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ARTICLE TYPE

Synthesis of functional 4*H*-chromenes from phenols and acetophenones under solvent- and metal-free conditions

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Sulfuric-acid-promoted tandem reaction of phenols with acetophenones under solvent- and metal-free conditions has been developed, which afforded functional 4*H*-chromenes in good yields with water as the side product. Sulfuric acid appeared to serve the dual role of an efficient promoter and a suitable dehydrating agent.

Introduction

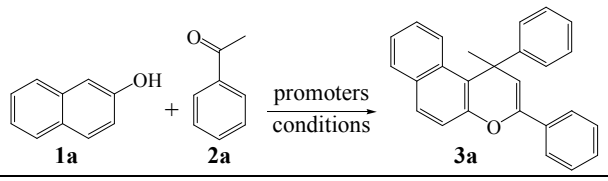
4*H*-Chromenes have been a subject of consistent interest due to the presence of their structural motifs in a large number of natural products[1] and pharmaceuticals. Some of the biological activities attributed to naturally occurring and synthetic 4*H*-chromenes include antioxidant[2], antifungal[3], antimicrobial[4], antileishmanial[5], antiviral[6], antitubercular[7], antiproliferative[8] and anticancer[9]. The significance and prevalence of this class of compounds has served to stimulate continual interest in synthetic community. Accordingly, various synthetic methods have been developed for the construction of 4*H*-chromenes, which usually require a transition metal-catalyst or/and an organocatalyst, a high temperature, and use of an organic solvent and unavailable starting materials[10–11]. Recently, Liu and Xu have developed an elegant $AuCl_3$/3AgOTf-catalyzed synthesis of 4*H*-chromenes from readily available ketones and phenols in 1,2-dichloroethane under reflux[12], in which trifluoromethanesulfonic acid and aqueous hydrochloric acid were found to be not the suitable promoters. Wu and co-workers have also developed an impressive synthesis of chromenes from active polyphenols and acetophenones in the presence of *p*-toluenesulfonic acid in *n*-hexane under reflux (100 °C, sealed tube)[13]. As witnessed in the above two examples, it is still a challenge to develop an efficient Brønsted-acid-promoted synthesis of 4*H*-chromenes from readily available phenols and acetophenones. Considering dehydrating agents should be favourable in this kind of dehydrative reaction, we envisioned that the addition of a little concentrated sulfuric acid (H_2SO_4) to the reaction mixture would absorb the water produced, and thereby facilitate the reaction of phenols with acetophenones.

On the other hand, a huge amount of effort has been dedicated to the development of chemical reactions in agreement with the principles of green chemistry. Although various green solvents, such as ionic liquids and water, have been extensively studied, not using a solvent at all is definitely the best option, which makes the development of solvent-free reactions a high priority. The progress in the field of solvent- and metal-free reactions is gaining much attention for their low cost, safety, and eco-friendliness. In connection with our consistent interest in the development of practical strategies for the selective synthesis of various functional heterocycles[14], herein we would like to report a facile synthesis of functional 4*H*-chromenes via H_2SO_4-promoted reaction of phenols with acetophenones without use of any solvent or metal-catalyst.

Results and Discussion

The reaction of 2-naphthol (**1a**) with acetophenone (**2a**) was used as a probe for evaluating the reaction conditions, and the representative results are summarized in Table 1. Reaction of **1a** with **2a** in the presence of one equivalent of concentrated H_2SO_4 could take place at 15 °C to afford 2,4-bis(aryl)-4*H*-chromene **3a** in 5% yield within 1 day (entry 1). An increased yield was observed when the reaction was performed at 25 °C, reflecting the temperature factor effect on this reaction (entries 1–2). Aqueous hydrochloric acid (HCl), formic acid (HCO_2H), acetic acid (CH_3CO_2H), trichloroacetic acid (CCl_3CO_2H), trifluoroacetic acid (CF_3CO_2H), diphenylphosphoric acid [$(PhO)_2P(O)OH$] and trifluoromethanesulfonic acid (TfOH) were not effective promoters for this reaction. Treatment of **1a** with **2a** in *n*-hexane at 25 °C for 1 day in the presence of these Brønsted acids did not generate any products and the starting materials were recovered (entries 3–9). Otherwise, *p*-toluenesulfonic acid (*p*TsOH) displayed some efficiency for this reaction, which afforded a trace of 4*H*-chromene **3a** at 25 °C within 1 day (entry 10). Instead, H_2SO_4 is the most efficient promoter for this reaction in all screened Brønsted acids (entries 1–10). The yield of **3a** was increased to 78% by improving the reaction temperature to 60 °C (entries 1–2 and 11–12). No further increase was observed when the reaction temperature exceeded 60 °C, and by-product **4a** (Fig. 1) was observed when this reaction was performed at 70 °C (entries 12–13). With the use of toluene, 1,2-dichloroethane(DCE) and nitromethane (CH_3NO_2) in comparison to *n*-hexane, relatively lower yields were observed (entries 12 and 14–16). In contrast, H_2SO_4/CH_3CO_2H was an effective system for this kind

Table 1 Survey of conditions for the reaction of 2-naphthol (**1a**) with acetophenone (**2a**)[a]



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

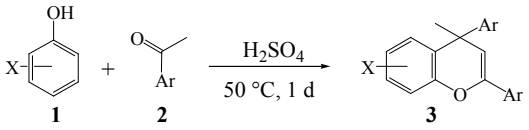
Entry	Promoters	Conditions	Yield
1	1.0 equiv. H_2SO_4	*n*-hexane, 15 °C	5%
2	1.0 equiv. H_2SO_4	*n*-hexane, 25 °C	18%
3	1.0 equiv. HCl (37%, H_2O)	*n*-hexane, 25 °C	0
4	1.0 equiv. HCO_2H	*n*-hexane, 25 °C	0
5	1.0 equiv. CH_3CO_2H	*n*-hexane, 25 °C	0
6	1.0 equiv. CCl_3CO_2H	*n*-hexane, 25 °C	0
7	1.0 equiv. CF_3CO_2H	*n*-hexane, 25 °C	0
8	1.0 equiv. $(PhO)_2P(O)OH$	*n*-hexane, 25 °C	0
9	1.0 equiv. TfOH	*n*-hexane, 25 °C	0
10	1.0 equiv. *p*TsOH	*n*-hexane, 25 °C	trace
11	1.0 equiv. H_2SO_4	*n*-hexane, 40 °C	43%
12	1.0 equiv. H_2SO_4	*n*-hexane, 60 °C	78%
13	1.0 equiv. H_2SO_4	*n*-hexane, 70 °C	54%
14	1.0 equiv. H_2SO_4	toluene, 60 °C	73%
15	1.0 equiv. H_2SO_4	$ClCH_2CH_2Cl$, 60 °C	75%
16	1.0 equiv. H_2SO_4	CH_3NO_2, 60 °C	72%
17	1.0 equiv. H_2SO_4	CH_3CO_2H, 60 °C	79%
18	1.0 equiv. H_2SO_4	solvent-free, 60 °C	80%
19	0.1 equiv. H_2SO_4	solvent-free, 60 °C	68%
20	1.5 equiv. H_2SO_4	solvent-free, 50 °C	81%
21[b]	1.5 equiv. H_2SO_4	solvent-free, 50 °C	80%
22	1.5 equiv. H_2SO_4	H_2O, 50 °C	0

[a] General conditions: **1a** (1.0 mmol), **2a** (3.0 mmol) and promoter in solvent (0.5 mL) or under solvent-free conditions for 1 day.
[b] Reaction was carried out at 1.45 g scale of **1a** (10.0 mmol) under an air atmosphere.

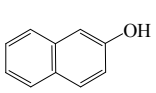
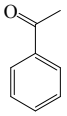
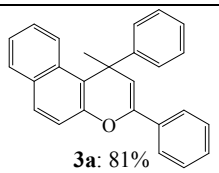
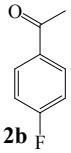
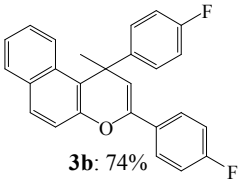
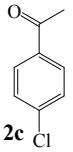
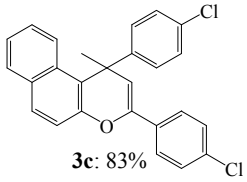
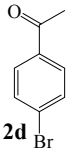
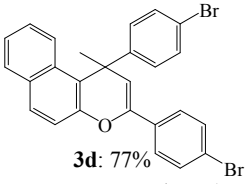
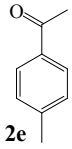
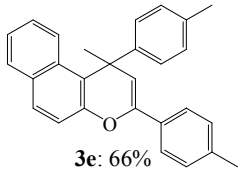
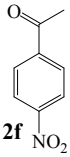
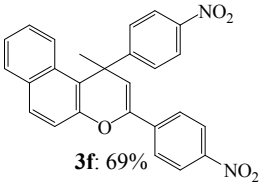
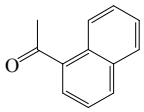
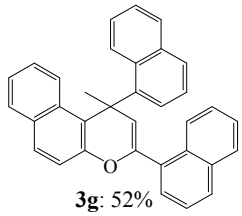
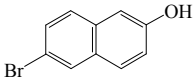
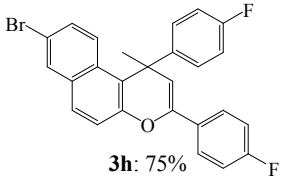
of reaction and might be useful for a large scale process with a solid mixture of substrates (entry 17). Fortuitously, **3a** was obtained in 80% yield when the reaction was performed under solvent-free conditions (entry 18). The yield of **3a** was decreased to 68% when the loading of H_2SO_4 was decreased from one equivalent to 10 mol% (entry 19), indicating the H_2SO_4 loading effect on this reaction. We envisioned that the reaction could go smoothly when a more amount of H_2SO_4 was used. Gratifyingly, by treating **1a** (1 mmol), **2a** (3 mmol) with one and a half equivalents of concentrated H_2SO_4, 4*H*-chromene **3a** was obtained in 81% yield at 50 °C under otherwise identical conditions (entries 18 and 20). Furthermore, scaling up **1a** to 1.45 g the reaction provided the yield at an excellent level, which was easy to perform without the need of using an anhydrous solvent (entry 21). The reaction did not work in the presence of water (several drops) under otherwise identical conditions (entries 20 and 22), indicating that concentrated H_2SO_4 serves also as a dehydrating agent.

With the optimized reaction conditions in hand, the scope of the reaction was subsequently investigated, and the representative results are summarized in Table 2. With the *para* position of acetophenones bearing a hydrogen atom (entry 1), a weak electron-withdrawing group (entries 2–4) and a weak electron-donating group (entry 5), acetophenones **2a**–**e** reacted smoothly with 2-naphthol (**1a**) in the presence of H_2SO_4 (150 mol%) at 50 °C to afford 2,4-bis(aryl)-4*H*-chromenes **3a**–**e** in 66–83% yields within 1 day (entries 1–5). 4′-Nitroacetophenone (**2f**) reacted

Table 2 H_2SO_4-promoted tandem reaction of phenols with acetophenones under solvent-free conditions[a]

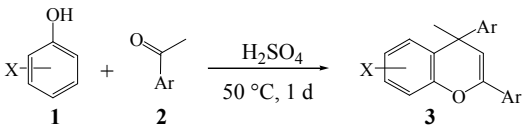


1 **2** **3**

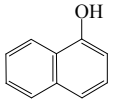
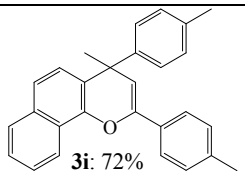
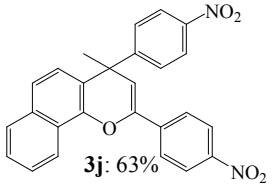
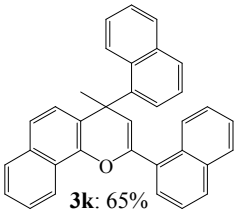
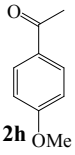
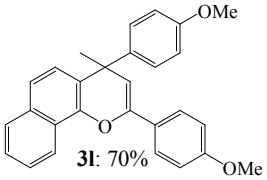
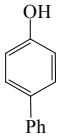
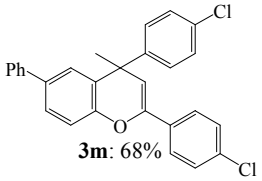
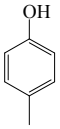
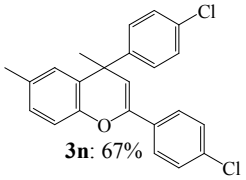
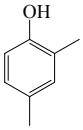
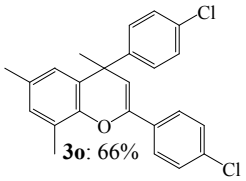
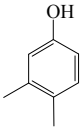
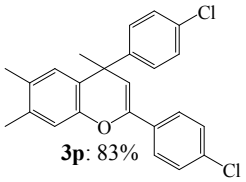
Entry	Phenols **1**	Acetophenones **2**	Products **3**
1	 **1a**	 **2a**	 **3a**: 81%
2	**1a**	 **2b** F	 **3b**: 74%
3	**1a**	 **2c** Cl	 **3c**: 83%
4	**1a**	 **2d** Br	 **3d**: 77%
5	**1a**	 **2e**	 **3e**: 66%
6	**1a**	 **2f** NO_2	 **3f**: 69%
7	**1a**	 **2g**	 **3g**: 52%
8	 **1b**	**2b**	 **3h**: 75%

[a] General conditions: **1** (1.0 mmol), **2** (3.0 mmol) and H_2SO_4 (1.5 mmol) at 50 °C for 1 day under solvent-free conditions.

Table 2 (Contd.)



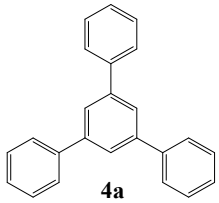
1 **2** **3**

Entry	Phenols **1**	Acetophenones **2**	Products **3**
9	 **1c**	**2e**	 **3i**: 72%
10	**1c**	**2f**	 **3j**: 63%
11	**1c**	**2g**	 **3k**: 65%
12	**1c**	 **2h**	 **3l**: 70%
13	 **1d**	**2c**	 **3m**: 68%
14	 **1e**	**2c**	 **3n**: 67%
15	 **1f**	**2c**	 **3o**: 66%
16	 **1g**	**2c**	 **3p**: 83%

[a] General conditions: **1** (1.0 mmol), **2** (3.0 mmol) and H_2SO_4 (1.5 mmol) at 50 °C for 1 day under solvent-free conditions.

equally well with **1a** under the standard conditions to give 4*H*-chromene **3f** in 69% yield (entry 6). It is worth mentioning that deactivated acetophenone **2f** prevented the tandem reaction in *p*-toluenesulfonic acid system[13]. 1'-Acetonaphthone (**2g**), a commercially available sterically hindered acetophenone, reacted with 2-naphthol under the standard conditions to generate 4*H*-chromene **3g** in 52% yield (entry 7). It is note worthy that sterically hindered acetophenones resisted the $AuCl_3$/3AgOTf system in the tandem reaction of acetophenones with phenols[12]. These results indicated that the present protocol might expand the substrate scopes of acetophenones and phenols.

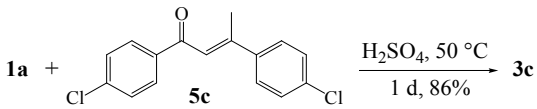
The tandem reaction of 6-bromo-2-naphthol (**1b**) with acetophenone **2a** went smoothly under the standard conditions to generate 4*H*-chromene **3h** in 75% yield (entry 8). 1-Naphthol (**1c**) has also been investigated, which reacted with acetophenones **2e**–**h** under the standard conditions to afford 4*H*-chromenes **3i**–**l** in good yields (entries 9–12). 4-Phenylphenol (**1d**) reacted with acetophenone **2c** uneventfully (entry 13). *p*-Cresol (**1e**) reacted smoothly with acetophenone **2c** under the standard conditions to give 4*H*-chromene **3n** in 67% yield (entry 14). 2,4-Dimethylphenol (**1f**), a phenol more sterically hindered than *p*-cresol, reacted equally well with acetophenone **2c** to give 4*H*-chromene **3o** in 66% yield (entry 15). By treatment of active 3,4-dimethylphenol (**1g**) with acetophenone **2c** under the standard conditions, 4*H*-chromene **3p** was obtained in 83% yield (entry 16). A homogeneous reaction system is formed in each case under the proposed reaction conditions. The yields of these 4*H*-chromenes could be improved under the standard conditions, albeit with a lower temperature and a longer reaction time. When these tandem reactions were performed at higher temperatures, by-products **4** would be partially formed. For example, compound **4a** (Fig. 1, 15–20% yields) along with 4*H*-chromenes **3a** (60–65% yields) was obtained when the reaction of acetophenone **2a** with phenol **1c** was performed at 65–70 °C.



4a

Fig. 1 Structure of by-product **4a**

Chalcone **5c** could be detected in the sulfuric-acid-promoted tandem reaction of phenol **1a** with acetophenone **2c**. Treatment of chalcone **5c** with **1a** in the presence of H_2SO_4 at 50 °C afforded 4*H*-chromene **3c** in 86% yield within 1 day (Scheme 1), indicating that chalcones **5** are the intermediates in the tandem reaction of phenols with acetophenones.



Scheme 1 Tandem reaction of chalcone **5c** with phenol **1a**

Based on the above results, a possible reaction mechanism for the sulfuric-acid-promoted tandem reaction of phenols with acetophenones is outlined in Fig. 2. The self-condensation of

acetophenones **2** generates chalcones **5**, which are in turn converted to the intermediates **6** by an intermolecular Michael addition with phenols **1**. Compounds **6** undergo a tautomerization to form the intermediates **7**. Finally, the cyclodehydration of compounds **7** affords 4*H*-chromenes **3**. On the other hand, chalcones **5** undergo an enolization followed by an aldol-type addition with acetophenones **2** and a subsequent dehydration to generate the intermediates **11**. The intramolecular addition of compounds **11** leads to the intermediates **12**, which undergo a dehydration to afford by-products **4**.

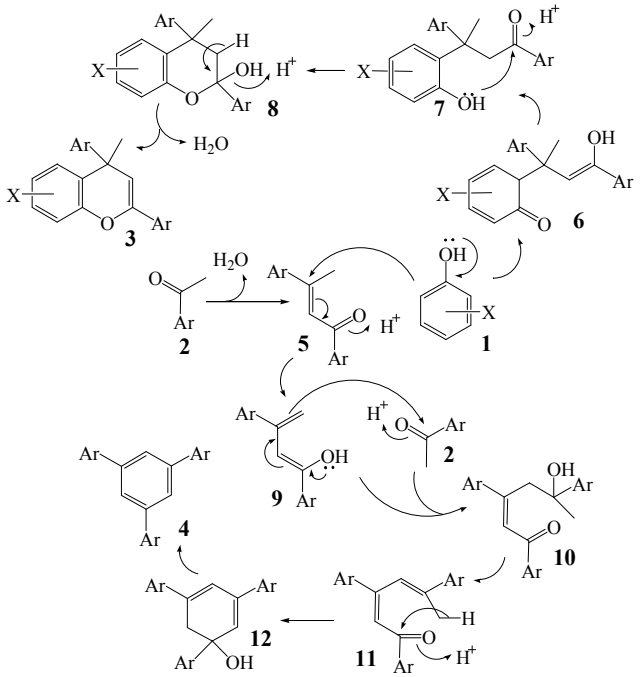


Fig. 2 A possible reaction mechanism for the sulfuric-acid-promoted tandem reaction of phenols with acetophenones

The tandem reaction of chalcones **5** with acetophenones **2** to generate by-products **4** went slowly at a temperature less than 50 °C. However, a remarkable rate-enhancement was observed when the temperature exceeded 60 °C. To prevent the formation of compounds **4**, the sulfuric-acid-promoted tandem reaction of phenols **1** with acetophenones **2** to afford 4*H*-chromenes **3** should be performed at 30–50 °C. The completion of the reaction should be accomplished by prolong the reaction time rather than by improving the reaction temperature. When deactivated phenols, such as 4-nitrophenol and 4-chlorophenol, were used, higher temperatures were required. In these cases, by-products **4** became the major products, indicating that deactivated phenols are not the suitable substrates.

Conclusions

In summary, sulfuric-acid-promoted tandem reaction of phenols with acetophenones proceeds smoothly under solvent- and metal-free conditions, which expands the substrate scopes of acetophenones and phenols. The process provided a convenient, cheap and environmentally benign approach for the synthesis of functional 4*H*-chromenes, a structural motif for a large number of natural products, pharmaceuticals and functional materials. Applications of this protocol to the related natural product synthesis are in progress in our research group.

Experimental

Procedure for H_2SO_4-promoted tandem reaction of phenols with acetophenones under solvent-free conditions (Table 2)

The mixture of a phenol (**1a**–**g**, 1.0 mmol), an acetophenone (**2a**–**h**, 3.0 mmol) and concentrated sulfuric acid (98% H_2SO_4, 81.0 μL, 1.5 mmol) was stirred at 50 °C for 1 day. The reaction was quenched with water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography over silica gel to afford the 4*H*-chromene (**3a**–**p**).

4*H*-Chromene 3a: Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.33–7.04 (m, 9H), 5.27 (s, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 148.9, 142.9, 133.8, 131.9, 131.4, 129.3, 128.8, 128.5, 128.3, 128.2, 127.0, 126.3, 125.8, 125.6, 124.5, 123.5, 118.8, 118.3, 109.1, 40.8, 29.0; FTIR (film): 3055, 2960, 2925, 2853, 1678, 1671, 1599, 1572, 1506, 1490, 1465, 1396, 1372, 1313, 1288, 1261, 1227, 1204, 1094, 1077, 1014, 962, 893, 858, 814, 748 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{21}O$ $[M+H]^+$: 349.1587. Found: 349.1585.

4*H*-Chromene 3b: White solids; m.p. = 159–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.62 (m, 4H), 7.54–7.31 (m, 4H), 7.25–7.11 (m, 2H), 7.06–6.93 (m, 4H), 5.18 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, $^1J_{C\text{-}F}$ = 188 Hz, 1C), 160.3 (d, $^1J_{C\text{-}F}$ = 185 Hz, 1C), 148.7, 145.9 (d, $^4J_{C\text{-}F}$ = 4 Hz, 1C), 142.3, 131.9, 131.2, 129.8 (d, $^4J_{C\text{-}F}$ = 4 Hz, 1C), 129.5, 128.9, 128.5 (d, $^3J_{C\text{-}F}$ = 10 Hz, 1C), 126.4 (d, $^3J_{C\text{-}F}$ = 11 Hz, 1C), 126.1, 125.7, 123.7, 118.5, 118.2, 115.3 (d, $^2J_{C\text{-}F}$ = 28 Hz, 1C), 115.2 (d, $^2J_{C\text{-}F}$ = 29 Hz, 1C), 108.6, 40.3, 29.2; FTIR (film): 1640, 1599, 1494, 1437, 1381, 1089, 1008, 813 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{19}F_2O$ $[M+H]^+$: 385.1399. Found: 385.1401.

4*H*-Chromene 3c: White solids; m.p. = 172–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.38–7.12 (m, 9H), 5.21 (s, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 148.5, 142.4, 134.3, 132.1, 131.9, 131.8, 131.1, 129.6, 128.9, 128.7, 128.6, 128.5, 128.4, 126.0, 125.8 (d), 123.7, 118.1, 108.9, 40.5, 29.0; FTIR (film): 3056, 2966, 2926, 2853, 1713, 1673, 1598, 1575, 1490, 1468, 1397, 1381, 1369, 1319, 1289, 1202, 1094, 1074, 1012, 830, 812, 748 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{19}Cl_2O$ $[M+H]^+$: 417.0808. Found: 417.0792.

4*H*-Chromene 3d: White solids; m.p. = 181–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.56–7.23 (m, 11H), 7.15 (t, *J* = 8.4 Hz, 1H), 5.22 (s, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.6, 142.5, 132.5, 131.9, 131.7, 131.4, 131.1, 129.6, 129.0, 128.8, 126.1, 126.0, 125.9, 123.8, 122.5, 120.0, 118.1, 118.0, 108.9, 40.6, 28.9; FTIR (film): 3025, 2966, 2924, 2855, 1667, 1621, 1491, 1453, 1401, 1324, 1289, 1262, 1093, 1014, 828 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{19}Br_2O$ $[M+H]^+$: 504.9797. Found: 504.9790.

4*H*-Chromene 3e: White solids; m.p. = 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.56 (m, 5H), 7.32–7.08 (m, 9H), 5.21 (s, 1H), 2.34 (s, 3H), 2.28 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 147.4, 142.8, 138.1, 135.2, 131.8, 131.5,

131.0, 129.2, 129.1, 128.9, 128.7, 126.9, 126.3, 125.5, 124.4, 123.4, 119.0, 118.3, 108.5, 40.4, 29.1, 21.2, 20.9; FTIR (film): 2920, 2849, 1647, 1513, 1322, 1232, 812, cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{21}O$ $[M+H]^+$: 377.1900. Found: 377.1910.

4*H*-Chromene 3f: Yellow foam; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25–8.10 (m, 5H), 7.84–7.62 (m, 6H), 7.36–7.25 (m, 3H), 5.42 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 148.4, 147.8, 147.4, 146.3, 142.5, 139.3, 130.3, 129.3, 127.9, 126.33, 126.28, 125.6, 125.3, 124.2, 124.1, 123.7, 123.4, 118.0, 110.7, 41.4, 29.0; FTIR (film): 1622, 1514, 1347, 854 cm^{-1}. Anal. Calcd. for $C_{26}H_{18}N_2O_5$: C, 71.23; H, 4.14; N, 6.39. Found: C, 71.45; H, 4.01; N, 6.58.

4*H*-Chromene 3g: Green foam; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21–6.92 (m, 20H), 5.28 (s, 1H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 143.5, 140.8, 136.6, 135.0, 134.0, 133.5, 131.9, 130.2, 129.1, 128.9, 128.8, 128.3, 127.7, 127.4, 126.7, 126.3, 126.1, 126.0, 125.9, 125.8, 125.5, 125.4, 125.1, 124.3, 120.3, 115.1, 104.2, 102.5, 102.0, 38.4, 29.7; FTIR (film): 3054, 2959, 2923, 2851, 1626, 1595, 1511, 1454, 1396, 1373, 1259, 1210, 1163, 1015, 862, 815, 798, 778, 747 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{34}H_{25}O$ $[M+H]^+$: 449.1900. Found: 449.1903.

4*H*-Chromene 3h: White solids; m.p. = 199–200 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 8.4 Hz, 1H), 7.85–7.77 (m, 3H), 7.62–7.38 (m, 5H), 7.17–7.13 (m, 2H), 7.03–7.00 (m, 2H), 5.45 (s, 1H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, $^1J_{C\text{-}F}$ = 179 Hz, 1C), 160.9 (d, $^1J_{C\text{-}F}$ = 176 Hz, 1C), 145.7 (d, $^4J_{C\text{-}F}$ = 3 Hz, 1C), 145.1, 144.6, 133.1, 130.4 (d, $^4J_{C\text{-}F}$ = 3 Hz, 1C), 129.2 (d, $^3J_{C\text{-}F}$ = 8 Hz, 1C), 127.6, 126.6 (d, $^3J_{C\text{-}F}$ = 8 Hz, 1C), 126.4, 126.2, 125.6, 124.1, 123.2, 121.8, 121.7, 115.3 (d, $^2J_{C\text{-}F}$ = 50 Hz, 1C), 115.1 (d, $^2J_{C\text{-}F}$ = 49 Hz, 1C), 106.8, 39.6, 30.5; FTIR (film): 3057, 2967, 2927, 1674, 1602, 1508, 1381, 1370, 1319, 1232, 1160, 1014, 837, 813, 746 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{18}BrF_2O$ $[M+H]^+$: 463.0504. Found: 463.0507.

4*H*-Chromene 3i: Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 8.7 Hz, 1H), 7.78–7.49 (m, 5H), 7.44–7.27 (m, 4H), 7.25–7.05 (m, 4H), 5.49 (s, 1H), 2.41 (s, 3H), 2.32 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 145.8, 144.8, 138.3, 135.7, 133.0, 131.7, 129.1, 128.9, 127.6, 127.5, 126.1, 125.9, 125.8, 124.7, 124.3, 122.8, 122.4, 121.9, 106.7, 39.7, 29.7, 21.3, 20.9; FTIR (film): 3054, 3025, 2961, 2923, 2854, 1672, 1574, 1511, 1454, 1380, 1319, 1289, 1201, 1100, 1074, 1015, 810, 748 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{26}H_{21}O$ $[M+H]^+$: 377.1900. Found: 377.1910.

4*H*-Chromene 3j: Yellow foam; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H), 7.83–7.57 (m, 6H), 7.47 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 5.30 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 147.1, 145.8, 145.2, 144.3, 133.3, 129.7, 127.7, 126.9, 126.5, 125.6, 124.2, 123.42, 123.37, 122.5, 121.9, 121.8, 121.6, 120.7, 105.3, 43.3, 29.7; FTIR (film): 2958, 2923, 2852, 1599, 1517, 1395, 1368, 1346, 1261, 1211, 1106, 810, 752 cm^{-1}. Anal. Calcd. for $C_{26}H_{18}N_2O_5$: C, 71.23; H, 4.14; N, 6.39. Found: C, 71.32; H, 4.05; N, 6.53.

4*H*-Chromene 3k: Green foam; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.0 Hz, 1H), 7.71–7.30 (m, 15H), 7.12 (d, J = 8.4 Hz, 1H), 5.63 (s, 1H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 145.6, 144.8, 141.3, 140.7, 140.6, 139.0, 133.3, 133.1, 128.9, 128.7, 128.1, 127.54, 127.49, 127.2, 127.1, 127.0, 126.4, 126.3, 126.1, 125.9, 125.2, 124.3, 123.0, 122.0, 121.8, 107.3, 39.9, 29.7; FTIR (film): 2960, 2922, 2851, 1487, 1378, 1260, 1080, 808, 766 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{34}H_{25}O$ $[M+H]^+$: 449.1900. Found: 449.1902.

4*H*-Chromene 3l: Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.6 Hz, 2H), 7.61(d, J = 7.6 Hz, 2H), 7.59 (d, J = 8.3 Hz, 1H), 7.35–7.11 (m, 5H), 6.88 (d, J = 6.4 Hz, 2H), 6.70 (d, J = 6.4 Hz, 2H), 5.14 (s, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 157.5, 148.9, 142.8, 142.5, 131.8, 131.6, 129.1, 128.8, 128.0, 126.5, 126.4, 125.9, 125.5, 123.4, 119.0, 118.3, 113.8, 113.6, 107.8, 55.3, 55.1, 40.1, 29.2; FTIR (film): 3053, 2957, 2926, 2853, 1609, 1596, 1578, 1511, 1461, 1385, 1277, 1251, 1179, 1083, 1034, 831, 814, 794, 772 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{28}H_{25}O_3$ $[M+H]^+$: 409.1798. Found: 409.1793.

4*H*-Chromene 3m: Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.60 (m, 3H), 7.47–7.29 (m, 11H), 7.21–7.15 (m, 2H), 5.41 (s, 1H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.2, 145.4, 140.8, 135.1, 132.4, 132.2, 129.1, 128.8, 128.7, 128.6, 128.4, 128.2, 127.1, 127.0, 126.8, 126.5, 126.0, 117.0, 106.9, 39.7, 30.5; FTIR (film): 2964, 2924, 2854, 1666, 1490, 1276, 1085, 833, 819 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{28}H_{21}Cl_2O$ $[M+H]^+$: 443.0964. Found: 443.0961.

4*H*-Chromene 3n: Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.60 (m, 4H), 7.36–7.28 (m, 4H), 7.03–6.72 (m, 2H), 6.72 (s, 1H), 5.35 (s, 1H), 2.22 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 148.0, 141.4, 134.3, 133.1, 129.1, 128.8, 128.53, 128.47, 128.4, 128.3, 127.5, 126.0, 125.0, 116.3, 106.7, 39.5, 29.7, 20.8; FTIR (film): 2968, 2928, 2857, 1664, 1591, 1494, 1397, 1316, 1291, 1234, 1089, 1008, 813, 724 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{23}H_{19}Cl_2O$ $[M+H]^+$: 381.0807. Found: 381.0810.

4*H*-Chromene 3o: Pale yellow solids; m.p. = 105–108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H), 7.28–7.17 (m, 6H), 6.77 (s, 1H), 6.47 (s, 1H), 5.28 (s, 1H), 2.32 (s, 3H), 2.09 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 146.2, 145.3, 134.2, 132.8, 132.3, 131.9, 129.8, 128.8, 128.5, 128.3, 127.2, 126.1, 125.9, 125.4, 106.7, 39.7, 29.7, 20.7, 16.2; FTIR (film): 2966, 2924, 2852, 1670, 1598, 1492, 1438, 1401, 1375, 1329, 1296, 1278, 1260, 1216, 1147, 1093, 1040, 1012, 919, 859, 833, 808, 744, 716, 678 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{24}H_{21}Cl_2O$ $[M+H]^+$: 395.0964. Found: 395.0963.

4*H*-Chromene 3p: Pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.32 (m, 8H), 7.01 (s, 1H), 6.75 (s, 1H), 5.42 (s, 1H), 2.30 (s, 3H), 2.19 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.0, 145.4, 136.2, 134.2, 132.7, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 125.9, 125.0, 117.2, 106.8, 39.2, 30.3, 19.4, 19.1; FTIR (film): 2969, 2921, 1672, 1494, 1397, 1324, 1283, 1089, 1008, 837, 805 cm^{-1}. HRMS (ESI) m/z: Calcd for $C_{24}H_{21}Cl_2O$ $[M+H]^+$: 395.0964. Found: 395.0969.

By-product 4a: White solids; m.p. = 172–174 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 3H), 7.73–7.71 (m, 6H), 7.51–7.48 (m, 6H), 7.42–7.39 (m, 3H); ^{13}C NMR (100 MHz, DMSO-*d*6) δ 141.6, 140.0, 128.8, 127.6, 127.1, 124.3; FTIR (film): 1648, 1048, 1026, 997, 827, 766, 633 cm^{-1}. Anal. Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 94.18; H, 5.99.

Chalcone 5c: White solids; m.p. = 151–152 °C; ^1H NMR (400

MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 7.08 (q, J = 1.2 Hz, 1H), 2.56 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 154.4, 140.9, 139.1, 137.5, 135.3, 129.7, 128.9, 128.8, 127.8, 121.8, 18.8; FTIR (film): 2923, 2852, 1738, 1657, 1591, 1488, 1364, 1278, 1213, 1093, 1011, 817 cm^{-1}. Anal. Calcd. for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.15. Found: C, 66.11; H, 4.06.

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and copies of NMR spectra (^{1}H NMR and ^{13}C NMR) of compounds **3a**–**p**, **4a** and **5c**. See DOI: 10.1039/b000000x/

1 (*a*) S. Hatakeyama, N. Ochi, H. Numata and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1988, 1202; (*b*) R. Gonzalez, N. Martin, C. Seoane, J. L. Marco, A. Albert and F. H. Cano, *Tetrahedron Lett*, 1992, **33**, 3809; (*c*) V. Jeso and K. C. Nicolaou, *Tetrahedron Lett*., 2009, **50**, 1161; (*d*) C. Yao, B. Jiang, T. Li, B. Qin, X. Feng, H. Zhang, C. Wang and S. Tu, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 599.

2 T. Symeonidis, M. Chamilos, D. J. Hadjipavlou-Litina, M. Kallitsakis and K. E. Litinas, *Bioorg. Med. Chem. Lett*., 2009, **19**, 1139.

3 Z. Q. Xu, K. Pupek, W. J. Suling, L. Enache and M.T. Flavin, *Bioorg. Med. Chem.*, 2006, **14**, 4610.

4 C. B. Sangani, N. M. Shah, M. P. Patel, R. G. Patel, *Med. Chem. Res*., 2013, **22**, 3831.

5 T. Narender, Shweta, S. Gupta, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3913.

6 A. Martínez-Grau and J. L. Marco, *Bioorg. Med. Chem. Lett*., 1997, **7**, 3165.

7 N. R. Kamdar, D. D. Haveliwala, P. T. Mistry, S. K. Patel, *Med. Chem. Res*., 2011, **20**, 854.

8 H. Aryapour, M. Mahdavi, S. R. Mohebbi, M. R. Zali and A. Foroumadi, *Arch Pharm Res*., 2012, **35**, 1573.

9 S. G. Das, D. L. Hermanson, N. Bleeker, X. Lowman, Y. Li, A. Kelekar and C. Xing, *ACS Chem. Biol*., 2013, **8**, 327.

10 For selected examples, see: (*a*) J. Fan and Z. Wang, *Chem. Commun*., 2008, 5381; (*b*) S. Gao, C. H. Tsai, C. Tseng and C. F. Yao, *Tetrahedron*, 2008, **64**, 9143; (*c*) A. Shaabani, R. Ghadari, A. Sarvary and A. H. Rezayan, *J. Org. Chem.*, 2009, **74**, 4372; (*d*) K. Kumaravel and G. Vasuki, *Green Chem*., 2009, **11**, 1945; (*e*) M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, P. A. Belyakov, A. O. Chizhov and G. I. Nikishin, *Tetrahedron*, 2010, **66**, 4043; (*f*) M. R. Naimi-Jamal, S. Mashkouri, A. Sharifi, *Mol. Divers*, 2010, **14**, 473; (*g*) H. J. Li, J. L. Wang, R. Wang, D. H. Luo and Y. C. Wu, J. Chem., Doi:10.1155/2013/106908; (*h*) M. Boominathan, M. Nagaraj, S. Muthusubramanian and R. V. Krishnakumar, *Tetrahedron*, 2011, **67**, 6057; (*i*) S. R. Kolla, Y. R. Lee, *Tetrahedron*, 2011, **67**, 8271; (*j*) Z. Du, W. Y. Siau and J. Wang, *Tetrahedron Lett*., 2011, **52**, 6137; (*k*) M. Gyuris, R. Madácsi, L. G. Puskás, G. K. Tóth, J. Wölfling and I. Kanizsai, *Eur. J. Org. Chem.*, 2011, 848; (*l*) B. Sadeghi, A. Hassanabadi, S. Bidaki, *J. Chem. Res*., 2011, 666; (*m*) R. Ghorbani-Vaghei, Z. Toghraei-Semiromi and R. Karimi-Nami, *J. Braz. Chem. Soc*., 2011, **22**, 905; (*n*) Q. Ren, W. Y. Siau,Z. Du,K. Zhang and J. Wang, *Chem. Eur. J*., 2011, **17**, 7781; (*o*) H. Dou, S. Gao, Z. Fu, S. Liu, *Chin. J. Org. Chem*., 2011, **31**, 1056; (*p*) B. Mohtat, H. Djahaniani, I. Yavari, M. G. Dehbalaei and S. A. Jam, *Chinese Chem. Lett*., 2011, **22**, 771; (*q*) Z. Dong, X. Liu, J. Feng, M. Wang, L. Lin and X. Feng, *Eur. J. Org. Chem*., 2011, 137.

11 For selected recent examples, see: (*a*) S. I. Bhat, A. R. Choudhury and D. R. Trivedi, *RSC Adv*., 2012, **2**, 10556; (*b*) V. A. Osyanin, D. V. Osipov and Y. N. Klimochkin, *Tetrahedron*, 2012, **68**, 5612; (*c*) Y. Gao, W. Yang and D. M. Du, *Tetrahedron: Asymmetry*, 2012, **23**, 339; (*d*) Y. Sarrafi, E. Mehrasbi, A. Vahid and M. Tajbakhsh, *Chin. J. Catal*., 2012, **33**, 1486; (*e*) H. Mehrabi and N. Kamali, *J. Iran. Chem. Soc*., 2012, **9**, 599; (*f*) C. B. Sangani, N. M. Shah, M. P. Patel and Ranjan G. Patel, *J. Serb. Chem. Soc*., 2012, **77**, 1165; (*g*) M. G. Dekamin, M. Eslami and A. Maleki, *Tetrahedron*, 2013, **69**, 1074; (*h*) L. Bian, J. Xu, L. Xie, J. Chen, H. Deng, M. Shao, T. Ding, H. Zhang and W. Cao, *Tetrahedron*, 2013, **69**, 6121; (*i*) J. H. Park, Y. R. Lee and S. H. Kim, *Tetrahedron*, 2013, **69**, 9682; (*j*) Y. Gao, D. M. Du, *Tetrahedron: Asymmetry*, 2013, **24**, 1312; (*k*) N. K. Shah, N. M. Shah, M. P. Patel and R. G. Patel, *J. Chem. Sci.*, 2013, 125, 525; (*l*) H. S. P. Rao and V. S. Tangeti, *J. Chem. Sci.*, 2013, 125, 777; (*m*) S. R. Kale, S. S. Kahandal, A. S. Burange, M. B. Gawande and R. V. Jayaram, *Catal. Sci. Technol*., 2013, **3**, 2050; (*n*) G. Yin, H. Shi, L. Xu, X. Wei and Q. Tao, *Synthesis*, 2013, **45**, 334; (*o*) R. L. Magar, P. B. Thorat, V. B. Jadhav, S. U. Tekale, S. A. Dake, B. R. Patil and R. P. Pawar, *J. Mol. Catal. A: Chem*., 2013, **374**–**375**, 118; (*p*) S. M. Baghbanian, N. Rezaei and H. Tashakkorian, *Green Chem*., 2013, **15**, 3446; (*q*) A. Molla, E. Hossain and S. Hussain, *RSC Adv*., 2013, **3**, 21517.

12 Y. Liu, J. Qian, S. Lou, J. Zhu and Z. Xu, *J. Org. Chem*., 2010, **75**, 1309.

13 (*a*) W. J. Xue, Q. Li, F. F. Gao, Y. P. Zhu, J. G. Wang, W. Zhang and A. X. Wu, *ACS Comb. Sci*., 2012, **14**, 478; for reactions of resorcinols with ketones in the presence of *p*-toluenesulfonic acid, see: (*b*) S. I. Filimonov, N. G. Savinsky and E. M. Evstigneeva, *Mendeleev Commun*., 2003, **13**, 194.

14 (*a*) Y. C. Wu, X. M. Zou, F. Z. Hu and H. Z. Yang, *J. Heterocycl. Chem.*, 2005, **42**, 609; (*b*) Y. C. Wu, L. Liu, H. J. Li, D. Wang and Y. J. Chen, *J. Org. Chem.*, 2006, **71**, 6592; (*c*) Y. C. Wu, Y. J. Chen, H. J. Li, X. M. Zou, F. Z.Hu and H. Z. Yang, *J. Fluorine Chem.*, 2006, **127**, 409; (*d*) Y. C. Wu, L. Liu, D. Wang and Y. J. Chen, *J. Heterocycl. Chem.*, 2006, **43**, 949; (*e*) Y. C. Wu, L. Liu, Y. L. Liu, D. Wang and Y. J. Chen, *J. Org. Chem.*, 2007, **72**, 9383; (*f*) Y. C. Wu, H. J. Li, L. Liu, D. Wang, H. Z. Yang and Y. J. Chen, *J. Fluoresc.*, 2008, **18**, 357; (*g*) Y. C. Wu, H. J. Li and H. Z. Yang, *Org. Biomol. Chem.*, 2010, **8**, 3394; (*h*) Y. C. Wu, H. J. Li, L. Liu, N. Demoulin, Z. Liu, D. Wang and Y. J. Chen, *Adv. Synth. Catal.*, 2011, **353**, 907; (*i*) Y. C. Wu, H. J. Li, L. Liu, N. Demoulin, Z. Liu, D. Wang and Y. J. Chen, *Synlett*, 2011, 1573; (*j*) Y. C. Wu, H. J. Li, L. Liu, Z. Liu, D. Wang and Y. J. Chen, *Org. Biomol. Chem.*, 2011, **9**, 2868.

Graphical Abstract

Synthesis of functional 4*H*-chromenes from phenols and acetophenones under solvent- and metal-free conditions

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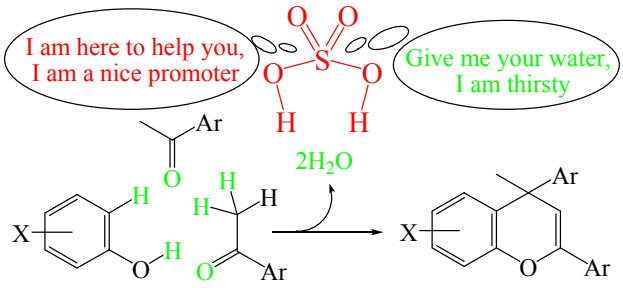

Sulfuric-acid-promoted tandem reaction of phenols with acetophenones under solvent- and metal-free conditions has been developed, which afforded functional 4*H*-chromenes in good yields with water as the side product.