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One-pot reaction of *ortho*-acylphenols and terminal alkynoates for synthesis of 2-alkyl-substituted chromanones

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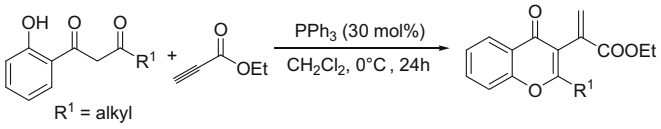
ABSTRACT

A facile synthesis of 2-alkyl-substituted chromanones from *ortho*-acylphenols and terminal alkynoates is described. The method contains two consecutive processes in one-pot reaction through a DABCO-catalyzed condensation reaction and a KOBu^t-mediated intramolecular cycloaddition to afford the desired products.

Structural motifs which are observed in many naturally occurring organic compound possessing varying biological activities have come to be known as 'privileged structures'.[1] The chromanone is one of the important scaffold that can be obtained from natural compounds exhibiting favorable pharmacological properties such as antioxidant, antitumour, antibacterial activities.[2] They have also used as key intermediates in the synthesis of chromone derivatives.[3] Consequently, great efforts have been devoted to the synthesis of this privileged structure.[4] Generally, most of synthetic methods are known to produce chromanone derivatives by carrying an aryl substituent in the 2-position, so-called flavanones.[5] But these conditions are not suitable for the preparation of 2-alkyl-substituted 4-chromanones.[3] To the best of our knowledge, there were limited methods to synthesize 2-alkyl-substituted chromanone derivatives in previous reports.[6] However, these compounds are commonly obtained under harsh conditions or by multi-step reaction. In order to circumvent these problems, the development of an easy and efficient method for 2-alkyl-substituted chromanones has been strongly desired.

In recent years, one of the rapidly growing research areas in the field of organic synthesis is that of application of organic base to catalyze reactions based on the electron-deficient alkynes or alkenes.[7] In our group, we are interested in the application of organic bases catalyzed cycloaddition reactions based on electron-deficient alkynes.[8] Recently, we have reported PPh_3-catalyzed cycloaddition of 1-(*o*-hydroxyaryl)-3-alkyl-1,3-diketones to ethyl propiolates to provide various chromone derivatives (Scheme 1).[9] As a continuation of annulation reaction research, we further investigate the possibility of cyclization reaction of *ortho*-acylphenols with terminal alkynoates. To our delight, a chromanone derivative was formed by two consecutive reaction processes: (1) condensation of *ortho*-acylphenol with ethyl propiolate in the presence of 1,4-diazabicyclo[2,2,2]-octane (DABCO); (2) followed by addition of KOBu^t to accomplish intramolecular cyclization. Herein, we wish to report this facile one-pot synthetic method of 2-alkyl-substituted chromanones starting from commercial available materials.

The reaction of 2-hydroxyacetophenone **1a** with ethyl propiolate **2a** was carried out in the presence of DABCO (10 mol %) in *N*,*N*-dimethylformamide (DMF) at room temperature for 0.5 h,[10] followed by addition of 1.2 equiv KOBu^t in a one-pot manner under various conditions, and the results were shown in Table 1. The functionalized 2-alkyl-substituted chromanone **3a** was obtained in 65% yield when the reaction was stirred for another 2 h at room temperature after addition of KOBu^t (Table 1, entry 2). Its structure was determined by NMR and HRMS spectra. Surprisingly, only a trace amount of the product **3a** was observed when DABCO and KOBu^t were added simultaneously to the reaction. A small amount of **3a** (<10%) was afforded when the reaction was performed at 60 °C (Table 1, entry 5). However, the yield of the product was unsuccessfully improved by reducing the reaction temperature from room temperature to 0 °C (Table 1, entry 4). On the other hand, other inorganic bases, in place of KOBu^t, were examined and had significant influence on the reaction. The application of NaH to the reaction afforded **3a** with comparable yield (Table 1, entry 6). Compared with KOBu^t, KOH afforded the product with lower yield (43%) (Table 1, entry 7). With the utilization of NaOEt



Scheme 1.

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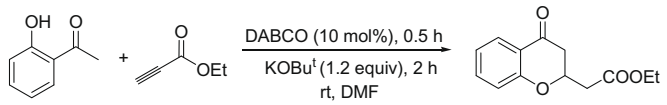
Table 1
Optimization of the reaction conditions



1a **2a** **3a**

Entry	Base	Solvent	Yield[a] (%)
1	KOBu^t	DMF	62[b]
2	KOBu^t	DMF	65
3	KOBu^t	DMF	52[c]
4	KOBu^t	DMF	58[d]
5	KOBu^t	DMF	<10[e]
6	NaH	DMF	64
7	KOH	DMF	43
8	EtONa	DMF	<10
9	K_2CO_3	DMF	NR[f]
10	KOBu^t	CH_3CN	37
11	KOBu^t	Toluene	22
12	KOBu^t	CH_2Cl_2	<10

[a] Isolated yield.
[b] Performed for 1 h.
[c] Performed for 4 h.
[d] At 0 °C.
[e] At 60 °C.
[f] NR = no reaction.

or K_2CO_3, the yields of the reaction gave bad results (Table 1, entries 8 and 9). Further investigation conducted with a solvent screen and a significant solvent effect was observed. When shifting solvent to CH_3CN or toluene, the desired product **3a** was afforded in 37% and 22% (Table 1, entries 10 and 11), respectively. With CH_2Cl_2 as solvent, the yield of the reaction was produced in a relatively low yield (Table 1, entry 12).

Under these optimized conditions,[11] we next explored the scope of one-pot synthesis of 2-alkyl-substituted chromanones **3**. As shown in Table 2, a variety of *ortho*-acylphenols **1** were employed as reaction substrates and the reaction can afford the corresponding chromanone derivatives in moderate to good yields regardless of the different substitutions on aromatic ring of *ortho*-acylphenol. Clearly, substrate with an electron-donating group on the aromatic ring gave better yield than that of an electron-withdrawing group on the aromatic ring. For example, substrates with methyl, methoxy or ethoxy group, the yields of corresponding products were afforded in good yields (Table 2, entries 2–6). While the substrate with a chloro group in the phenyl ring gave the corresponding product in moderate yield, a low yield of 25% was obtained under typical conditions when naphthyl substrate **1i** was submitted to the reaction. After optimized conditions for this substrate, 53% yield of **3i** was obtained when the reaction of substrate **1i** with ethyl propiolate was performed in the presence of DABCO for 4 h, followed by addition of KOBu^t with stirring for another 0.5 h (Table 2, entry 9). Notably, the multi-substituted *ortho*-acylphenols, such as **1k** and **1l**, also reacted smoothly to give the corresponding products in moderate yields. But the reaction became complex when 1-(2-hydroxyphenyl)propan-1-one **1m** was used as substrate, which might be due to steric hindrance. On the other hand, when other electron-deficient alkynes, such as methyl propiolate, but-3-yn-2-one, and 1-phenylprop-2-yn-1-one, were applied into the reaction, the corresponding products were given in moderate to good yields.

The proposed mechanism for the formation of 2-alkyl-substituted chromanone **3** is shown in Scheme 2. *Ortho*-acylphenol **1** is added to ethyl propiolate via Michael-type reaction catalyzed by DABCO to give enol ether **4**.[10] The enol ether **4** will undergo an intramolecular cycloaddition mediated by KOBu^t to generate intermedi-

Table 2
Reactions of *ortho*-acylphenols **1** with electron-deficient alkynes for synthesis of 2-alkyl-substituted chromanones

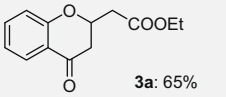
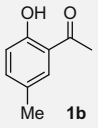
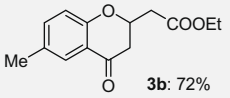
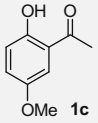
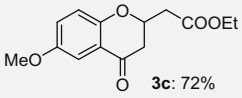
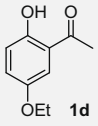
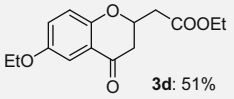
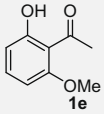
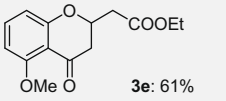
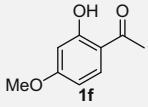
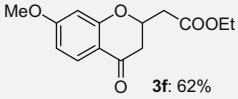
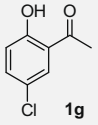
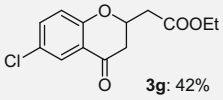
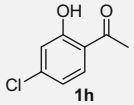
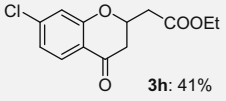
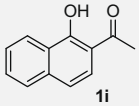
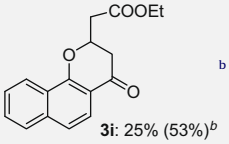
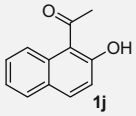
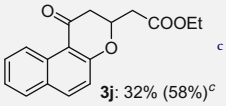
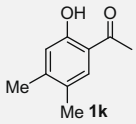
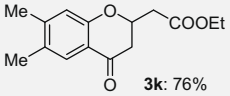
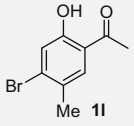
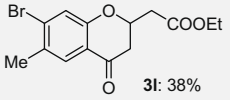
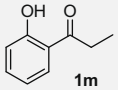
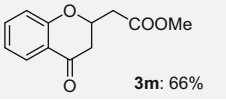
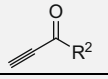
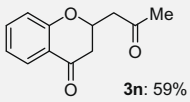
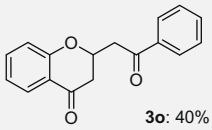
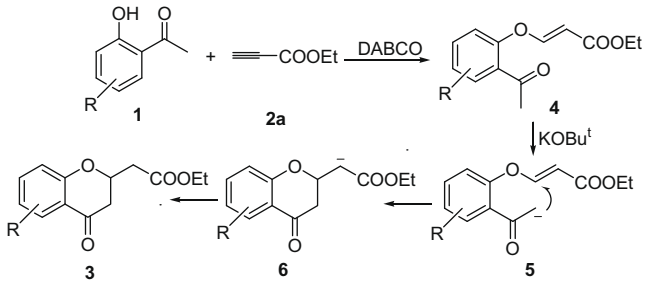
Entry	Substrate		Product, yield[a]
1	 **1a**	EtO	 **3a**: 65%
2	 **1b**	EtO	 **3b**: 72%
3	 **1c**	EtO	 **3c**: 72%
4	 **1d**	EtO	 **3d**: 51%
5	 **1e**	EtO	 **3e**: 61%
6	 **1f**	EtO	 **3f**: 62%
7	 **1g**	EtO	 **3g**: 42%
8	 **1h**	EtO	 **3h**: 41%
9	 **1i**	EtO	 [b] **3i**: 25% (53%)[b]
10	 **1j**	EtO	 [c] **3j**: 32% (58%)[c]
11	 **1k**	EtO	 **3k**: 76%
12	 **1l**	EtO	 **3l**: 38%
13	 **1m**	EtO	Complex
14	 **1a**	MeO	 **3m**: 66%

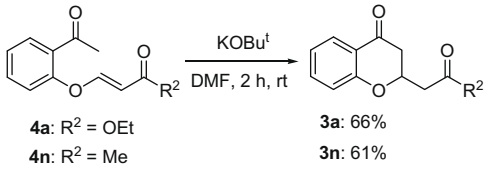
Table 2 (*continued*)

Entry	Substrate		Product, yield[a]
15	 **1a**	Me	 **3n**: 59%
16	 **1a**	C_6H_5	 **3o**: 40%

[a] Isolated yield.
[b] The reaction of substrate **1i** with ethyl propiolate was performed in the presence of DABCO for 4 h, followed by addition of $KOBu^t$ with stirring for another 0.5 h.
[c] The reaction was stirred for 0.5 h after $KOBu^t$ was added.



Scheme 2. Possible mechanism for the formation of chromanone derivative **3**.



Scheme 3. The intramolecular cycloaddition of enol ethers mediated by $KOBu^t$.

ate **6**, which could be subsequently hydrolyzed to give the desired product **3**. In order to further understand the reaction procedure, enol ethers **4a** and **4n** were synthesized from the reaction of 2-hydroxyacetophenone **1a** with electron-deficient alkynes in the presence of DABCO. The reaction of **4a** and **4n** mediated by $KOBu^t$ in DMF at room temperature did give the expected products **3a** and **3n** in 66% and 61% isolated yields, respectively, as shown in Scheme 3.

In summary, we have developed a facile one-pot synthetic method of 2-alkyl-substituted chromanones starting from commercially available *ortho*-acylphenols. With the application of this synthetic method, a series of chromanone derivatives were prepared in moderate to good yields.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.093.

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11. *General reaction procedure*: To a solution of *ortho*-acylphenols (0.5 mmol) and terminal alkynoates (0.6 mmol) in DMF was added DABCO (0.05 mol, 6 mg), and the resulting mixture was performed at room temperature for 0.5 h. Subsequently, $KOBu^t$ (0.6 mmol, 70 mg) was added and the reaction was stirred for another 2 h. Then the reaction was quenched by ice water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine and then dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give crude products, which were purified by column chromatograph packed with silica gel using petroleum ether/ethyl acetate (20:1) as eluent to afford the pure products.