Facile construction of functionalized 4*H*-chromene *via* tandem benzylation and cyclization†

Jinmin Fan and Zhiyong Wang*

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A series of functionalized 4*H*-chromenes have been constructed by using a novel $FeCl_3$-catalyzed benzylation–cyclization tandem reaction.

Chromenes (2*H*-chromenes and 4*H*-chromenes) constitute one of the major classes of naturally occurring compounds,[1] and interest in their chemistry continues unabated because of their usefulness as biologically active agents[2] behaving as β-cell KATP channel openers, DNA-dependent protein kinase (DNA-PK), DNA polymerase β inhibitors, anti-tyrpanosomal agents, anti-bacterial, agentsapoptosis inducers, as well as their utility as key intermediates in the synthesis of numerous natural products and medicinal reagents.[3] Among the overwhelming chromene family members, 4*H*-chromenes are rather unusual and several examples of natural products and biologically active compounds containing this structure have been reported.[4] Some examples are the miroestrol (**A** in Fig. 1), antibiotic rhodomyrtone (**B** in Fig. 1), α-glucosidase inhibitor myrtucommulone-E (**C** in Fig. 1) and HA14-1, apoptosis inducer (**D** in Fig. 1). Previously, the conventional methods for synthesizing 4*H*-chromenes are (1) the cycloaddition of propargylic alcohols with phenol derivatives catalyzed thiolate-bridged diruthenium complexes $[(\eta^5\text{-}C_5Me_5)RuCl(\mu_2\text{-}SMe)_2Ru(\eta^5\text{-}C_5Me_5)Cl]$ and NH_4BF_4;[5] (2) DABCO-catalyzed reaction of salicyl *N*-tosylimines with Allenic Esters or diethyl cetylenedicarboxylate;[6] (3) copper-mediated aryl vinyl ether formation followed by a ruthenium-mediated RCM reaction;[7] (4) CuI/DMEDA-catalyzed intramolecular coupling of aryl bromides with 1,3-dicarbonyls *via* a six-membered ring closure;[8] (5) the tetrahydrothiophene-catalyzed ylide annulation reaction, *via* tandem Michael addition/elimination/substitution.[9] However, all of these approaches suffer from either the limited diversity of available starting materials or the use of expensive catalysts. In order to circumvent these problems, the development of a general, efficient and conventional method for 4*H*-chromenes has been strongly desired.

In recent years, benzylic alcohols and their derivatives have received considerable attention as carbon electrophiles capable of reacting with various carbon, oxygen and sulfur nucleophiles.[10,11] The benzylation of 1,3-dicarbonyl compounds is definitely a useful tool for the formation of C–C bonds in organic synthesis, and has been investigated extensively.[11] Among a variety of approaches for the benzylation of 1,3-dicarbonyl compounds, alcohols are arguably among the most ideal substrates that have received increasing attention. Brønsted acid or Lewis acid-catalyzed nucleophilic substitution of alcohols have gained great attentions in recent years, involving $BF_3{\cdot}OEt_2$, $AuCl_3$,[10b] $InCl_3$,[11a] H-montmorillonite[11b] and $Bi(OTf)_3$.[11d] Compared to the classical benzylation reactions, this new methodology offers several potential advantages, such as the wide availability of starting materials and generation of H_2O as an only side product.

Herein, we present a novel approach to synthesize functionalized 4*H*-chromenes with a readily available catalyst-$FeCl_3$ *via* tandem benzylation and cyclization. In this simple domino assembly, readily obtained electrophile substituted 2-(hydroxymethyl)phenols **1** and β-ketoesters or β-diketones **2** are used as starting materials to produce functionalized 4*H*-chromene products **3** (Scheme 1).

Initial studies were performed in nitromethane using 2-(hydroxy(phenyl)methyl)phenol and ethyl 3-oxobutanoate as model substrates (Table 1). Different Lewis acids were first examined and it was found that iron(III) chloride was the best catalyst for this transformation (Table 1, entry 6). Further investigation conducted with a solvent screen and a significant solvent effect was observed. When shifting the solvent to dioxane or acetonitrile, only a trace or small amount of desired product was detected (Table 1, entries 10 and 8). To our delight, the reaction yield can be enhanced to 76% when dichloromethane (DCM) was employed as the solvent. In addition, because two equivalents of water was generated in

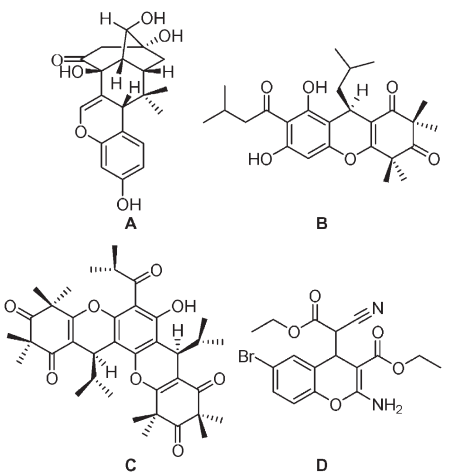

Fig. 1 Some 4*H*-chromenes embodied natural products and biological compounds.

Hefei National Laboratory for Physical Science at Microscale, Joint- Lab of Green Synthetic Chemistry and Department of Chemistry, University of Science and Technology of China, Hefei, 230026, P. R. China. E-mail: zwang3@ustc.edu.cn; Fax: (+86) 551-360-3185; Tel: (+86) 551-360-3185

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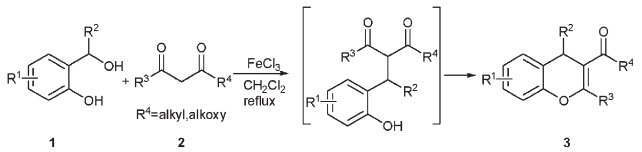
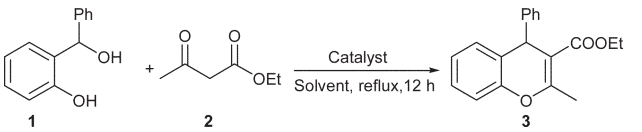


Scheme 1 Synthesis of 4*H*-chromene **3** from substituted 2-(hydroxymethyl)phenol **1** and β-ketoester or β-diketone **2**.

Table 1 Catalysts and solvents screened for construction functionalized 4*H*-chromene[a]



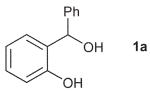
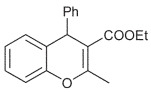
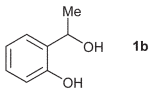
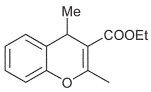
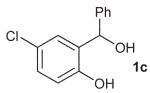
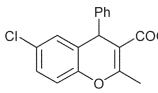
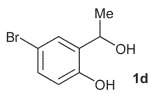
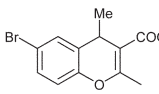
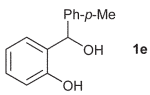
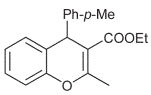
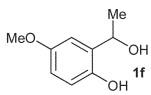
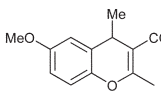
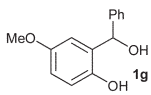
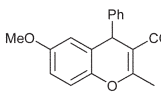
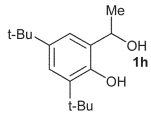
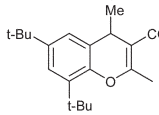
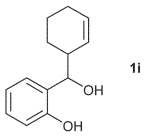
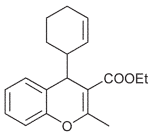
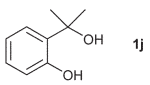
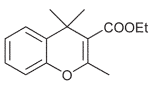
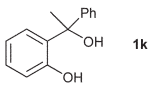
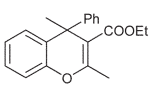
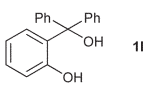
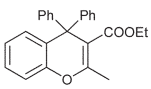
Entry	Catalyst (10 mol%)	Solvent	Yield[b] (%)
1	$CoCl_2$	CH_3NO_2	0
2	$Cu(OTf)_2$	CH_3NO_2	Trace
3	$Zn(OTf)_2$	CH_3NO_2	Trace
4	$Bi(OTf)_3$	CH_3NO_2	32
5	$Sn(OTf)_2$	CH_3NO_2	0
6	$FeCl_3$	CH_3NO_2	53
7	$FeCl_2{\cdot}4H_2O$	CH_3NO_2	0
8	$FeCl_3$	CH_3CN	17
9	$FeCl_3$	CH_2Cl_2	76
10	$FeCl_3$	Dioxane	Trace
11	$Fe(acac)_3$[c]	CH_2Cl_2	0
12[d]	$FeCl_3$	CH_2Cl_2	88

[a] *Reaction conditions*: 2-(hydroxy(phenyl)methyl)phenol **1** (0.5 mmol), ethyl 3-oxobutanoate **2** (1.0 mmol), solvent (1.5 ml). [b] Yield of isolated product. [c] acac = acetylacetone. [d] 0.5 g of 4 Å MS was added.

this process, the removal of the water from this reaction mixture can facilitate the reaction, which was confirmed in entry 12, Table 1.

After the optimization of the reaction conditions, we examined the scope and the generality of the transformation.‡ First, we focused on the reactivity of different substituted 2-(hydroxymethyl)phenols **1**. As shown in Table 2, a variety of substituted 2-(hydroxymethyl)phenols with electron-donating or -withdrawing groups were employed as the reaction substrates and the reactions can afford the corresponding 4*H*-chromene products in good to excellent yields regardless of the different substitutions. The presence of an electron-withdrawing substituent on the 2-(hydroxymethyl)phenol appeared to be only a slight influence on the reactivity (Table 2, entries 3 and 4). On the other hand, a strong electron-donating groups on the 2-(hydroxymethyl)phenol favored the reaction and the corresponding 4*H*-chromenes were obtained in excellent yields (Table 2, entries 5–8), perhaps due to the higher stability of the corresponding carbocation intermediates. Surprisingly, 2,4-di-*tert*-butyl-6-(1-hydroxyethyl)phenol **1h** yielded ethyl 6,8-di-*tert*-butyl-2,4-dimethyl-4*H*-chromene-3-carboxylate **3h** with a yield of 95% in spite of the strong steric hindrance on the aromatic ring. When substrate with 3-cyclohex-1-ene substituent was used, the annulation produced the corresponding 4*H*-chromene product with a moderate yield (Table 2, entry 9). Tertiary alcohol **1j**, which possess six β-H, gave the lowest

Table 2 Reaction of substituted 2-(hydroxymethyl)phenols **1** with ethyl 3-oxobutanoate **2a**[a]

Entry	Substrate **1**	4*H*-Chromene **3**	Yield (%)[b]
1	 **1a**	 **3a**	88
2	 **1b**	 **3b**	81
3	 **1c**	 **3c**	80
4	 **1d**	 **3d**	74
5	 **1e**	 **3e**	89
6	 **1f**	 **3f**	87
7	 **1g**	 **3g**	92
8	 **1h**	 **3h**	95
9	 **1i**	 **3i**	66
10	 **1j**	 **3j**	34
11	 **1k**	 **3k**	64[c]
12	 **1l**	 **3l**	78

[a] *Reaction conditions*: substrate **1** (0.5 mmol), ethyl 3-oxobutanoate **2** (1.0 mmol), $FeCl_3$ (0.05 mmol), CH_2Cl_2 (1.5 ml), 4 Å MS (0.5 g), reflux, 12 h. [b]Yield of isolated product. [c]Yield of isolated product after 24 h.

yield of the corresponding products (Table 2, entry 10). When **1k** was employed as the reaction substrate 50% yield of the elimination product 2-(1-phenylvinyl)phenol was obtained after reaction for 8 h. Prolonging the reaction time to 24 h, the annulation product **3k** can be obtained with a yield of 64% (Table 2, entry 11). Combining the above results and theoretic analysis, we speculate that annulation occurs *via* a carbocation intermediate and the elimination of β-H is a main side reaction. Tertiary alcohol **1l** without a β-H adjacent to benzyl alcohol group gave the corresponding 4*H*-chromene product with a yield of 78% (Table 2, entry 12). Compared to the

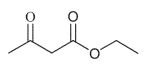
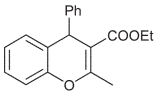
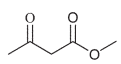
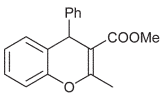
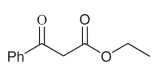
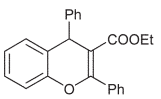
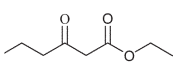
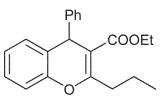
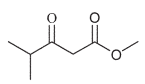
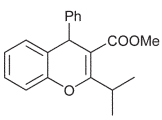
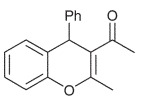
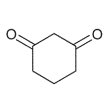
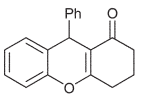
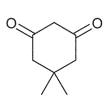
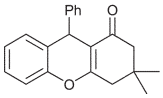
reaction of **1g** or **1h** as the reaction substrate, this reaction in entry 12 gave the product with a lower yield, perhaps due to a strong steric hindrance from the two phenyl groups.

Subsequently, we set out to study the scope and limitation of β-ketoester or β-diketone reactants in detail. As shown in Table 3, a range of different β-ketoesters or β-diketones were employed as the reaction substrates and the corresponding reactions were carried out smoothly with excellent yields. For β-ketoesters, no significant influences of various β-ketoesters were observed except for methyl 4-methyl-3-oxopentanoate (Table 3, entry 5) probably due to the bigger hindrance adjacent to the carbonyl group. For β-diketones, higher yields were obtained compared to β-ketoesters, which showed that the reaction activity of β-diketones is higher that of β-ketoesters in this annulation reaction.

In conclusion, we have developed a novel annulation for convenient and effective construction of functionalized 4*H*-chromenes from easily available substrates under mild conditions. The use of a simple iron salt as catalyst renders the protocol suitable for large-scale synthesis, providing a valuable access to assemble biologically active molecules.

This work was supported by the National Natural Science Foundation of China (20628202).

Table 3 Reaction of 2-(hydroxy(phenyl)methyl)phenol **1a** with different β-ketoesters or β-diketones **2**[a]

Entry	β-ketoester/β-diketone **2**		4*H*-Chromene **3**		Yield (%)[b]
1		**2a**		**3a**	88
2		**2b**		**3m**	92
3		**2c**		**3n**	97
4		**2d**		**3o**	88
5		**2e**		**3p**	68
6		**2f**		**3q**	94
7		**2g**		**3r**	95
8		**2h**		**3s**	92

[a] *Reaction conditions*: 2-(hydroxy(phenyl)methyl)phenol **1** (0.5 mmol), β-ketoester or β-diketone **2** (1.0 mmol), $FeCl_3$ (0.05 mmol), CH_2Cl_2 (1.5 ml), 4 Å MS (0.5 g), reflux, 12 h. [b]Yield of isolated product.

Notes and references

‡ *Representative procedure* for $FeCl_3$-catalyzed construction functionalized 4*H*-chromene: $FeCl_3$ (8.1 mg, 0.05 mmol), and 0.50 g of 4 Å MS were added to a solution of **1a** (0.5 mmol) and **2a** (1.0 mmol) in freshly distilled CH_2Cl_2 (1.5 mL). The resulting mixture was refluxed for 12 h, then cooled to room temperature and quenched with saturated $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 twice. The combined organic extracts were dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using PE–EtOAc (10 : 1, v/v) as eluent to give **3a** as a colorless oil (129.0 mg, 88%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 7.13–7.11 (m, 4 H), 7.04–6.99 (m, 2 H), 6.94–6.85 (m, 3 H), 4.93 (s, 1 H), 4.00–3.95 (m, 2 H), 2.39 (s, 3 H), 1.06 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 167.2, 160.1, 149.6, 146.8, 129.4, 128.5, 128.0, 127.6, 126.6, 125.0, 124.6, 116.3, 106.3, 60.2, 41.7, 19.6, 14.2; IR (liquid film, cm^{-1}): v = 3063, 2979, 2872, 1711, 1643, 1585, 1488, 1456, 1380, 1331, 1288, 1218, 1106, 1064, 985, 754, 698, 621; HRMS calc. $C_{19}H_{18}O_3$ (M^+): 294.1256. Found: 294.1263.

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