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Facile Synthesis of Acacetin and Its Derivatives

Yuan Zhao [a], Li Cai [b,*], Qiang Sui [a], Feng Lin [a], Wen Jiang [c], Jianli Chen [a], Weigeng Lu [a,*], Qi Gao [a,*]

[a] China State Institute of Pharmaceutical Industry, 285 Gebaini Road, Shanghai, 200120, China
[b] Division of Mathematics and Science, University of South Carolina Salkehatchie, Walterboro, SC 29488, United States
[c] China National Pharmaceutical Industry Information Center, 1320 West Beijing Road, Shanghai, 200040, China

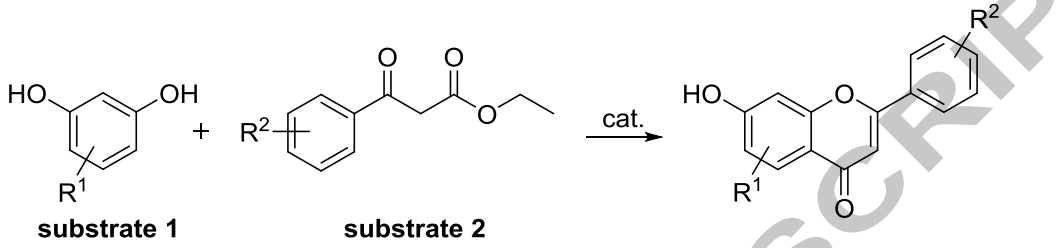
* Corresponding author

Tel: +1 843-7828681 (L. Cai); +86 21-20572000 ext. 6045 (Q. Gao)

Email address: CAILI@mailbox.sc.edu (L. Cai); sipiluwg@163.com (W. Lu); gao.qi@sipi.com.cn (Q. Gao)

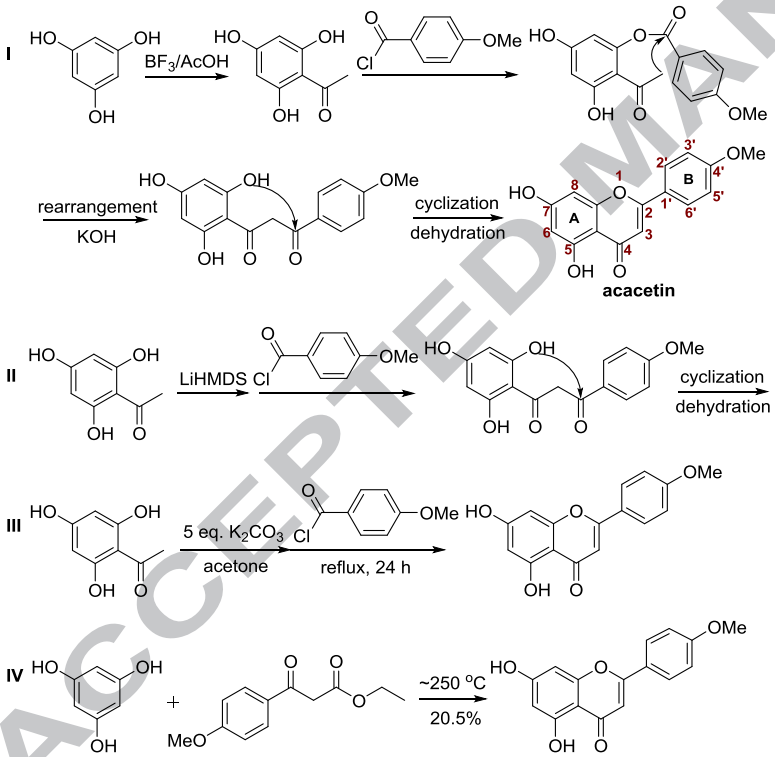
Abstract: Acacetin, a *O*-methylated bioflavonoid isolated from the traditional Chinese medicine *Xuelianhua* (*Saussurea tridactyla*), is a promising orally effective atrium-selective antiarrhythmic agent for the treatment of atrial fibrillation (AF). Here we describe an efficient two-component method for the synthesis of acacetin and its derivatives.

Graphic Abstract



Key words: Flavones, acacetin, synthesis, Fries rearrangement, atrial fibrillation, catalysis

Flavones are a class of flavonoids based on the backbone of 2-phenyl-1-benzopyran-4-one. These compounds have been shown to possess antioxidant[1], anti-proliferative, anti-tumor, anti-microbial[2], estrogenic[3], acetylcholinesterase inhibitory, and anti-inflammatory activities[4] and thus been used in cancer, cardiovascular disease, neurodegenerative disorders, etc.[5] Therefore, wide attention has been attracted to the design and optimization of polyfunctional flavone derivatives for the development of new therapeutic agents.[6-7] Atrial fibrillation (AF) is the most common form of sustained cardiac dysrhythmia and a major cause of morbidity and mortality because it increases the risk of death, congestive heart failure, and embolic phenomena including stroke.[8] Acacetin (4'-methoxy-5,7-dihydroxyflavone, Scheme 1) is a natural flavone compound extracted from the Chinese medicine *Xuelianhua* that selectively inhibits ultrarapid delayed rectifier potassium current (I_{Kur}, a major target for the treatment of AF) in human atria and effectively prevents AF in anesthetized dogs after intraduodenal administration.[9] Further studies revealed that acacetin mainly blocks hKv1.5 channels (coding I_{Kur}) in a use- and frequency-dependent manner by binding to the S6-domain.[10] These results indicate that oral acacetin is a promising atrium-selective agent for the treatment of AF. In addition, other novel pharmacological properties of acacetin, including antinociceptive/anti-inflammatory[11] and anti-proliferative/anti-cancer[12-14] activities, have also been discovered recently.



Scheme 1. Previous methods for the preparation of acacetin and its associated derivatives.

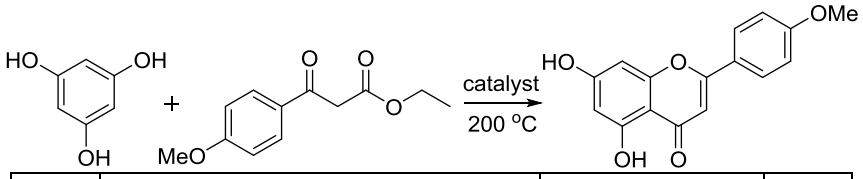
While many pathways on the synthesis of various flavones have been reported[15], less attention has been drawn to the preparation of acacetin. Thus the main source of acacetin is usually through extraction and isolation from plant materials.[16-17] Traditional methods for acacetin synthesis were mainly based on the Baker-Venkataraman rearrangement in which a base promoted intramolecular acyl transfer in 2-acetoxyacetophenone leads to a 1,3-diketone intermediate (a quick cyclization-dehydration step is thus followed to afford the acacetin

backbone) (Scheme 1, routes I-III). For example, Chatterjee et al. reported a low-yield route utilizing phloroglucinol to synthesize 2,4,6-trihydroxyacetophenone which was then coupled with 4-methoxybenzoyl chloride to give the rearrangement precursor (Scheme 1, route I).[16] Costantino et al. treated the 2,4,6-trihydroxyacetophenone with adequate amount of LiHMDS to deprotonate all of the phenols and generate the lithium enolate before the acid chloride was added; and the 1,3-diketone intermediate was afforded directly (Scheme 1, route II). However, the 28% yield of acacetin was still not satisfying.[18] Gao improved the overall yield to 45% by treating the 2,4,6-trihydroxyacetophenone with aroyl chloride in the presence of an excess amount of potassium carbonate in a one-step fashion (Scheme 1, route III).[19-20] In a different way (Scheme 1, route IV), Mentzer reported a two-component thermal cyclocondensation between phenols and β-ketoesters to yield a wide number of acacetin related flavones under high temperature.[21-22] Later, Seijas et al. enhanced this two-component synthesis by applying microwave irradiation.[23] Although with microwave heating the relatively high temperature reached (~225 ^{o}C) was similar to the one required under Mentzer's approach[22], the reaction time was greatly reduced to minutes and thus yields were significantly improved (>80% *vs.* ~20%).[23] Given that Seijas's study reported consistently higher yields for flavones with different substituted patterns on the B ring, a more broadly applicable method for flavones with substitution on both aromatic rings is still needed, specifically to those researchers who do not have ready access to microwave reactors. After studying the proposed mechanism of the two-component synthesis that involves several key steps (transesterification, Fries rearrangement, and cyclization)[23-24], we hypothesize that adding a catalyst that promotes these key steps will enhance and favor the product formation (Scheme 2).

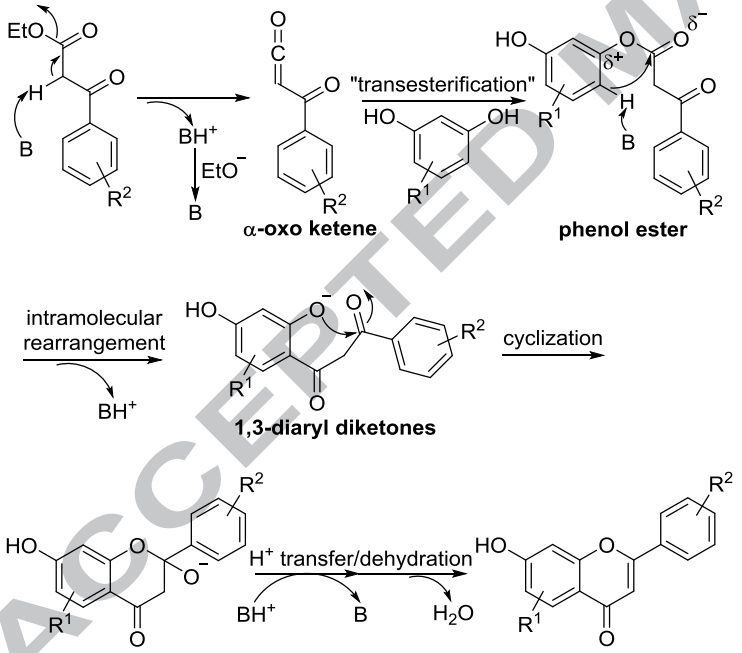
As shown in Table 1, we started with several copper (II) salts as it was previously reported that $CuCl_2$ could greatly facilitate the dehydrative cyclization step under microwave conditions.[25] However, from the outset we did not set high expectations for these reactions to offer significant improvement given that the particular step involved (cyclization) is non-rate-determining for this two-component conversion. Just as we anticipated, no product was observed for $CuCl_2$ while the other two copper (II) salts were relatively ineffective (Table 1, entries 1-3). We thus decided to switch to an acylation catalyst such as DMAP and tributylphosphine[26] that could act as a weak base and facilitate the transesterification and Fries rearrangement steps. In fact, DMAP-mediated Fries rearrangement has already been reported recently and successfully used in the synthesis of complex structures.[27-29] As expected, the model reactions catalyzed by DMAP, PPY (a DMAP derivative) and Bu_3P all offered greatly improved yields with best result obtained with DMAP (Table 1, entries 4-6). With the addition of the acylation catalyst, this thermal cyclocondensation proceeded in an enhanced fashion and we speculate that the reason for the enhancement can be seen in the mechanism of this reaction (Scheme 2). The acylation promoter acted as a base that activated the β-ketoester starting material to yield an α-oxo ketene intermediate.[23,30] Addition of the phenol to the α-oxo ketene yielded a phenol ester intermediate, completing the "transesterification" step. Then the phenol ester (*O*-acylation product) underwent a base-promoted ortho-Fries rearrangement, followed by cyclization of the resulting 1,3-diaryl diketone (formation of the hemiketal). Final proton transfer and dehydration drove the reaction sequence forward.[24] As a result, we successfully extended this method for the synthesis of a series of acacetin derivatives using DMAP as the catalyst and the results were summarized in Table 2. In order to investigate the substrate scope of this reaction, several substituted phloroglucinol type phenols (e.g. Table 2, entries 1-4) and β-ketoesters (e.g. Table 2, entries 1, 5, 6 and 9) were tried. These results demonstrate that the reaction can tolerate a variety of

substitution patterns and electron donating/withdrawing groups on the aromatic rings. It also provided a series of acacetin derivatives for prospective structure-activity relationship analysis.

Table 1. Catalyst screening for two-component synthesis of acacetin.

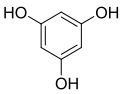
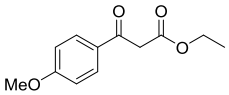
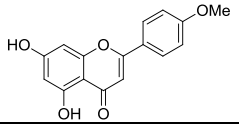
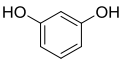
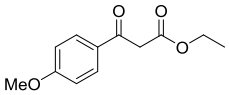
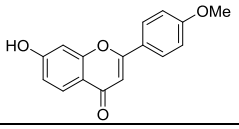
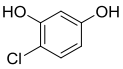
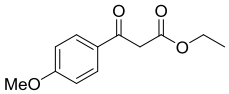
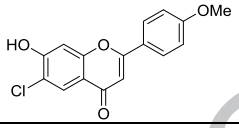
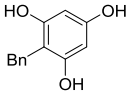
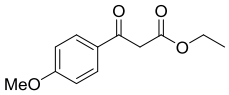
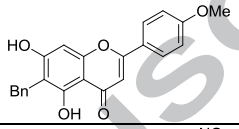
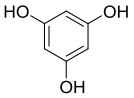
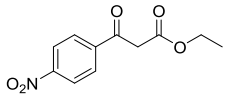
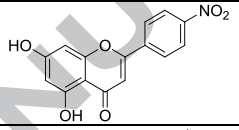
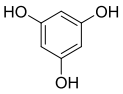
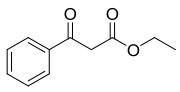
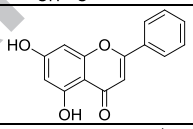
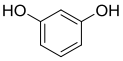
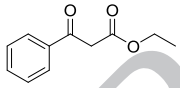
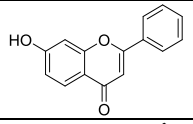
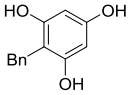
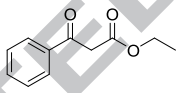
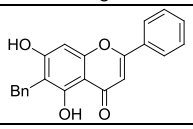
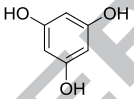
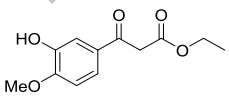
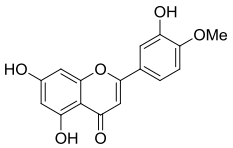


entry	cat. (5%)	reaction time (h)	yield
1	$CuCl_2$	5	0
2	$CuSO_4$	5	23%
3	$Cu(OTf)_2$	5	15%
4	4-dimethylaminopyridine (DMAP)	2.5	56%
5	4-pyrrolidinopyridine (PPY)	2.5	50%
6	Bu_3P	2.5	53%



Scheme 2. Proposed mechanism for base catalyzed two-component acacetin synthesis.

Table 2. Substrate scope of DMAP-catalyzed cyclocondensation

entry	substrate 1	substrate 2	Time (h)	product	comp.	yield
1			3		**1a**	71%
2			3		**1b**	49%
3			3		**1c**	73%
4			3		**1d**	16%
5			3		**2a**	53%
6			3		**3a**	86%
7			3		**3b**	80%
8			3		**3c**	23%
9			3		**4a**	67%

In conclusion, we report herein an efficient one-pot synthesis of acacetin and its derivatives, where DMAP acted as an effective catalyst for the two-component condensation reaction. Based on the previously reported mechanism of this reaction, we speculate that the weak base catalyst facilitated the formation of the α-oxo ketene intermediate and especially the ortho-Fries rearrangement. This method is valid for flavones with different substitution patterns on the aromatic rings. The pharmacological and pharmacokinetics studies of the obtained molecules are ongoing.

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Supplementary data: Supplementary data (experimental procedures and characterization of compounds) associated with this article can be found, in the online version, at doi:

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