One-Pot Synthesis of 4*H*-Chromenes by Tandem Benzylation and Cyclization in the Presence of Sodium Bisulfate on Silica Gel

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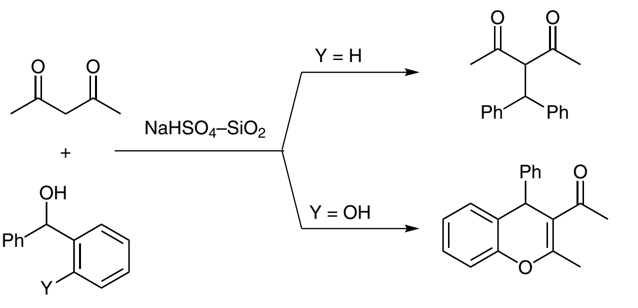
Abstract: A simple and efficient method has been developed for the synthesis of 4*H*-chromenes from *o*-hydroxybenzylic alcohols and dicarbonyl compounds containing active methylene groups by using silica gel supported sodium bisulfate. Various dicarbonyl compounds such as diketones, keto esters, and keto amides can be used in the synthesis of the 4*H*-chromenes.

Key words: cyclizations, benzylations, supported reagents, chromenes, one-pot syntheses

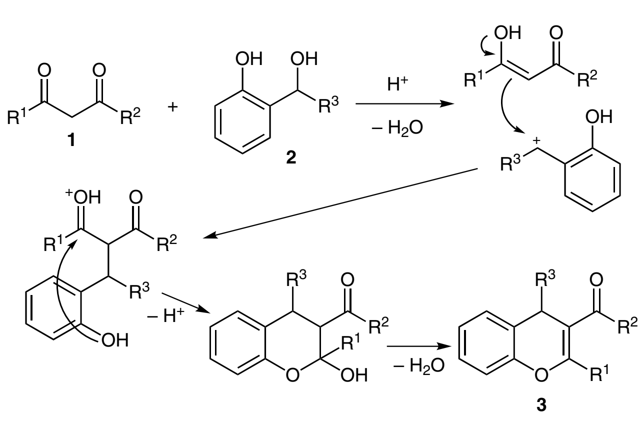
Derivatives of 4*H*-chromene have attracted growing interest in recent years because of their wide range of pharmacological and biological activities, including diuretic, spasmolytic, anticoagulant, anticancer, and anti-anaphylactic activities.[1] As a result, many methods have been developed for the synthesis of 4*H*-chromene derivatives, including three-component reactions catalyzed by L-proline,[2] reactions of salicylic aldehydes with β-dicarbonyl compounds in the presence of iodo(trimethyl)silane,[3] gold(III)-catalyzed tandem reaction of ketones with phenols,[4] *p*-toluenesulfonic acid monohydrate catalyzed reactions of acetophenones with 3-methoxybenzene-1,2-diol,[5] 1,4-diazabicyclo[2.2.2]octane-catalyzed reactions of salicyl *N*-tosylimines with allenic esters or ketones,[6] iron(III) chloride catalyzed benzylation and cyclization of 1,3-dicarbonyl compounds,[7] copper(I) iodide catalyzed intramolecular coupling of aryl bromides with 1,3-dicarbonyl compounds,[8] intramolecular ring-closing metathesis in the presence of the second-generation Grubbs catalyst,[9] tetrahydrothiophene-catalyzed ylide annulation,[10] and other methods.[11]

We recently reported C–C bond formation reactions of 1,3-dicarbonyl compounds with benzylic alcohols in the presence of sodium bisulfate supported on silica gel.[12] In the course of this study, we found out that 4*H*-chromene derivative were easily formed when 2-[hydroxy(phenyl)methyl]phenol was used instead of diphenylmethanol in the presence of sodium bisulfate on silica gel (Scheme 1).



Scheme 1 Reactions of acetylacetone with benzylic alcohols

A similar reaction using a Brønsted acid as a catalyst in an ionic liquid has been reported by Funabiki and co-workers;[13] however, their procedure involves laborious workup to obtain a pure product. We therefore attempted to develop a simpler method for the synthesis of 4*H*-chromenes from various alcohols and dicarbonyl compounds such as diketones, keto esters, or keto amides. Here, we describe a one-pot synthesis of 4*H*-chromenes by a tandem benzylation and cyclization in the presence of sodium bisulfate on silica gel (Scheme 2).



Scheme 2 Synthesis of chromenes in the presence of sodium bisulfate on silica gel

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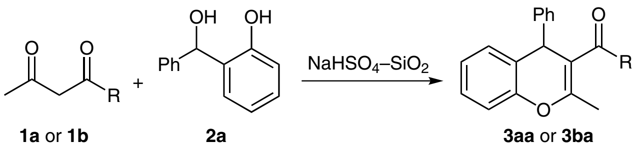
Conditions such as the solvent, the acid catalyst, and the amount of sodium bisulfate for alkylation of 1,3-dicarbonyl compounds had previously been optimized, as described in our earlier report.[12] In the construction of chromenes, compound **3aa** was obtained in high yield when the reaction of acetylacetone (**1a**; 2 mmol) with 2-[hydroxy(phenyl)methyl]phenol (**2a**; 2 mmol) was carried out in the presence of 2.1 mmol of sodium bisulfate on silica gel at 60 °C for 0.5 hours (Table 1, entry 1). The corresponding reaction of ethyl acetoacetate (**1b**) gave the chromene **3ba** in low yield; however, by using five equivalents of **1b**, we obtained chromene **3ba** in 90% yield (entry 5).

Table 1 Reaction of Diol **2a** with Acetylacetone (**1a**) or Ethyl Acetoacetate (**1b**)



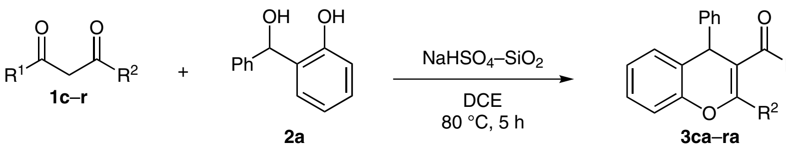
Entry	R	**1**/**2a** (mmol)	Temp (°C)	Time (h)	Product	Yield[a] (%)
1	Me	2:2	60	0.5	**3aa**	94
2	OEt	2:2	80	0.5	**3ba**	28
3	OEt	2:2	80	3	**3ba**	52
4	OEt	6:2	80	5	**3ba**	69
5	OEt	10:2	80	5	**3ba**	90

[a] Isolated yield.

We then examined the reactions of various β-diketones, keto esters, and keto amides with diol **2a** (Table 2). In the reaction of symmetrical diketones with diol **2a**, 2,6-dimethylheptane-3,5-dione (**1c**) gave the corresponding chromene **3ca** in 63% yield, along with 6% of a structural isomer (entry 1). 2,2,6,6-Tetramethylheptane-3,5-dione (**1d**) did not give **3da** at all; in this reaction, alkylation of **1d** with **2a** did not occur, and dimers, trimers, and tetramers of **2a** were formed by self-alkylation (entry 2). On the other hand, the reaction of 1,3-diphenylpropane-1,3-dione (**1e**) with diol **2a** gave the corresponding chromene **3ea** in excellent yield (entry 3). Cyclic diketones **1f**–**h** also gave the corresponding chromenes **3fa**, **3ga**, and **3ha** in moderate to good yields (entries 4–6). In the reaction of the nonsymmetrical cyclic diketone **1h**, chromene **3ha** was formed selectively, and no structural isomer was obtained.

On the basis of these results, we examined the reactions of various aliphatic nonsymmetrical diketones (**1i**, **1j**, and **1k**) with diol **2a** to determine whether the corresponding chromenes could be obtained selectively (entries 7–9). Not all the diketones gave the corresponding chromenes selectively. The reactions of **1i** and **1k** gave mixtures of the corresponding chromenes and their regioisomers in 83% and 94% total yields. In contrast, the reaction of diketone **1j** gave the expected chromene in 23% yield, along an unexpected product, 2-*tert*-butyl-4-phenyl-4*H*-chromene (**4**), in 29% yield.

Table 2 Reaction of Diol **2a** with Various β-Dicarbonyl Compounds



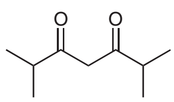
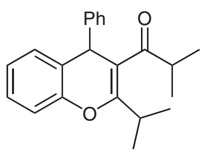
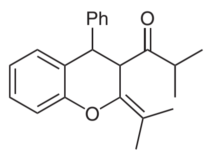
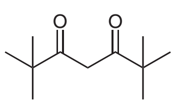
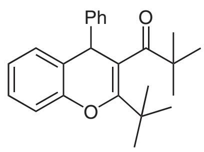
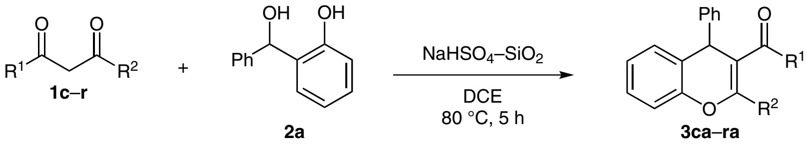
Entry		Diketone	**1**/**2a** (mmol)	Product		Yield (%)[a]
1	**1c**		6:2		**3ca**	63
					**3′ca**	6
2	**1d**		6:2		**3da**	N.D.

Table 2 Reaction of Diol **2a** with Various β-Dicarbonyl Compounds (continued)



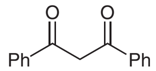
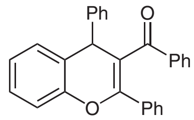
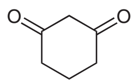
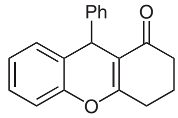
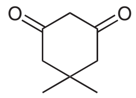
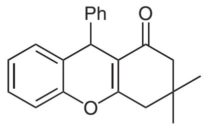
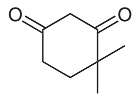
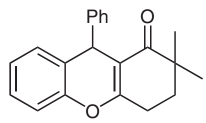
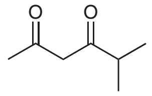
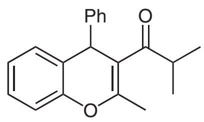
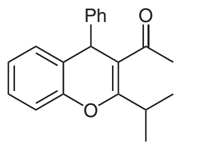
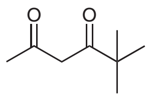
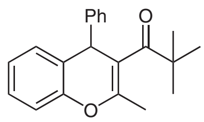
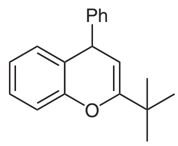
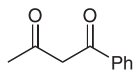
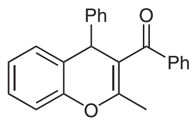
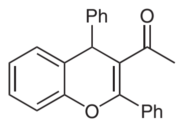
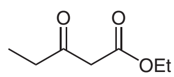
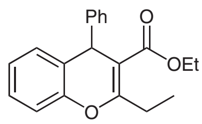
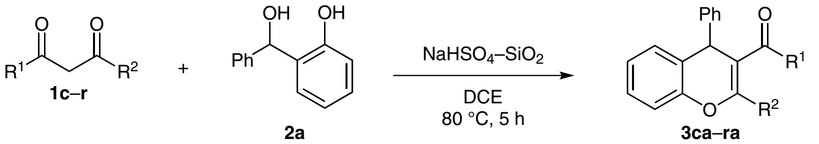
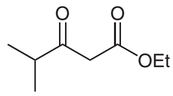
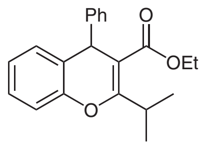
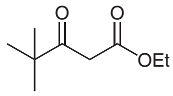
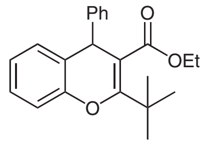
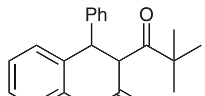
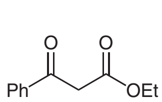
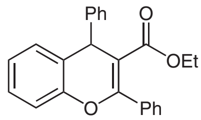
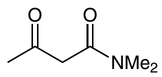
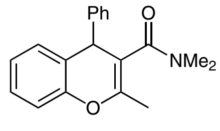
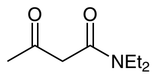
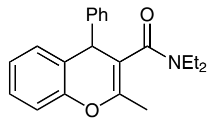
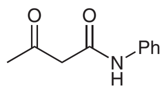
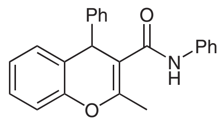
Entry		Diketone	**1**/**2a** (mmol)	Product		Yield (%)[a]
3	**1e**		6:2		**3ea**	98
4	**1f**		6:2		**3fa**	89
5	**1g**		6:2		**3ga**	66
6	**1h**		6:2		**3ha**	86
7	**1i**		6:2		**3ia**	47
					**3ia′**	36
8	**1j**		6:2		**3ja**	23
					**4**	29
9	**1k**		6:2		**3ka**	72
					**3ka′**	22
10	**1l**		10:2		**3la**	78

Table 2 Reaction of Diol **2a** with Various β-Dicarbonyl Compounds (continued)



Entry		Diketone	**1**/**2a** (mmol)	Product		Yield (%)[a]
11	**1m**		10:2		**3ma**	51
12	**1n**		10:2		**3na**	6
					**3na′**	10
13	**1o**		6:2		**3oa**	84
14	**1p**		6:2		**3pa**	88
15	**1q**		6:2		**3qa**	82
16	**1r**		6:2		**3ra**	61

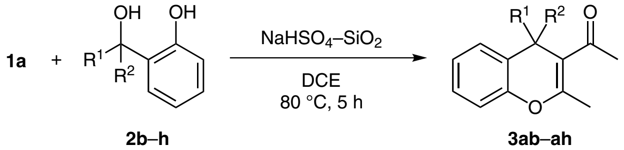
[a] Isolated yield.

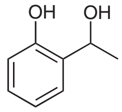
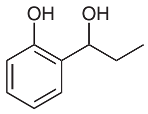
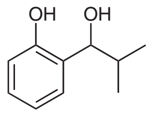
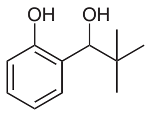
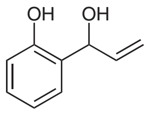
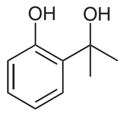
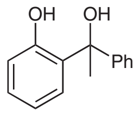
In the reactions of β-keto esters, yields of the products decreased as the number of methyl group attached to the acetyl carbon increased (Table 1, entry 5 and Table 2, entries 10–12). The reaction of ethyl acetoacetate (**1b**) gave chromene **3ba** in 90% yield, whereas the reaction of keto ester **1l** gave chromene **3la** in 78% yield and keto ester **1m** gave **3ma** in 51% yield (Table 2, entries 10 and 11). In the reaction of keto ester **1n**, intramolecular cyclization occurred at the carbons of the carbonyl group and the ester group, and a mixture of the expected chromene **3na** and the chroman derivatives **3na′** was obtained (entry 12). The use of three equivalents of ethyl benzoylacetate (**1o**) or β-keto amides **1p**–**r** was necessary to obtain good yields of the corresponding chromene derivatives (entries 13–16).

We also tested other benzylic diols instead of **2a** in the reaction with acetylacetone (**1a**) (Table 3). Reaction of acetyl acetone (**1a**) with diol **2b** gave **3ab** in 58% yield (Table 3, entry 1). Other secondary benzylic alcohols **2c** and **2d** also reacted with **1a** to give the corresponding chromenes (entries 2 and 3).

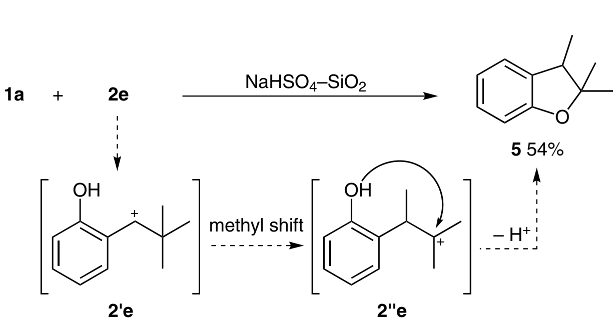
However, the reaction of diol **2e** did not give the corresponding chromene **3ae**, and 2,2,3-trimethyl-2,3-dihydrobenzofuran (**5**) was obtained instead in 54% yield (Table 3, entry 4). In a plausible pathway for this reaction (Scheme 3), the cationic intermediate **2′e** is generated by sodium bisulfate on silica gel and undergoes a methyl shift to give **2″e**, which cyclizes intramolecularly to form **5**.

Table 3 Reactions of Acetylacetone (**1a**) with *o*-Hydroxybenzylic Alcohols



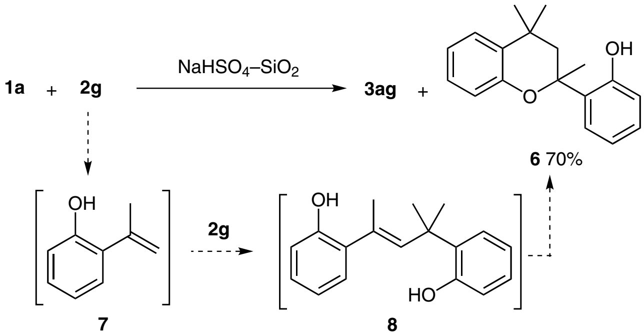
Entry[a]		Diol	Product	Yield[b] (%)
1	**2b**		**3ab**	58
2	**2c**		**3ac**	58
3	**2d**		**3ad**	40
4	**2e**		**3ae**	N.D.[c]
5	**2f**		**3af**	6
6	**2g**		**3ag**	15[d]
7	**2h**		**3ah**	N.D.[e]

[a] A **1a**/**2** ratio of 6:2 was used in all the reactions.
[b] Isolated yield.
[c] 2,2,3-Trimethyl-2,3-dihydrobenzofuran (**5**) was obtained instead; see Scheme 3.
[d] Chromane **6** was the main product; see Scheme 4.
[e] The dehydration product, 2-(1-phenylvinyl)phenol, was the main product.



Scheme 3 Plausible reaction path for the formation of 2,2,3-trimethyl-2,3-dihydrobenzofuran (**5**)

When diol **2g** was used in the reaction, the expected chromene **3ag** was obtained in only 15% yield, along with the unexpected chromane **6** in 70% yield (Table 3, entry 6). The formation of **6** can be explained as follows (Scheme 4): dehydration of diol **2g** in the presence of sodium bisulfate gives enol **7**, which reacts with a further molecule of diol **2g** to form the ene diol **8**;[14] this then undergoes intramolecular cyclization to give chromane **6** as the final product.



Scheme 4 Plausible reaction path for the formation of chromane **6**

The formation of chromane ring systems by coupling of alcohols is not a known reaction, and this represents a novel method for the synthesis of chromanes. In the reaction of diol **2h**, the corresponding chromene was not formed, and the dehydration product, 2-(1-phenylvinyl)phenol, was obtained as the main product (Table 3, entry 7).

In conclusion, we have developed a simple method for the synthesis of 4*H*-chromenes by tandem benzylation and cyclization in the presence of sodium bisulfate on silica gel. Various diketones, keto esters, and keto amides can be used in the synthesis of 4*H*-chromenes. In addition, we discovered novel routes to 2,3-dihydrobenzofurans and chromanes; these are now under investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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