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# A novel route to synthesis of flavones from salicylaldehyde and acetophenone derivatives ☆

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ABSTRACT

Convenient, facile, and alternate synthesis of medicinally important flavones is reported. The 2-hydroxychalcones derived from condensation between acetophenones and salicylaldehyde, underwent oxidative cyclization on heating in the presence of catalytic iodine, generating diversified flavones under solvent-free conditions. Eleven compounds have been synthesized in good to excellent yields and their mechanism of formation is described.



Flavonoids, one of the important group of plant secondary metabolites,[1] are well known for having a wide range of pharmacological activities such as anti-cancer,[2] anti-inflammatory,[3] anti-osteoporotic,[4] anti-diabetic,[5] and metal chelating activities.[6] Because of their broad range of significant biological activities, this family of molecules has been extensively investigated and more than 4000 chemically unique flavonoids have been isolated from plants. Figure 1 shows the representative chemical structures of some naturally occurring bioactive flavone derivatives.[15–18] As a result, this important ring system continues to hold a charm for chemist worldwide.

Traditionally, flavones have been prepared by the Baker–Venkatraman–rearrangement which involves the conversion of 2-hydroxyacetophenones into benzoyl esters, followed by rearrangement in base into 1,3-diphenylpropane 1,3-diones, which upon cyclization under acidic conditions furnishes flavones.[7] On the other hand, 2-hydroxychalcone, synthesized from 2-hydroxyacetophenone and benzaldehyde under Claisen–Schmidt conditions can undergo oxidative cyclization to furnish flavones ring system (Scheme 1).[8] These reactions suffer from the use of strong bases, acids, and particularly 2-hydroxychalcone synthesized from 2-hydroxyacetophenone and benzaldehyde, utilize long reaction time and low yields. Furthermore, the palladium catalyzed carbonylation of *o*-iodophenols with terminal alkynes has become an attractive alternative to synthesize chromones,[9] however, in some situations, this reaction produces a mixture of six-membered chromones and five-membered aurones. Thus, the classical methods possess a number of drawbacks, such as, moderate yields, moderate purity of products, and poor reaction selectivity.

Intrigued by the above observations and our earlier work on biologically active alpha-chromones,[10] we herein, wish to report

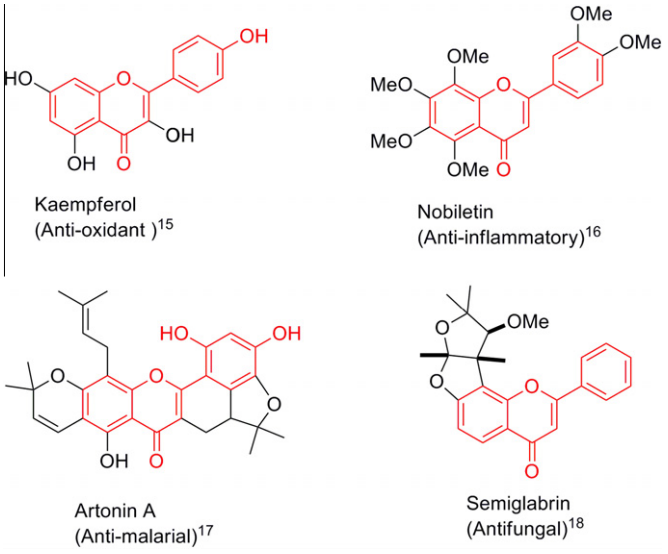


**Figure 1.** Naturally occuring flavones with potent biological activities.

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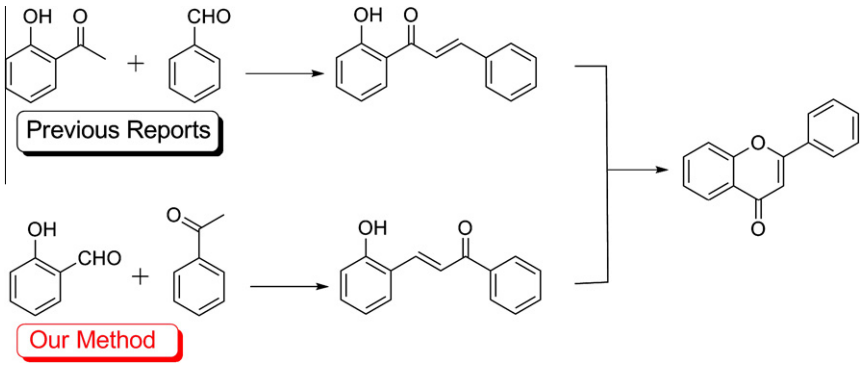
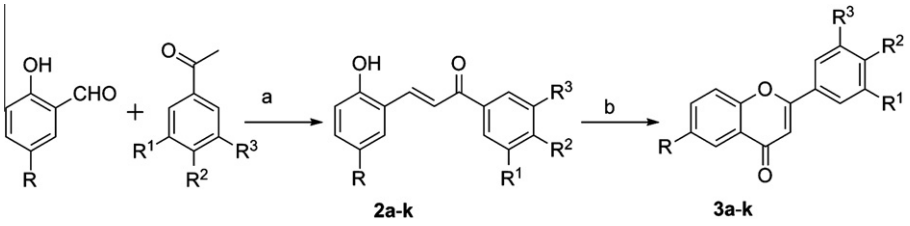
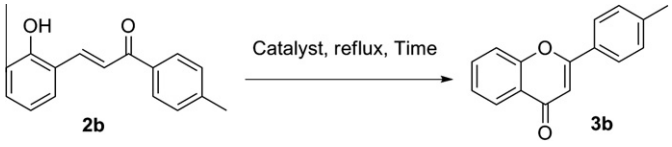



**Scheme 1.** Our protocol for synthesis of flavones using salicylaldehyde as a key substrate.




**Scheme 2.** Reagents and conditions: (a) 10% aq. KOH, ethanol, reflux, 2.5 h. (b) $I_2$, 110–130 °C, 1.5 h.

**Table 1**
Optimization of reaction conditions for the synthesis of flavones **3b**




| Entry | Product | Catalyst | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | **3b** | $AlCl_3$ | 2.5 | 28 |
| 2 | **3b** | $ZnCl_2$ | 3.0 | 10 |
| 3 | **3b** | $BF_3{\cdot}OEt_2$ | 3.0 | 0 |
| 4 | **3b** | $SnCl_2{\cdot}2H_2O$ | 2.0 | 54 |
| 5 | **3b** | $HgCl_2$ | 3.0 | 5 |
| 6 | **3b** | $FeCl_3$ | 3.0 | 5 |
| 7 | **3b** | $SnCl_4$ | 3.0 | 0 |
| 8 | **3b** | Iodine | 1.5 | 74 |

[a] Isolated yield.

**Table 2**
Optimization of reaction solvents[b]

| Entry | Product | Solvent | Yield[a] (%) |
|---|---|---|---|
| 1 | **3b** | 1,4-Dioxane | 56 |
| 2 | **3b** | Acetonitrile | 0 |
| 3 | **3b** | Ethanol | 33 |
| 4 | **3b** | Methanol | 12 |
| 5 | **3b** | THF | 15 |
| 6 | **3b** | DMSO | 20 |
| 7 | **3b** | Neat | 74 |

[a] Isolated yield.
[b] All reactions were run up to 1.5 h.

our finding on solvent-free synthesis of flavones using molecular iodine as catalyst. In our methodology 2-hydroxychalcones were synthesized using easily accessible starting materials, salicylaldehyde, and acetophenones (Scheme 1) which furnished respective chalcones (**2a**–**k**) in good to excellent yields.[11]

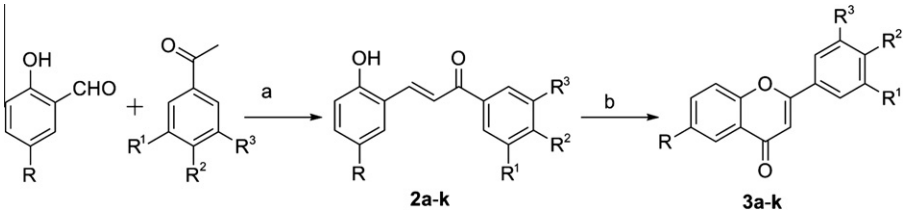
Our synthetic approach was initiated with the synthesis of various intermediate chalcones (**2a**–**k**) which was achieved through Claisen–Schmidt condensation between salicylaldehyde and acetophenone in a mixture of 10% KOH(aq) and ethanol under refluxing condition for 2–2.5 h (Scheme 2). These chalcones were then oxidatively cyclized in the presence of iodine to furnish the flavone derivatives (**3a**–**k**) in good yields.[12] All the compounds were characterized using $^1$H NMR, $^{13}$C NMR, 2D NMR, and mass spectrometry. The purity of these compounds was ascertained by TLC and spectral analysis.

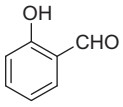
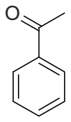
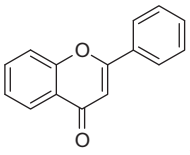
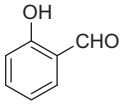
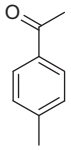
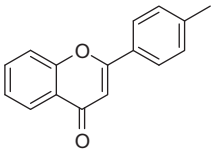
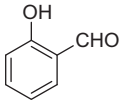
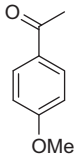
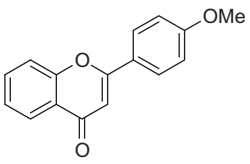
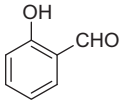
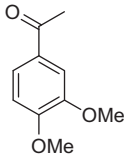
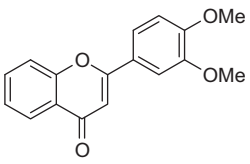
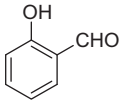
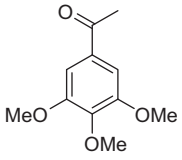
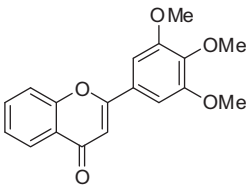
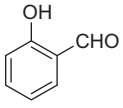
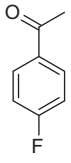
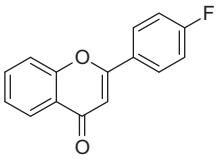
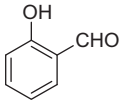
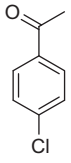
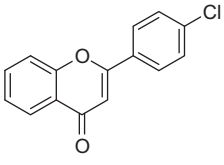
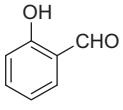
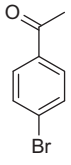
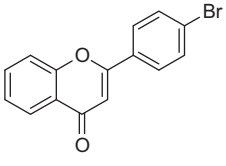
Initially, we have proceeded to a preliminary study of a catalytic evaluation of Lewis acids ($BF_3{\cdot}OEt_2$, $SnCl_2{\cdot}2H_2O$, $Bi(NO_2)_3$, $AlCl_3$, $SnCl_4$, $HgCl_2$, and Iodine) using chalcone **2b** as the starting substrate. It is quite apparent from Table 1 that among various Lewis acid catalysts screened, only iodine afforded the finest results with respect to the reaction time and yield. It was also found that the use of 10 mol % of iodine gave the best results, whereas, other Lewis acids completed the reaction in moderate yield or resulted in multiple products. Notably, the reaction was conducted under solvent-free conditions. Initially, the reaction was attempted with different solvents but the yields were found to be better in the absence of any solvent as shown in Table 2 (entry 8).

With these findings, to test the generality of this synthetic route, a variety of substituted acetophenones (with both electron withdrawing and electron donating) were reacted with salicylaldehydes under the conditions described above to give the corresponding final flavone derivatives in very satisfactory yields. These results are summarized in Table 3.

On the basis of the experimental results, a plausible mechanism for the formation of flavones **3b** from the 2-hydroxychalcone **2b** via iodine mediated oxidative cyclization is presented in Scheme 3. The mechanism involves the following steps: Isomerization (the possibility of thermally induced *trans- cis* chalcone isomerization cannot be ruled out) of the initial adduct, *trans*-3-(2-hydroxyphenyl)-1-(4-methylphenyl)prop-2-en-1-one to *cis* isomer[13]

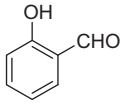
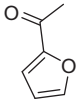
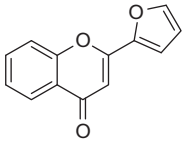
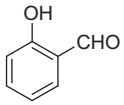
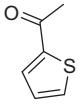
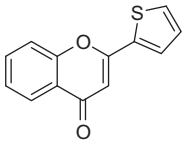
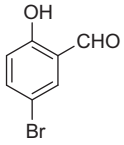
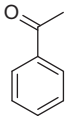
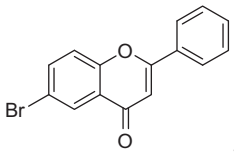
**Table 3**
Synthesis of flavones (**3a**–**k**)



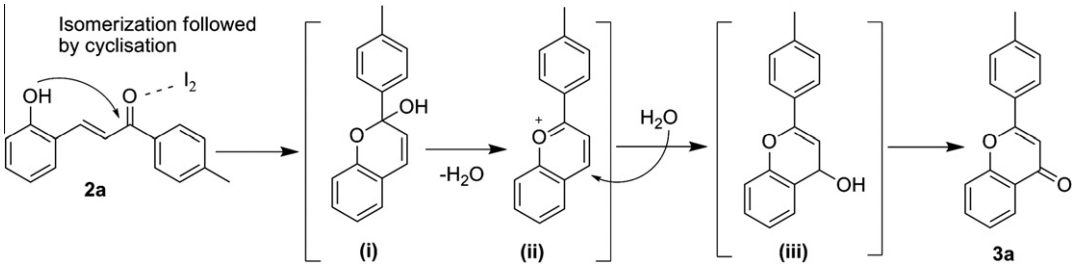

| Entry | Substrate (1) | Substrate (2) | Product | Reaction time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  |  |  **3a** | 1.5 | 72 |
| 2 |  |  |  **3b** | 1.5 | 74 |
| 3 |  |  |  **3c** | 1.4 | 76 |
| 4 |  |  |  **3d** | 1.4 | 78 |
| 5 |  |  |  **3e** | 1.5 | 72 |
| 6 |  |  |  **3f** | 2.0 | 68 |
| 7 |  |  |  **3g** | 2.0 | 70 |
| 8 |  |  |  **3h** | 2.5 | 66 |

(*continued on next page*)

**Table 3** (*continued*)

| Entry | Substrate (1) | Substrate (2) | Product | Reaction time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 9 |  |  |  **3i** | 2.4 | 62 |
| 10 |  |  |  **3j** | 2.4 | 65 |
| 11 |  |  |  **3k** | 2.5 | 60 |

Reagents and conditions: (a) 10% aq. KOH, ethanol, reflux, 2.5 h. (b) $I_2$, 110–130 °C, 1.5 h.
[a] Isolated yield.




**Scheme 3.** Plausible mechanism of reaction.

followed by intramolecular cyclization results in its hemiacetal species (**i**), which gets converted to more reactive flavylium ion (**ii**).[14] Furthermore, water molecules attack on the more reactive 3-position of (**ii**) to form adduct (**iii**), that on oxidation in the presence of iodine yields flavones (**3a**). To the best of our knowledge, this is the first report for the synthesis of flavones from chalcones, whereas the oxygen which forms the ether is introduced as salicylaldehyde, while previously reported procedure involves the oxygen derived from 2-hydroxyacetophenone.

In conclusion, we have demonstrated here a simple, efficient, and alternate route for the synthesis of flavones utilizing molecular iodine as a catalyst for the first time. This methodology involves the use of salicylaldehydes instead of 2-hydroxyacetophenone, in which formation of chalcone is quite easier with high yields. The advantages of this method comprise good substrate generality, the use of inexpensive reagents/ and catalyst and experimental operational ease. Additionally, our protocol is environmental friendly and devoid of organic solvents and metal catalysts.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.108.

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12. *Representative Synthesis of 2-p-tolyl-4H-chromen-4-one* (**3b**): A mixture (*E*)-3-(2-hydroxyphenyl)-1-*p*-tolylprop-2-en-1-one **2b** (0.4 mmol and $I_2$ (10 mol %) were charged in a 10 mL round bottom flask fitted with a reflux condenser and a calcium chloride guard tube. The mixture was stirred at 100–110 °C temperature for 1.5 h. After completion of the reaction (TLC monitoring), the mixture was treated with aq. $Na_2S_2O_3$ solution (5%, 10 mL) and the product was extracted with chloroform (3 × 20 mL). The combined organic layers were dried with anhydrous sodium sulphate, concentrated in vacuo and purified by column chromatography (100–200 mesh) (ethyl acetate:hexane) to afford the pure compound **3b**. White solid; yield: 74%; mp 109–110 °C; $^1$H NMR ($CDCl_3$, 300 MHz): 8.22 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 2H), 7.72–7.67 (m, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.80 (s, 1H), 2.44 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 178.6, 163.8, 156.4, 142.4, 133.8, 129.9, 129.1, 126.4, 125.8, 125.3, 124.2, 118.2, 107.1, 21.7; ESI-MS (*m*/*z*): 237 $(M+H)^+$.
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