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Synthesis of functionalized chromones via organocatalysis

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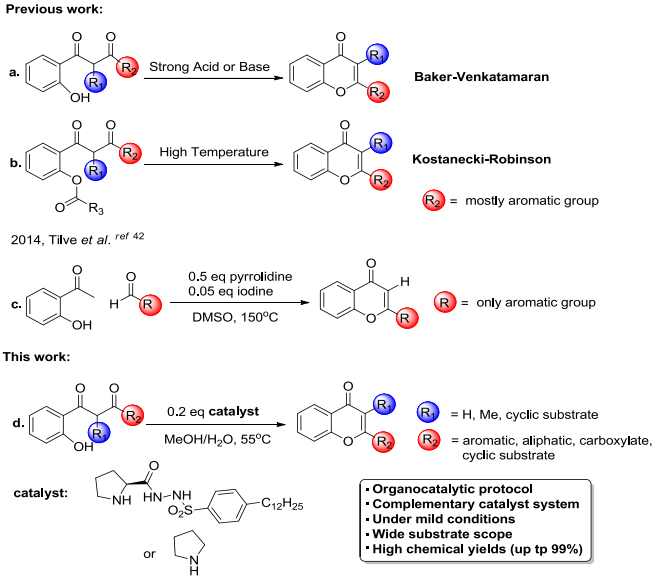
ABSTRACT

A facile and versatile organocatalytic approach to access 2-substituted and 2,3-disubstituted chromone derivatives under mild conditions was developed, which was effectively catalyzed by novel proline phenylsulphonylhydrazide or pyrrolidine. As a result, diversely functionalized chromones were obtained in up to 99% yield. In addition, further modification of the corresponding chromones afforded novel polycyclic chromones.

1. Introduction

Chromones are one of the most important classes of naturally occurring heterocyclic compounds, which widely exist in nature[1,2] and have been found as the secondary metabolites distributed in plant.[3] These kinds of compounds have drawn much attention in the past decades due to their considerable biological and pharmacological activities such as antimicrobial, antioxidant, antifungal and anticancer properties.[3–9]

Until now, a large number of synthetic methods have been developed to prepare chromones and their derivatives, including classic Claisen condensation,[10–18] Baker–Venkatamaran rearrangement,[19–25] Kostanecki–Robinson reaction[19,23,24,26–31] and so on (Scheme 1, **Eq. a & b**). Besides, other efforts involving metallic catalysts[32–35] or microwave[18,36] were also made in order to secure more efficient pathways. However, for most of the present methods, strong bases or acids were usually used and sometimes high temperatures were inevitable, which might lead to the unsatisfactory yield due to the formation of side-products and severe decomposition of starting materials.[1,3] On the other hand, although various synthetic approaches have been extensively studied, most of these developed synthetic methods were focused on the synthesis of flavones (R_2=aryl group in Scheme 1). A general synthetic method under mild reaction conditions is highly desirable for preparing diversely functionalized chromones, especially for 2-alkyl-substituted, 2,3-disubstituted and polycyclic chromones.[37–40]



Scheme 1. Synthetic routes of substituted chromones.

In the past decade, organocatalysis has evolved to be a versatile and powerful tool in organic synthesis since it possesses such advantages as low cost, easy operation, insensitivity to moisture and air, mild reaction condition, and environment-friendliness.[41,42] However, this useful strategy has been rarely employed in the synthesis of chromones. In 2002, Samant et al. found that a stoichiometric amount of morphline can convert 1-(2-hydroxyphenyl)-1,3-butanedione into 2-methylchromone when the reaction was

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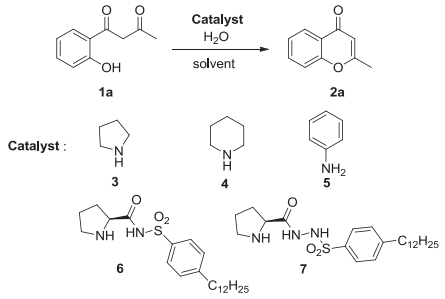
refluxed in ethanol;[43] and very recently, Tilve and co-workers reported the synthesis of flavones from aryl aldehyde and 2'-hydroxyacetophenone by using pyrrolidine as the catalyst, iodine as the oxidant in DMSO at high temperature (**Eq. c**).[44] Apparently, the organocatalytic preparation of structurally diversified chromones under mild conditions still remains an unsolved problem. Thus, our continued interest on the organocatalysis prompted us to seek an effective solution for this everlasting problem. We envisioned that the specifically designed organocatalysts with secondary amine motif might effectively activate the carbonyl group in 1,3-dioxophenoxy substrates, leading to the formation of chromones under mild conditions (Scheme 1, **Eq. d**). Consequently, a novel proline phenylsulphonylhydrazide was designed and prepared for this conversion. It was found that proline phenylsulphonylhydrazide and pyrrolidine can efficiently catalyze this reaction complementarily. As a result, a wide range of chromones were achieved in excellent chemical yields under quite mild conditions. Furthermore, this strategy was also extended to construct other polycyclic skeletons including tetrahydroxanthones (THXs).

2. Discussion

Initially, (2-hydroxyphenyl)-1,3-butanedione **1a** was chosen as the model reaction to investigate this reaction (Table 1). We were pleased to observe that the cyclization of diketone **1a** smoothly proceeded to afford the desired chromone **2a**, which was catalyzed by pyrrolidine **3**. Then, different solvents were firstly evaluated, and the highest yield of 66% was obtained in MeOH (entries 1–4). It was also found that H_2O could improve the yield when using THF as the solvent (entries 2 and 4). So the effect of water was also investigated (entries 5–7). As a result, the presence of 0.1 equiv of H_2O provided the optimum yield of 84% (entry 5). Next, the loading of catalyst **3** was studied. Higher catalyst loading (40 mol %) slightly decreased the yield of **2a** (entry 9) and low catalyst loading (10 mol %) severely eroded the chemical yield of **2a** (entry 8). The reaction temperature was also investigated for this reaction and a higher temperature of 55 °C can afford the maintained yield compared with room temperature (entry 10). But its reaction time can be significantly shortened to 12 h. It is worth noting that an unwanted by-product was also observed at higher temperature.[45] Herein, the optimum yield of 83% was reached with 0.2 equiv of **3** in MeOH containing 0.1 equiv of water at 55 °C. In addition, piperidine **4** and aniline **5** were also tested in this work, and the comparatively lower yields of 69% and 37% were obtained, respectively (entries 11–12). Prolinosulphonamide **6**, possessing the significantly improved solubilities in regular solvents and versatile catalytic activities, also showed mediocre catalytic activity toward this reaction with the yield of 37% (entry 13). Ultimately, a novel proline phenylsulphonylhydrazide **7** was designed and prepared from the direct coupling of Boc-protected proline and *p*-dodecylphenylsulphonylhydrazide followed by deprotection. Gratifyingly, proline phenylsulphonylhydrazide **7** can effectively catalyze this reaction and provide the highest yield of 99% under the optimized conditions despite a relatively longer reaction time of 36 h (entry 14). Accordingly, proline phenylsulphonylhydrazide **7** would be chosen as the superior organocatalyst for this transformation.

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst (mol %)	H_2O (mol %)	Solvent	T °C	Time (h)	Yield of **2a**[b] (%)
1	**3** (20)	0	MeOH	rt	52	66
2	**3** (20)	0	THF	rt	36	30
3	**3** (20)	0	Toluene	rt	36	28
4	**3** (20)	—	H_2O/THF (2:1)	rt	36	42
5	**3** (20)	10	MeOH	rt	24	84
6	**3** (20)	20	MeOH	rt	24	81
7	**3** (20)	40	MeOH	rt	24	80
8	**3** (10)	10	MeOH	rt	24	51
9	**3** (40)	10	MeOH	rt	12	74
10	**3** (20)	10	MeOH	55	12	83
11	**4** (20)	10	MeOH	55	24	69
12	**5** (20)	10	MeOH	55	24	37
13	**6** (20)	10	MeOH	55	24	37
14	**7** (20)	10	MeOH	55	36	99

[a] Unless otherwise noted, all reactions were carried out in sealed reaction vials at the designated temperature with diketone **1a** (0.50 mmol), pyrrolidine, and additives in solvent (5 mL).
[b] Isolated yields after silica gel chromatography.

With the optimal conditions in hand, scope of this reaction was next explored (Table 2). It is worth noting that the commercial availability and inexpensive cost of catalyst **3** necessitated its further investigation on the substrate tolerance. Consequently, catalyst **7** and **3** were subjected to the evaluation of various substrates side by side. In general, the cyclization of alkyl-substituted substrates (R_1=H, R_2=alkyl group) catalyzed by either **3** or **7** afforded the corresponding products in good yields (**2a**–**e**), no matter with steric effects of alkyl groups. Besides, higher yields were usually obtained by using catalyst **7**, except that a comparably higher yield was achieved for **2c** catalyzed by **3**. Surprisingly, a poor yield (37%) was observed on the carboxylated substrate **2f** using catalyst **3** as the catalyst. However, the employment of **7** significantly improved the yield to 87%. It should be noted that no matter, which catalyst was used, yields of flavone **2g** and styrylchromone **2h** were relatively lower due to the formation side-products and poor solubilities of starting materials. Moreover, as for the di-substituted substrates, good yields were generally achieved in widely varied reaction times from 12 to 108 h. Again, for most of the studied substrates, higher yields were achieved by using catalyst **7** (**2k**, **2l**, **2m** and **2n**). However, quite poor yield (35%) was obtained for **2j** by employing catalyst **7**. Pleasingly, using catalyst **3** afforded a satisfactory yield (71%). It seems that catalyst **3** could serve as a beneficial complement of catalyst **7** for specific substrates, although catalyst **7** generally performed better in this reaction.

Tetrahydroxanthones (THXs) and their hydrogenated derivatives are the core structure of natural products with important biological activities. Synthetic routes for this class of compounds are surprisingly limited and undeveloped.[38,46] Accordingly, preparation of THXs via this developed methodology was also investigated. Diketone **10** was prepared in reasonable yield starting from the aldol reaction between salicylic aldehyde **8** and cyclic ketone **9** followed by oxidation of the resulting alcohol. Satisfyingly, cyclizations of diketone **10a**–**c** catalyzed by **3** or **7** proceeded smoothly to furnish the corresponding THX derivatives **11a**–**c**. Interestingly, only low to moderate yields were obtained using catalyst **7**. However, excellent yields (>95%) were achieved for the reaction catalyzed by pyrrolidine **3** in even shorter reaction duration (Scheme 2). Presumably, the steric effect of substrate **10** might dramatically erode the catalytic effectiveness of the more steric-demanding catalyst **7**. Apparently, this developed protocol employing catalyst **3** could serve as an efficient pathway to prepare this class of polycyclic chromone derivatives.