

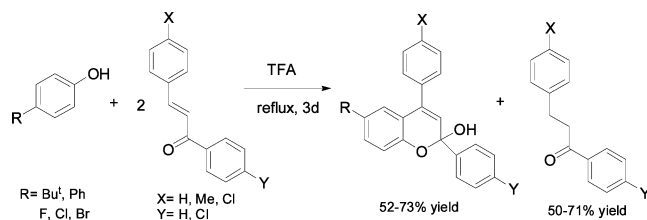
## TFA-Mediated Tandem Friedel–Crafts Alkylation/Cyclization/Hydrogen Transfer Process for the Synthesis of Flavylum Compounds

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The tandem reaction of phenols and chalcones in refluxing TFA gave the flavylum species of 2-hydroxy-2-phenyl-2H-chromenes in moderate to good isolated yields. The reaction was proposed to involve a tandem transformation of Friedel–Crafts alkylation, dehydrative cyclization, intermolecular hydrogen transfer, and hydration. As a multifunctional catalyst, TFA mediated the processes efficiently and cleanly.

The Friedel–Crafts alkylation reactions of phenols have been widely employed to construct numerous aromatic heterocyclics possessing special properties.<sup>1</sup> Among them, the addition reactions of phenols to  $\alpha,\beta$ -unsaturated carbonyl compounds provide various benzopyran derivatives.<sup>2</sup> Phenols can react with  $\alpha,\beta$ -unsaturated ester or acids through C-alkylation/O-acylation or C-acylation/O-alkylation to form coumarins, chromanones, chromones, etc.<sup>3</sup> Many Lewis acids, such as Cu(OTf)<sub>2</sub><sup>4</sup> and BF<sub>3</sub>·OEt<sub>2</sub>,<sup>5</sup> and protic acids, such as HCl<sup>6</sup> and sulfuric acid,<sup>7</sup> were

TABLE 1. The Reaction of Phenol 1a with Chalcone 2a under Different Conditions

entry	reagent	time <sup>a</sup> (d)	yield <sup>b</sup> of 3a (%)
1	TFA	1	44
2	TFA	2	62
3	TFA	3	73
4	TFA	4	71
5	Pd(OAc) <sub>2</sub> , TFA <sup>c</sup>	1	<5
6	Pd(OAc) <sub>2</sub> , TFA <sup>d</sup>	1	45
7	HCl <sup>e</sup>	3	<5
8	H <sub>2</sub> SO <sub>4</sub> <sup>f</sup>	3	<5
9	AcOH	3	<5

<sup>a</sup> 1a:2a = 1:2. Reaction temperature = 72 °C. <sup>b</sup> Isolated yield. <sup>c</sup> Pd(OAc)<sub>2</sub>: 10 mol %. Reaction temperature = room temperature. <sup>d</sup> Pd(OAc)<sub>2</sub>: 10 mol %. <sup>e</sup> Aqueous hydrochloric acid (37%). <sup>f</sup> Concentrated sulfuric acid (98%).

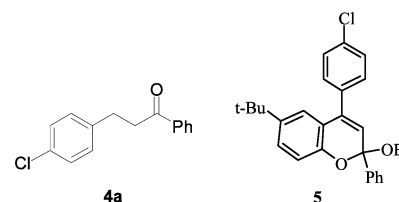


FIGURE 1. The structure of 4a and 5.

suitable catalysts for the Friedel–Crafts-type reaction. Fujiwara reported that the Friedel–Crafts C-alkylation of phenols with  $\alpha,\beta$ -unsaturated esters could be catalyzed by Pd(II) in TFA to give coumarin derivatives.<sup>8</sup> On the other hand, the reaction of phenols with  $\alpha,\beta$ -unsaturated ketones could provide flavylum compounds.<sup>9</sup> However, under such conditions, the substrates were limited to reactive phenols; furthermore, an additional oxidant such as DDQ was normally necessary for the formation of flavylum salts in the final step. Flavylum salts, e.g., anthocyanins, have long been considered as ubiquitous pigments responsible for the various colors in fruits and flowers,<sup>10</sup> effective food colorants,<sup>11</sup> and biologically active substances.<sup>12</sup>

(1) (a) Rappoport, Z. *The chemistry of phenols*; John Wiley and Sons: New York, 2003. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 733–752. (c) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, UK, 1991; Vol. 3, pp 293–339.

(2) (a) Ellis, G. P. *Chromenes, chromanones, and chromones*; Wiley-Interscience: New York, 1977. (b) Ellis, G. P.; Lockhart, I. M. *Chromans and Tocopherols*; Wiley-Interscience: New York, 1981.

(3) (a) Fillion, E.; Dumas, A. M.; Kuropatwa, B. A.; Malhotra, N. R.; Sittler, T. C. *J. Org. Chem.* **2006**, *71*, 409–412. (b) Krawczyk, H.; Bodalski, R. *J. Chem. Soc., Perkin Trans. I* **2001**, 1559–1565. (c) Gunnewegh, E. A.; Hoefnagel, A. J.; vanBekkum, H. *J. Mol. Catal. A: Chem.* **1995**, *100*, 87–92.

(4) van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jorgensen, K. A. *Org. Biol. Chem.* **2003**, *1*, 1953–1958.

(5) Roelens, F.; Huvaere, K.; Dhooze, W.; Van Cleemput, M.; Comhaire, F.; De Keukeleire, D. E. *J. Med. Chem.* **2005**, *40*, 1042–1051.

(6) Singh, I.; Prasad, A. K.; Sharma, A. K.; Saxena, R. K.; Olsen, C.; Cholli, A. L.; Samuelson, L. A.; Kumar, J.; Watterson, A. C.; Parmar, V. S. *Bioorg. Med. Chem.* **2003**, *11*, 529–538.

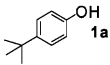
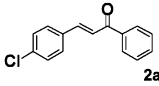
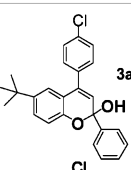
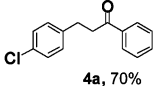
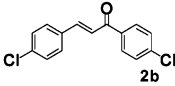
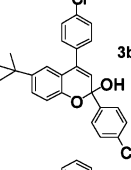
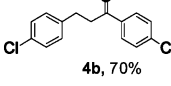
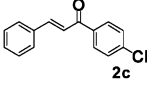
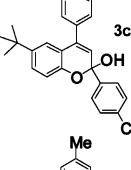
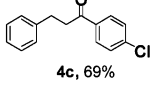
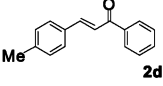
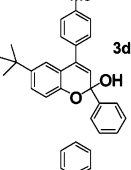
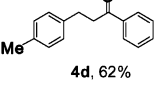
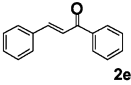
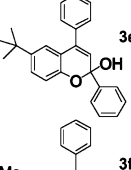
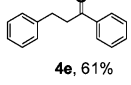
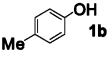
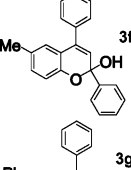
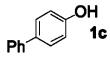
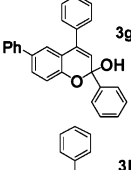
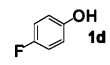
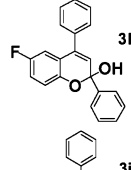
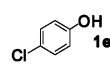
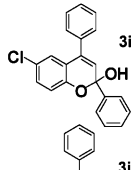
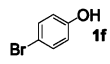
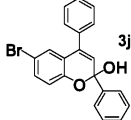
(7) Buu-Hoi, N. P.; Le Bihan, N.; Binon, F.; Maleyran, P. *J. Org. Chem.* **1952**, *17*, 1122–1127.

(8) (a) Jia, C. G.; Piao, D. G.; Oyamada, J.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995. (b) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440–6444.

(9) (a) Hill, D. W. *Chem. Rev.* **1936**, *19*, 27–54. (b) Broadbent, P.; Robertson, A.; Whalley, W. B. *J. Chem. Soc.* **1952**, 4957–4959. (c) Johnson, A. W.; Melhuish, R. R. *J. Chem. Soc.* **1947**, 346–350. (d) Chassaing, S.; Kueny-Stotz, M.; Isorez, G.; Brouillard, R. *Eur. J. Org. Chem.* **2007**, *15*, 2438–2448.

(10) (a) Goto, T.; Kondo, T. *Angew. Chem., Int. Ed.* **1991**, *30*, 17–33. (b) Santos, H.; Turner, D. L.; Lima, J. C.; Figueiredo, P.; Pina, F.; Macianita, A. L. *Phytochemistry* **1993**, *33*, 1227–1232. (c) Brouillard, R.; Dangles, O. In *The Flavonoids, Advances in Research since 1986*; Harborne, J. B., Ed.; Chapman and Hall: London, UK, 1993.

TABLE 2. Reaction of Phenols (1a–f) with Chalcones (2a–e)<sup>a</sup>

Entry	Phenol	chalcone	Product 3 <sup>b</sup>	Product 4 <sup>b</sup>
1				
2	1a			
3	1a			
4	1a			
5	1a			
6		2e		4e
7		2e		4e
8		2e		4e
9		2e		4e
10		2e		4e

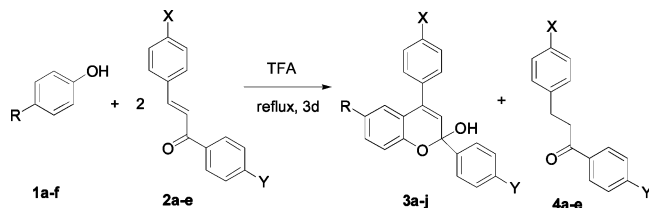
<sup>a</sup> Reaction condition: in refluxed TFA for 3 d. <sup>b</sup> Isolated yield.

The multistate/multifunctional chemical system existing in flavylium compounds has attracted considerable attention in molecular information processing, optical memories, and logic gates.

(11) (a) Markakis, P. Anthocyanins as Food Additives. In *Anthocyanins as Food Colors*; Markakis, P., Ed.; Academic Press: New York, 1982. (b) Timberlake, C. F.; Henry, B. S. Anthocyanins as Natural Food Colorants. In *Plant Flavonoids in Biology and Medicine II Biochemical, Cellular and Medicinal Properties*; Cody, V., Middleton, E., Harborne, J. B., Beretz, A., Alan, R., Eds.; Liss: New York, 1988.

The development of tandem reactions in which one catalyst promotes all transformation in a one-pot process is a challenging task for synthetic chemists. Inspired by the tandem reaction involving the Friedel–Crafts reaction of phenols with  $\alpha,\beta$ -unsaturated carbonyl compounds providing various heteroaro-

(12) (a) Harborne, J. B.; Grayer, R. J. The Anthocyanins. In *The Flavonoids: Advances in Research Since 1980*; Harborne, J. B., Ed.; Chapman and Hall: London, 1988. (b) Costantino, L.; Rastelli, G.; Albasini, A. *Pharmazie* **1995**, *50*, 573–574. (c) Tamura, H.; Yamagami, A. *J. Agric. Food Chem.* **1994**, *42*, 1612–1615.

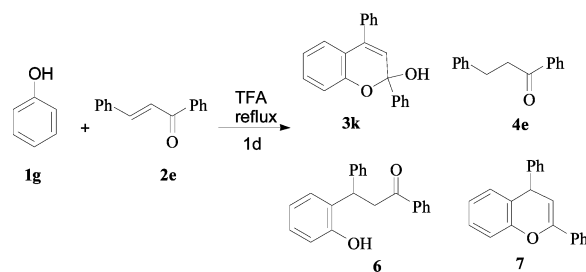
**SCHEME 1. The Reaction of Phenols **1** with Chalcones **2** in TFA**


maticyclics, we would like to report the Friedel–Crafts alkylation of phenols with chalcone derivatives in TFA without the use of other catalysts for the direct synthesis of flavylium compounds in a one-pot process.

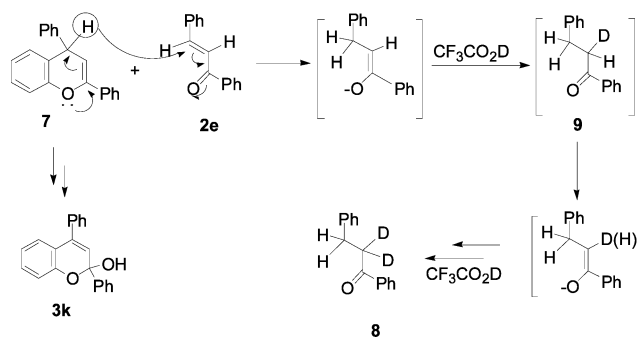
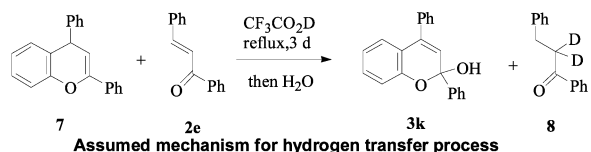
Reaction of 4-*tert*-butylphenol (**1a**) and 4-chloro-*trans*-chalcone (**2a**) was carried out initially at room temperature in trifluoroacetic acid (TFA) in the presence of Pd(OAc)<sub>2</sub> (10 mol %) as a catalyst.<sup>8</sup> However, no flavylium product was detected (Table 1, entry 5). Then, the reaction of **1a** and **2a** (**1a/2a** = 1:2) was performed in refluxing TFA for 1 day in the absence of Pd(OAc)<sub>2</sub> (entry 1). To our delight, the product of the desired tandem reaction, 6-*tert*-butyl-4-(4-chlorophenyl)-2-hydroxy-2-phenyl-2H-chromene **3a**, was obtained in 44% yield, together with the corresponding reduction product, 3-(4-chlorophenyl)-1-phenylpropan-1-one **4a** (45% yield on the basis of **1a** used, Figure 1). The same results were obtained when 10 mol % of Pd(OAc)<sub>2</sub> in refluxing TFA was used, which indicated that Pd(OAc)<sub>2</sub> was not essential in this reaction (entry 6 vs entry 1 in Table 1). The yield of **3a** was increased to 73% by prolonging the reaction time (Table 1, entries 1–3). No further increase was observed when the reaction time exceeded 3 days (entry 4). In this case, the yield of the reduction product **4a** was increased to 70% (Table 1, entry 3 and Table 2, entry 1). Hydrochloric acid, sulfuric acid, and acetic acid were ineffective for this reaction (entries 7–9). TFA appeared to serve the dual role of catalyst and solvent. However, if TFA was mixed with organic solvents (v/v = 1:1) such as dichloromethane, water, and toluene, the yields of **3a** decreased dramatically, and only a trace amount of the product **3a** was detected. The structure of **3a** was supported by X-ray crystallographic analysis of 6-*tert*-butyl-4-(*p*-chlorophenyl)-2-ethoxy-2-phenyl-2H-chromene **5** (see the Supporting Information), which was obtained from **3a** by etherification with ethanol.

The interesting preliminary results encouraged us to examine the scope of substrates suitable to this tandem reaction. Various phenols (**1a–f**) and chalcones (**2a–e**) were employed. It was found in Table 2 that a wide range of **1** and **2** subjected to this procedure (**1/2** = 1:2) could afford the corresponding flavylium compounds (**3a–j**) in moderate to good yields (Scheme 1). 4-Chloro-*trans*-chalcone (**2a**), 4,4'-dichloro-*trans*-chalcone (**2b**), and 4'-chloro-*trans*-chalcone (**2c**) provided similar yields of the flavylium products (**3a–c**) in yields of 68–73% (entries 1–3). 4-Methyl-*trans*-chalcone (**2d**) and chalcone (**2e**) were relatively less reactive than **2a** (entries 4 and 5). In the selected halogen-substituted phenols (**1e,f**) (entries 9–11), 4-bromophenol (**1f**) was the most reactive one. It is worth mentioning that no metal catalyst was required in the reaction. Furthermore, after the reaction TFA could be distilled out for reuse. In addition, the reduction products (**4a–e**) of chalcones (**2**) were also isolated from the product mixture in yields almost equal to that of the flavylium compounds (**3**) (Table 2).

To obtain further information on the reaction mechanism, the tandem reaction was quenched under certain reaction conditions



**FIGURE 2.** Reaction intermediates.

**SCHEME 2. Hydrogen Transfer between **7** and **2e** in TFA-*d***


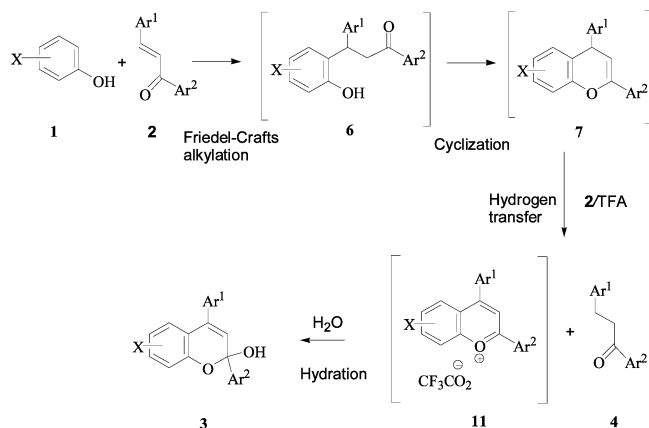
to trap the reaction intermediates. When the reaction of phenol **1g** with **2e** in refluxing TFA was quenched after only 1 day, apart from the isolation of the product **3k** in 13% yield, a small amount of the Friedel–Crafts alkylation product **6** and the related cyclization product **7**, 2,4-diphenyl-4*H*-chromene, were also isolated in 6% and 1% yields, respectively (Figure 2). The structure of intermediate **7** was determined by spectroscopy and X-ray crystallographic analysis.

In a separate reaction, **6** could be converted to **7** in almost quantitative yield after 12 h in refluxing TFA. The conversion of **7** into **3k** involved a dehydrogenation process, whereas during the reaction chalcone **2e** was reduced to **4e**. A reasonable postulation was the conversion of **7** to **3k** would be through an intermolecular hydrogen shift process, in which **2e** was involved as a hydrogen acceptor.<sup>13</sup> Indeed, when **7** was reacted with **2e** in refluxing TFA for 3 days, followed by quenching with water, the product **3k** could be obtained in 72% yield.

The intermolecular hydrogen transfer between **7** and **2e** was further proved by hydrogen/deuterium (H/D) exchange experiments (Scheme 2). The mixture of **7** and **2e** in refluxing deuteriotrifluoroacetic acid (CF<sub>3</sub>CO<sub>2</sub>D, TFA-*d*) was stirred for 3 days, followed by hydration with water to afford 2,2-dideuterio-1,3-diphenylpropan-1-one (**8**, 71%) and **3k** (70%). The generation of **8** as the sole deuterio product demonstrated that the hydrogen transfer proceeded with high chemoselectivity. The hydrogen transfer is proposed to take place as shown in Scheme 2. In the initial step, hydrogen is selectively transferred

(13) Mishrikey, M. M.; Østensen, E. T. *Acta Chem. Scand. B* **1976**, *30*, 329–335.

## SCHEME 3. Reaction Mechanism



from the 4-position of **7** to the  $\beta$ -carbon of the enone **2e** to afford 2-deuterio-1,3-diphenylpropan-1-one (**9**). The latter is subsequently converted to **8** by further hydrogen/deuterium exchange.<sup>14</sup> Transfer hydrogenation reactions of  $\alpha,\beta$ -unsaturated ketones catalyzed by Ru-complex are known to proceed chemoselectively for C=O function, and C=C bonds are unaffected.<sup>15</sup> In contrast, under refluxing TFA conditions, the hydrogen transfer process involved in the tandem reaction of phenols with chalcones took place exclusively for the reduction of the C=C bond. The result might provide an approach to the development of new methods of selective reductions of the C=C bond in  $\alpha,\beta$ -unsaturated ketones via transfer hydrogenation.

On the basis of the foregoing results we propose the putative general mechanism in Scheme 3 for the TFA-mediated synthesis of 2-aryl-2-hydroxy-2H-chromenes such as **3**: (a) Friedel-Crafts alkylation of chalcones (**2**) with phenols (**1**) to form the alkylation products (**6**),<sup>16</sup> (b) dehydrative cyclization of **6** to form

(14) When trityl fluoroborate (Ph<sub>3</sub>CBF<sub>4</sub>) (1 equiv) was added in the reaction of phenol **1a** with chalcone **2a** (**1a**:**2a** = 1:1), **3a** was obtained in 70% yield by saving 1 equiv of **2a**.

(15) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584–3591.

4H-chromenes (**7**), (c) intermolecular hydrogen transfer between **2** and **7** to form 2-arylbenzopyrylium ion **11** and 1,3-bisarylpropan-1-ones **4**, and (d) reaction of **11** with a molecule of water to form **3**. Unlike stepwise approaches, this tandem process efficiently avoids the handling of multiple intermediates.

## Experiment Section

**General Procedure for the Synthesis of 2-Hydroxy-2-phenyl-2H-chromenes.** A mixture of phenols **1** (0.2 mmol) and chalcones **2** (0.4 mmol) in TFA (2 mL) under atmospheric N<sub>2</sub> was stirred at reflux for 3 d, after which TFA was distilled out for reuse. The residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), and the solution was washed with 5 mL of saturated aqueous NaHCO<sub>3</sub> and 5 mL of water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure at a bath temperature of <30 °C. The crude products were isolated by flash chromatography on silica gel (200–300 mesh) (eluent: ethyl acetate/petroleum ether = 1:10) to obtain the products **3** and **4**.

**6-tert-Butyl-4-(4-chlorophenyl)-2-phenyl-2H-chromen-2-ol (3a):** 73%, foam; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.71 (dd, *J* = 7.8, 1.1 Hz, 2H), 7.44–7.33 (m, 8H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 5.86 (s, 1H), 3.25 (s, 1H), 1.25 (s, 9H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  149.2, 144.4, 143.1, 136.1, 135.9, 134.2, 130.2, 128.7, 128.6, 128.4, 127.2, 125.8, 124.2, 122.7, 119.2, 117.0, 96.5, 34.4, 31.5; IR (film)  $\nu$  (cm<sup>-1</sup>) 3407, 3035, 2961, 1489, 1258, 1088, 1015, 825, 763, 699. Anal. calcd for C<sub>25</sub>H<sub>23</sub>ClO<sub>2</sub>: C, 76.81; H, 5.93. Found: C, 76.85; H, 6.17.

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**Supporting Information Available:** Experimental procedures; characterization data; copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra; and X-ray crystallographic data of **5** and **7** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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