological properties, such as antimicrobial, estrogen receptor β-selective ligands, cytotoxicity against some cancer cell lines, etc.[3]

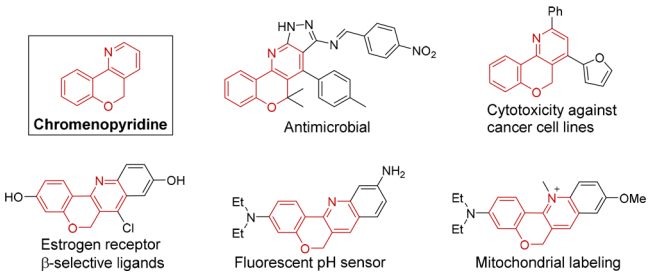


Figure 1. Significance of chromenopyridines.

Chroman-4-one is a privileged structural motif found in many natural and synthetic products that display a wide range of biological activities such as antitumor, anti-HIV, antioxidant, antibacterial, anticancer, antimicrobial, SIRT2 inhibitors, and estrogenic properties.[4] A number of synthetic methods have been developed for the preparation of those scaffolds in the past half century.[5] Among them is the Stetter reaction, a frequently used classical method for the preparation of 1,4-dicarbonyl-containing chroman-4-ones,[6] as demonstrated by the first example developed by Ciganek in 1995 (Scheme 1a). In the past 10 years, rapid development of radical cascade reactions for the concise construction of diverse complexes and usually polymolecular skeletons has been witnessed.[7] The distinguished merits of radical cascade reactions include high atom and step economy, as well as great reduction of work and time required to carry them out.[8] In 2016, Li's group developed a straightforward synthesis toward phosphorylmethyl-substituted chroman-4-ones via phosphoryl radical-initiated cascade cyclization of 2-(allyloxy)arylaldehydes as shown in Scheme 1b.[9] In 2017, Wu's group developed a synthesis toward 1,4-dicarbonyl-containing chroman-4-ones via acyl radical-initiated cascade cyclization reaction (Scheme 1c).[10] It is especially worth emphasizing here that, by far, there is a

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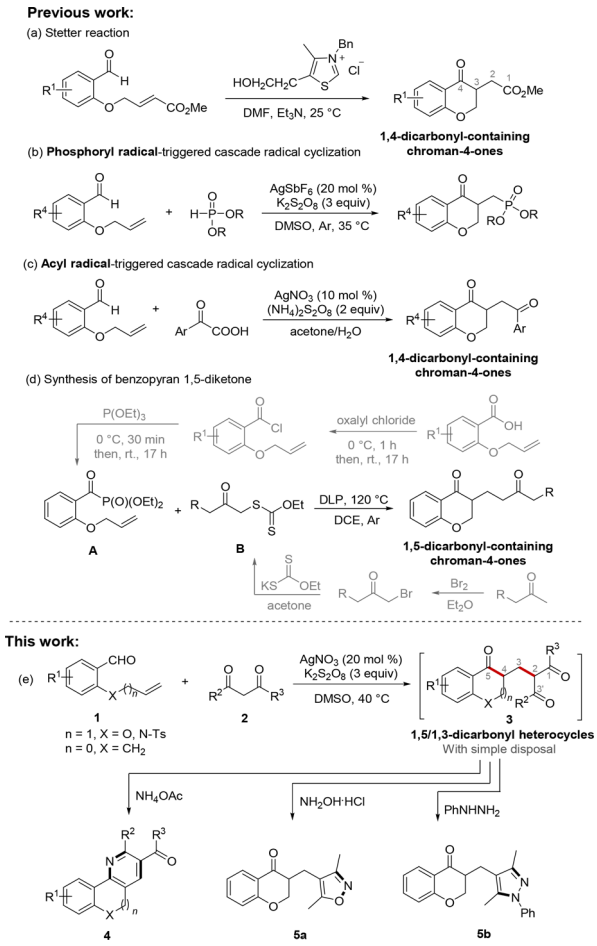
Scheme 1. Comparison with Previous Work

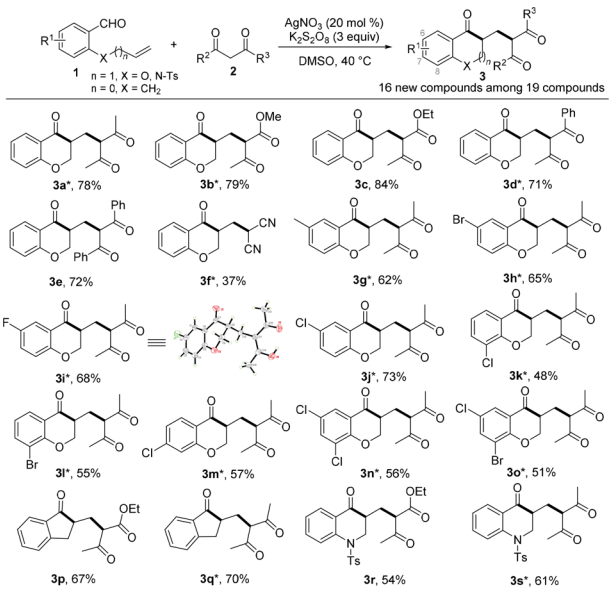


rare synthetic strategy being developed for the synthesis of chroman-4-ones with 1,3- or 1,5-dicarbonyl functional groups. Only one radical cascade cyclization strategy toward 1,5-dicarbonyl-containing chroman-4-ones has been reported by Zard's group in 2013 as shown in Scheme 1d;[11] unfortunately, two reactants (**A** and **B**) of this synthesis are especially tedious to synthesize. Herein, we present a novel and efficient silver-catalyzed radical cascade cyclization to access a large variety of 1,5/1,3-dicarbonyl heterocycles (**3**) containing chroman-4-one, indanone, or 2,3-dihydroquinolin-4(1*H*)-one moieties, by reacting various 2-functionalized benzaldehydes (**1**) with different 1,3-dicarbonyl compounds (**2**) in one pot under mild reaction conditions (Scheme 1e). Notably, the resulting 1,5-/1,3-dicarbonyl heterocycles (**3**) obtained could further react with NH_4OAc, $NH_2OH{\cdot}HCl$, or $PhNHNH_2$, to finally yield more structurally diverse polyheterocycles including **4**, **5a**, and **5b**, respectively, as depicted in Scheme 1e. Most of our newly synthesized heterocycles are new compounds. To the best of our knowledge, this is the first example of constructing a large variety of 1,5-/1,3-dicarbonyl heterocycles as well as the related polyheterocycles via a silver-catalyzed radical cascade cyclization reaction by directly using 1,3-dicarbonyl compounds as alkyl radical precursors.

We initiated the synthesis of 1,5/1,3-dicarbonyl-containing chroman-4-ones by establishing optimal experimental conditions using the model reaction of *o*-(allyloxy)benzaldehyde (**1a**) with acetylacetone (**2a**), as summarized in Table S1. After consulting previous reports[12] and doing an intensive experimentation, the optimized reaction conditions were thus established as follows: **1a** (0.5 mmol), **2a** (2 equiv), $AgNO_3$ (20 mol %), and $K_2S_2O_8$ (3 equiv) were stirred in 3 mL of DMSO at 40 °C for 24 h (yield 78%).

With the optimized conditions in hand, we further evaluated the scope of the substrates by examining various 2-functionalized benzaldehydes (**1**) and 1,3-dicarbonyl compounds (**2**), and the results are illustrated in Scheme 2. As it can be seen, *o*-

Scheme 2. Substrate Scope for the Synthesis of 1,5-/1,3-Dicarbonyl-Containing Heterocycles[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (2 equiv), $AgNO_3$ (20 mol %), and $K_2S_2O_8$ (3 equiv) were stirred in 3 mL of DMSO at 40 °C for 24 h. Isolated yields were given. * New compound.

(allyloxy)benzaldehyde (**1a**) reacted smoothly with different 1,3-dicarbonyl compounds under the optimized conditions, giving the resulting 1,5-/1,3-dicarbonyl-containing chroman-4-ones (**3a**−**e**) in good to excellent yields (71%−84%). Pleasingly, malononitrile was also suitable for this reaction, although with a relatively low yield of **3f**. Meanwhile, various *o*-(allyloxy)benzaldehyde derivatives, including those bearing an electron-donating group ($-CH_3$) and electron-withdrawing substituent (−F, −Cl, −Br), reacted smoothly with acetylacetone (**2a**), affording the corresponding 1,5-/1,3-dicarbonyl-containing chroman-4-ones (**3g**−**o**) in moderate to good yields (48%−73%). No obvious electronic effects of substituents at the C-6 position of benzene ring were observed as indicated in cases **3g**−**j**. In addition, compared with substituents at the C-6 position as in cases **3g**−**j**, *o*-(allyloxy)benzaldehyde with substituents at the C-8 and C-7 positions of the benzene ring gave relatively low yields as indicated in cases **3k**−**m**. Much to our delight, two other 2-functionalized benzaldehydes, 2-allyl benzaldehyde and 2-$N(Ts)CH_2{-}CH{=}CH_2$ substituted benzaldehyde, were compatible for reaction with ethyl acetoacetate as well as acetylacetone, yielding the corresponding 1,5-/1,3-dicarbonyl-containing indanones (**3p**, **3q**) and 2,3-dihydroquinolin-4(1*H*)-ones (**3r**, **3s**) in moderate to good yields, respectively. Among the target products obtained, the structure of **3i** was further confirmed by X-ray crystallography (CCDC 1861520). Afterward, we performed a scale-up reaction (gram level) with

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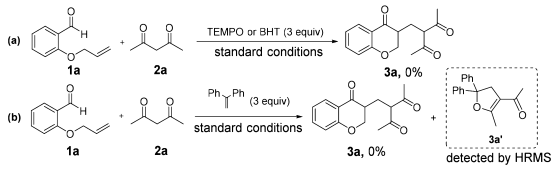
the desired product (**3a**) being obtained in 68% yield (see the Supporting Information, SI).

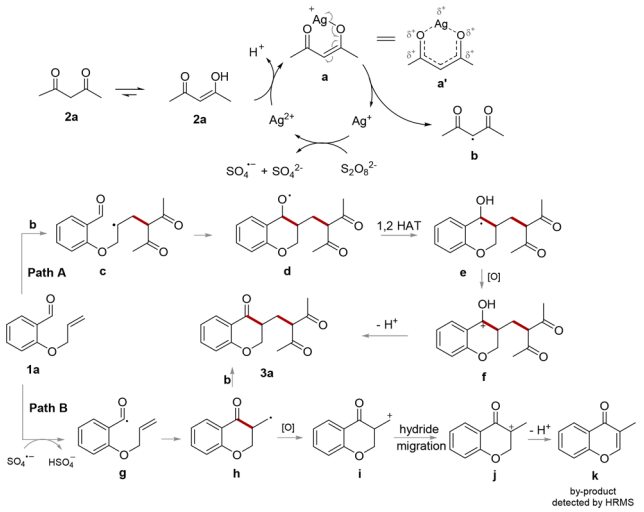
More control experiments were subsequently performed to deepen our understanding of the related mechanism (Scheme 3). When TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol), two widely used radical scavengers, were added into the reaction mixture under the optimized reaction conditions, respectively, both cascade cyclization reactions were completely inhibited (Scheme 3a), evidencing that the model reaction might proceed via a radical process. The model reaction was also performed in the presence of 1,1-diphenylethylene, another radical scavenger, under standard reaction conditions, as illustrated in Scheme 3b. It can be seen that a dihydrofuran product (**3a′**) was detected by HRMS (Figure S1), showing that a 1,3-dicarbonyl alkyl radical was produced from acetylacetone and trapped by 1,1-diphenylethylene. In addition, to determine important intermediates formed during the reaction process, the model reaction solution was also analyzed by HRMS. A peak at *m*/*z* 161.0601, which should correspond to hydrogen molecular ion $[C_{10}H_8O_2 + H]^+$ (Figure S2), was observed.

Scheme 3. Control Experiments



Based on the experimental results and previous reports,[9,13] a plausible mechanism is proposed as shown in Scheme 4.

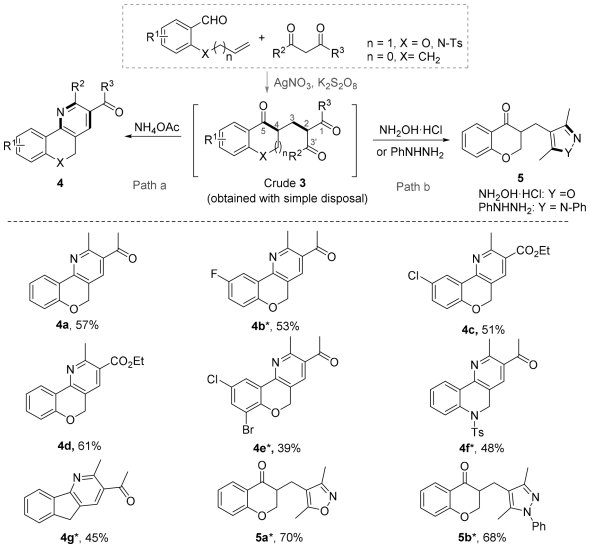
Scheme 4. Proposed Mechanism



Initially, peroxodisulfate oxidizes Ag(I) to Ag(II), which then reacts with acetylacetone (**2a**), affording a relatively stable silver ion complex **a** (or **a′**) with deprotonation. Afterward, the silver ion complex (**a**) undergoes a chain of intramolecular electron transfer, forming dicarbonyl radical **b** together with Ag(I). A cascade cyclization is thus triggered by dicarbonyl radical **b**. Radical **b** initially regioselectively adds to the double bond of *o*-(allyloxy)benzaldehyde (**1a**), giving radical intermediate **c**, which then experiences an intramolecular cyclization, affording radical intermediate **d**. Radical **d** subsequently undergoes a 1,2-hydrogen atom shift, generating more stable radical **e**. Finally, radical **e** is oxidized to carbocation intermediate **f**, which transforms immediately to final 1,5-/1,3-dicarbonyl-containing chroman-4-one **3a** along with deprotonation of **f**. Alternatively, the aldehyde group in **1a** is initially transformed to the corresponding acyl radical (**g**) via H-abstraction by a sulfate radical anion. Then the following intramolecular radical addition of **g** leads to the formation of an unstable radical intermediate (**h**) which quickly reacts with 1.3-dicarbonyl alkyl radical **b** to give the target product **3a**. Radical **h** is also possibly oxidized to yield carbocation **i**, which is subsequently transformed to more stable tertiary carbocation **j** via a hydride migration. Byproduct 3-methyl-4*H*-chromen-4-one (**k**) is eventually formed with loss of a proton from **j**. Moreover, the ion peak $[C_{10}H_8O_2 + H]^+$ appearing at *m*/*z* 161.0601 reasonably corresponds to 3-methyl-4*H*-chromen-4-one (**k**).

As mentioned above, dicarbonyl compounds are a kind of indispensable building block for the synthesis of abundant structurally specific heterocyclic skeletons. Our newly developed synthesis toward 1,5-/1,3-dicarbonyl containing heterocycles (**3**), for the first time, made it possible for us to use those heterocycles (**3**) as our starting reactants directly to synthesize more structurally complicated polyheterocycles in a significantly more atom- and step-economical manner. As exhibited in Scheme 5, the crude 1,5-/1,3-dicarbonyl heterocycles (**3**) could be employed directly to react with NH_4OAc, $NH_2OH{\cdot}HCl$, and $PhNHNH_2$, respectively, to access more structurally diverse polyheterocycles (**4a−g** and **5a−b**), among

Scheme 5. Synthesis of Polycyclic Heterocycles[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (2 equiv), $AgNO_3$ (20 mol %), and $K_2S_2O_8$ (3 equiv) were stirred in 3 mL of DMSO at 40 °C for 24 h. The mixture was quenched with water, extracted with ethyl acetate, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated to obtain crude product **3**. Synthesis of **4**: crude product **3**, acetic acid (2.5 mL), NH_4OAc (4 mmol), 120 °C, 3 h. Synthesis of **5a**: crude product **3**, EtOH (3 mL), aq HCl solution (37%, 1 drop), $NH_2OH{\cdot}HCl$ (0.75 mmol), 80 °C, 16 h. Synthesis of **5b**: crude product **3**, EtOH (3 mL), aq HCl solution (37%, 1 drop), $PhNHNH_2$ (0.75 mmol), 80 °C, 16 h. Isolated yields of two steps. * New compound.

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which **4a−e** are five chromenopyridines obtained via this newly developed synthetic strategy.

In conclusion, we reported a novel and convenient silver-catalyzed radical cascade cyclization to access a large variety of 1,5-/1,3-dicarbonyl heterocycles (**3**) containing chroman-4-one, indanone, or 2,3-dihydroquinolin-4(1*H*)-one moieties, by reacting various 2-functionalized benzaldehydes (**1**), including 2-allyloxy benzaldehydes, 2-allyl benzaldehyde, and 2-N(Ts)-CH_2−CH═CH_2 substituted benzaldehyde, with different 1,3-dicarbonyl compounds (**2**) in the presence of $AgNO_3/K_2S_2O_8$ in one pot under mild reaction conditions. To the best of our knowledge, this is the first example of constructing a large variety of 1,5-/1,3-dicarbonyl heterocycles via a silver-catalyzed radical cascade cyclization reaction by directly using 1,3-dicarbonyl compounds as alkyl radical precursors. More importantly, the newly developed silver-catalyzed radical cascade strategy toward the 1,5-/1,3-dicarbonyl containing heterocycles (**3**), for the first time, made it possible to build structurally complicated polyheterocycles (**4a−g** and **5a−b**) in a significantly more atom- and step-economical manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02627.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 1861520 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chenxl@zzu.edu.cn.
*E-mail: bingyu@zzu.edu.cn.

ORCID

Xiaolan Chen: 0000-0002-3061-8456
Kai Sun: 0000-0003-2135-0838
Bing Yu: 0000-0002-2423-1212
Yufen Zhao: 0000-0002-8513-1354

Notes

The authors declare no competing financial interest.

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