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Pyrrolidine and iodine catalyzed domino aldol-Michael-dehydrogenative synthesis of flavones

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ABSTRACT

A one pot synthesis of flavones is established from 2′-hydroxyacetophenones and substituted aromatic aldehydes. The method uses domino aldol-Michael-oxidation reaction catalyzed by pyrrolidine as a base and iodine as an oxidant in dimethyl sulfoxide.

Flavones or 2-phenylchromones are naturally occurring oxygen containing heterocyclic compounds belonging to the flavonoid family present in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine.[1] Owing to their broad range of biological activities, continuous investigation has led to the isolation of over 4000 chemically unique flavonoids from plants.[2] Multifarious biological activities exhibited by flavones include anti-inflammatory, anti-viral, anti-estrogenic, anticancer, antioxidant, leishmanicidal, ovipositor stimulant phytoalexins, anti-HIV, antimutagenic, antiallergic, etc.[3,4] Some flavonoids are known to show modulatory properties of enzymes such as activation of sirtuins[5] and inhibition of monoamine oxidase (MAO).[6] Some of the well known naturally occurring potent bioactive flavones are shown in Figure 1. As a consequence of these vital properties researchers constantly study these interesting flavonoids and come up with new strategies to synthesize them.

A variety of methods have been developed for flavone synthesis, traditionally used being Baker–Venkataraman rearrangement,[11] Allan–Robinson,[12] and Auwers synthesis.[13] Most of the reported syntheses make use of chalcones which on oxidation using numerous oxidizing agents such as molecular I_2,[14] DDQ, Ph-S-S-Ph, I_2-DMSO,[15] I_2-SiO_2,[16] I_2-Al_2O_3,[17] NH_4I,[18] $InBr_3$, and $InCl_3$[19] give flavones. Microwave irradiation technique is also used to obtain flavones.[20] Similarly oxidation of flavanones to flavones is well known in the literature.[21] Recently various reports have emerged using diverse Palladium catalysts,[22] however in many cases competitive side reactions leading to aurones as side products are detected. Ionic liquids are used to deliver the target molecule either by dehydrative cyclization of 1,3-(diaryl) diketones or using CuI catalyst.[23] Besides this, various other methods have appeared in the literature for dehydrative cyclization of 1,3-diketones to produce flavones.[23a,b,24] Some of the catalysts employed to furnish flavones comprise of $FeCl_3$-piperidine[25] and DMAP.[26] Intramolecular Wittig reaction has also been reported.[27] A convenient one pot method from hydrolysis of flavylium salt obtained from condensation of 2′-hydroxyacetophenone and aryl aldehydes using perchloric acid is also known.[28]

Recently flavanone synthesis is reported using aniline and catalytic amount of iodine from aryl aldehydes and 2′-hydroxyacetophenone.[29] Also it is well known that 2′-hydroxychalcone get cyclized to flavone using iodine and DMSO as a solvent.[15] In view of this we conjectured that it should be possible to devise synthesis of flavone directly from aryl aldehyde and 2′-hydroxyacetophenone.

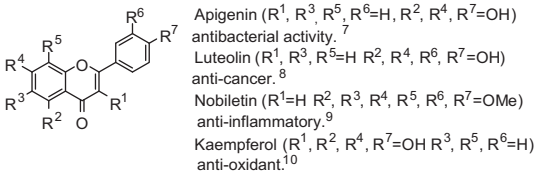

Figure. 1. Naturally occurring biologically active flavones. (See Refs. 7–10).

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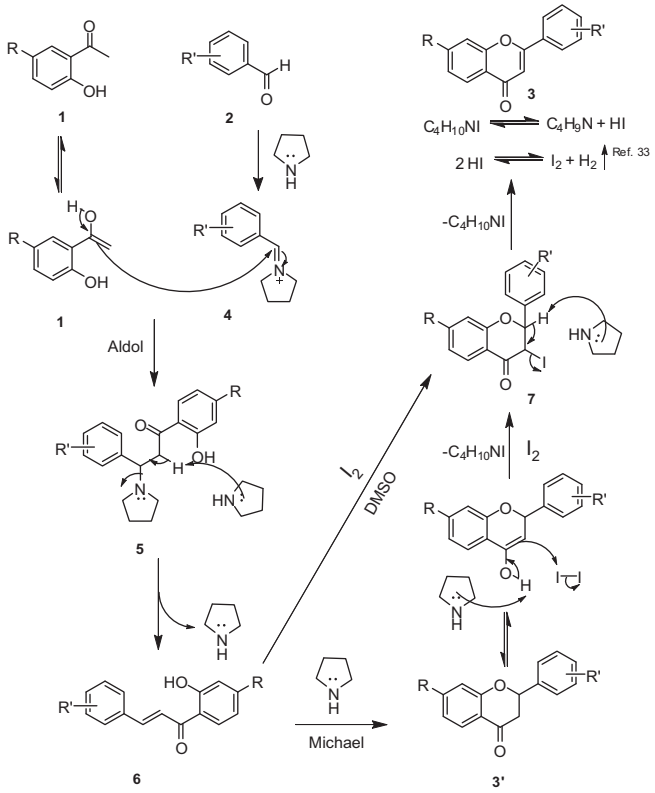
0040-4039/



Scheme 1. Probable mechanism for the formation of flavone **3** via chalcone **6** and flavanone **3′**. (See Ref. 33).

We speculated that a secondary amine could give chalcone followed by Michael reaction to form flavanone which could then get oxidized with iodine in DMSO to render flavone (Scheme 1). However, the crucial reaction for the catalytic sequence to be successful was the requirement of regeneration of pyrrolidine and iodine via oxidation of HI formed from dissociation of pyrrolidinium iodide.

We commenced our work by choosing 2′-hydroxyacetophenone **1a** and 3,4-dimethoxybenzaldehyde **2a** as model substrates in the presence of different bases (0.5 equiv) and iodine (10 mol %) catalyst as an oxidant in DMSO solvent to deliver flavone under reflux for 2 h (Scheme 2). Various bases such as pyrrolidine, L-proline, piperidine, N-methylaniline, and morpholine were screened individually. To our delight, required flavone **3a** was formed in 75% yield when pyrrolidine was employed as base catalyst. L-proline and piperidine were found to diminish the yields to 36 and 22% respectively. On pursuing the reaction with other bases viz. N-methylaniline and morpholine no product formation was observed.

The amount of pyrrolidine was standardized by investigating the reaction in the absence of iodine which furnished 2-(3,4-dimethoxyphenyl)chroman-4-one **3a′** exclusively (Fig. 2). Varying concentrations of pyrrolidine like 0.1, 0.2, 0.3, 0.5, 1.0, and 1.5 equiv

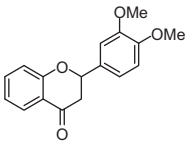
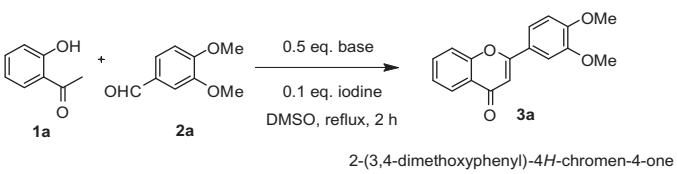


Figure 2. Flavanone **3a′** formed in absence of iodine.

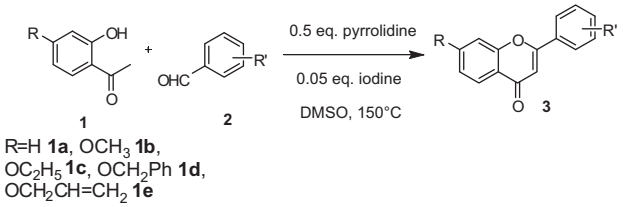
were tried which showed 0.5 equiv of pyrrolidine to be the optimum concentration as the reaction got completed in minimum time of 15 min.

With 0.5 equiv of pyrrolidine we proceeded with temperature studies in DMSO solvent at room temperature, 60, 100, and 150 °C which revealed 150 °C to be the optimum temperature for flavone formation providing maximum yield of 80%. Other solvents tried were ethanol, methanol, toluene, xylene, and tetrahydrofuran which showed no required product formation even after refluxing for 24 h. Similarly iodine concentration was varied from 1 mol % to 100 mol % which displayed 5 mol % of iodine to be the optimum concentration as it delivered flavone in highest yield of 88%. In the absence of iodine no flavone formation was observed even after prolonged heating.

After exploring various parameters we obtained the ideal reaction condition[32] shown in Scheme 3. Subsequently, we set different aromatic aldehydes to the optimized reaction condition in order to explore the generality of our methodology (Table 1). Electron rich aromatic aldehydes **2a**–**2c** furnished desired flavones **3a**–**3c** in good yields. Benzaldehyde too smoothly formed the required product **3d**. Halogenated aromatic aldehydes were well tolerated to provide **3e**–**3g** flavones in good yields which are good scaffolds for further functionalization. Aromatic aldehydes with *m*-substituted bromo as well as strong electron withdrawing nitro group resulted in flavone **3h** and **3i** formation but with slightly declined yields. Thus our methodology could be applied to both electron rich as well as electron deficient aromatic aldehydes which are well tolerated under the reaction condition as the yields were unchanged to the electronic effects. Furthermore, 3,4-methylenedioxy benzaldehyde smoothly favored the formation of desired flavone **3j** in satisfactory yield. Reports have shown that the biological activity of flavones is enhanced when five- or six-membered heterocyclic group is attached at its C-2 position.[30] Motivated from this we subjected different heterocyclic aromatic aldehydes to the reaction condition to achieve the desired flavone products **3k**–**3m** in good yields. After scanning numerous aromatic aldehydes, substituted 2′-hydroxyacetophenones **1b**–**1e** were put forth for determining the substrate scope. 4-Methoxy-2′-hydroxyacetophenone **1b** was reacted with benzaldehydes **2b** and **2d** to provide flavones **3n**–**3o** in good yields. Similarly 4-ethoxy-2′-hydroxyacetophenone **1c** and 4-benzyloxy-2′-hydroxyacetophenone **1d** reacted under standardized condition to furnish respective flavones **3p** and **3q** in reasonable yields. One of the reports had shown deprotection of 2′-allyloxychalcone leading to flavone in I_2-DMSO.[31] Interestingly, we got the desired flavone **3r** from 4-allyloxy-2′-hydroxyacetophenone **1e** without the cleavage of the



Scheme 2. Reaction of 2′-hydroxyacetophenone with 3,4-dimethoxybenzaldehyde.



Scheme 3. Standardized reaction condition for flavone formation.

Table 1
Derivatives of flavones **3a**–**r** using 2′-hydroxyacetophenones **1a**–**e** and substituted aromatic aldehydes **2a**–**m** under optimized reaction condition

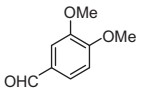
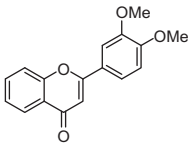
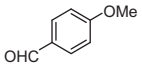
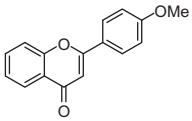
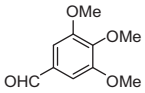
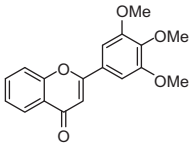
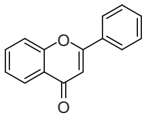
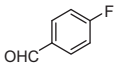
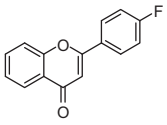
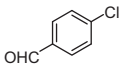
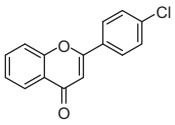
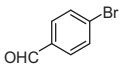
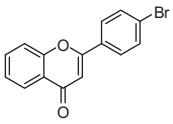
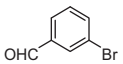
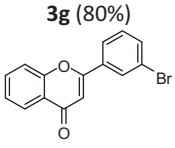
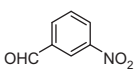
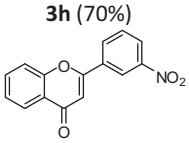
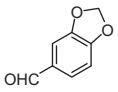
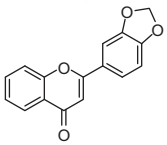
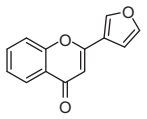
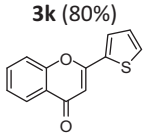
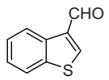
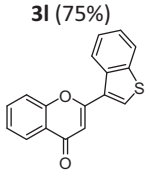
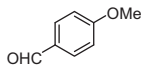
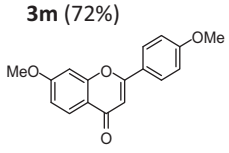
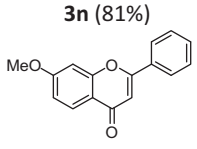
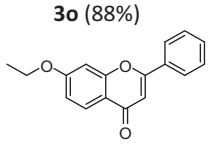
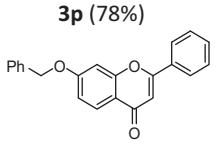
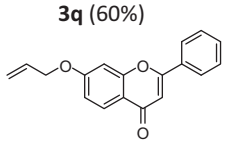
Substrate (**1**)	Substrate (**2**)	Time (h)	Product[a] (**3**)
1a	 **2a**	10	 **3a** (88%)
1a	 **2b**	24	 **3b** (82%)
1a	 **2c**	7	 **3c** (78%)
1a	 **2d**	9	 **3d** (85%)
1a	 **2e**	9	 **3e** (82%)
1a	 **2f**	12	 **3f** (84%)
1a	 **2g**	13	 **3g** (80%)
1a	 **2h**	6	 **3h** (70%)
1a	 **2i**	12	 **3i** (62%)
1a	 **2j**	24	 **3j** (74%)

Table 1 (*continued*)

Substrate (**1**)	Substrate (**2**)	Time (h)	Product[a] (**3**)
1a	 **2k**	9	 **3k** (80%)
1a	 **2l**	6	 **3l** (75%)
1a	 **2m**	8	 **3m** (72%)
1b	 **2b**	8	 **3n** (81%)
1b	 **2d**	10	 **3o** (88%)
1c	 **2d**	12	 **3p** (78%)
1d	 **2d**	12	 **3q** (60%)
1e	 **2d**	8	 **3r** (70%)

[a] Isolated yields.

allyloxy group. The reaction protocol was also successfully scaled up to 5 g of starting aryl aldehyde **2a** to get consistent yield of desired flavone **3a**. The present method is an alternative to the reported one pot method (Ref. 28a) avoiding the use of explosive perchloric acid.

In conclusion, one pot synthesis of flavones is described using pyrrolidine and iodine catalysts in DMSO solvent. Several advantages of this methodology including inexpensive catalysts, good substrate generality, lack of metal catalysts, and products in high yields with no side reactions make it a useful synthetic approach to flavones. Also, this method avoids the step of isolation of chalcone or flavanone intermediates and then subjecting them to further oxidation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.051.

References and notes

1. (a) Middleton, E., Jr. *Adv. Exp. Med. Biol.* **1998**, *439*, 175–182; (b) Aherne, S. A.; O'Brien, N. M. *Nutrition* **2002**, *18*, 75–81.
2. The Flavonoids, advances in research since 1986 In Harborne, J. B., Ed.; Chapman and Hall: London, 1986; p 1993.
3. Seijas, J. A.; Vázquez-Tato, M. P.; Carballido-Reboredo, R. *J. Org. Chem.* **2005**, *70*, 2855–2858. and references cited therein.
4. Verma, A. K.; Pratap, R. *Tetrahedron* **2012**, *68*, 8523–8538. and references cited therein.
5. Orallo, F. *Curr. Med. Chem.* **2008**, *15*, 1887–1898.
6. Han, X. H.; Hong, S. S.; Hwang, J. S.; Lee, M. K.; Hwang, B. Y.; Ro, J. S. *Arch. Pharm. Res.* **2007**, *30*, 13–17.
7. Öksüz, S.; Ayyildiz, H.; Johansson, C. *J. Nat. Prod.* **1984**, *47*, 902–903.
8. Lin, Y.; Shi, R.; Wang, X.; Shen, H. M. *Curr. Cancer Drug Targets* **2008**, *8*, 634–646.
9. Martens, S.; Mithöfer, A. *Phytochemistry* **2005**, *66*, 2399–2407.
10. Gabrielska, J.; Soczyńska-Kordala, M.; Przestalski, S. *J. Agric. Food Chem.* **2005**, *53*, 76–83.
11. (a) Baker, W. *J. Chem. Soc.* **1933**, 1381–1389; (b) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767–1769; (c) Mahal, H. S.; Venkataraman, K. *Curr. Sci.* **1933**, *4*, 214–216; (d) Wheeler, T. S. *Org. Synth.* **1952**, *32*, 72; (e) Wheeler, T. S. *Org. Synth.* **1963**, *4*, 478. For recent examples of the Baker–Venkataraman rearrangement, see:; (f) Riva, C.; De Toma, C.; Donadd, L.; Boi, C.; Pennini, R.; Motta, G.; Leonardi, A. *Synthesis* **1997**, 195–201; (g) Bois, F.; Beney, C.; Mariotte, A. M.; Boumendjel, A. *Synlett* **1999**, 1480–1482; (h) Ganguly, A. K.; Kaur, S.; Mahata, P. K.; Biswas, D.; Pramanik, B. N.; Chan, T. M. *Tetrahedron Lett.* **2005**, *46*, 4119–4121; (i) Ganguly, A. K.; Mahata, P. K.; Biswas, D. *Tetrahedron Lett.* **2006**, *47*, 1347–1349; (j) Chee, C. F.; Buckle, M. J. C.; Rahman, N. A. *Tetrahedron Lett.* **2011**, *52*, 3120–3123.
12. Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, *125*, 2192–2195.
13. (a) Auwers, K. V.; Markovists, T. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 2332–2340; (b) Auwers, K. V.; Pohl, P. *Ber. Dtsch. Chem. Ges.* **1915**, *48*, 85–90; (c) Auwers, K. V. *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 809–819; (d) Auwers, K. V.; Pohl, P. *Liebigs Ann. Chem.* **1914**, *405*, 243–294.
14. Sashidhara, K. V.; Kumar, M.; Kumar, A. *Tetrahedron Lett.* **2012**, *53*, 2355–2359.
15. (a) Venkatesan, P.; Maruthavanan, T. *Bull. Chem. Soc. Ethiop.* **2011**, *25*, 419–425; (b) Theja, D. N.; Choudary, T. P.; Reddy, M. I.; Avsss, G.; Reddy, K. U. *Int. J. Pharm. Pharm. Sci.* **2011**, *3*, 51–54.
16. Babu, K. R.; Kumar, K. V.; Vijaya, M.; Madhavarao, V. *Int. J. Pharm. Technol.* **2012**, *4*, 3943–3950.
17. Sarda, S. R.; Jadhav, W. N.; Pawar, R. P. *Int. J. ChemTech. Res.* **2009**, *1*, 539–543.
18. Kulkarni, P. S.; Kondhare, D. D.; Varala, R.; Zubaidha, P. K. *J. Serb. Chem. Soc.* **2012**, *77*, 1–12.
19. Ahmed, N.; Ali, H.; Van Lier, J. E. *Tetrahedron Lett.* **2005**, *46*, 253–256.
20. (a) Menezes, M. J.; Manjrekar, S.; Pai, V.; Patre, R. E.; Tilve, S. G. *Indian J. Chem.* **2009**, *48B*, 1311–1314; (b) Borse, S. L.; Patel, M. R.; Borse, L. B. *Int. J. Pharm. Res. Dev.* **2011**, *3*, 147–152; (c) Seijas, J. A.; Vázquez-Tato, M. P.; Carballido-Reboredo, R. *J. Org. Chem.* **2005**, *70*, 2855–2858; (d) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2005**, *46*, 6315–6317.
21. (a) Muthukrishnan, M.; Patil, P. S.; More, S. V.; Joshi, R. A. *Mendeleev Commun.* **2005**, *15*, 100–101. and references cited therein; (b) Singh, O. V.; Muthukrishnan, M.; Raj, G. *Synth. Commun.* **2005**, *35*, 2723–2728. and references cited therein; (c) Bovicelli, P.; D'Angelo, V.; Collalto, D.; Verzina, A.; D'Antona, N.; Lambusta, D. *J. Pharm. Pharmacol.* **2007**, *59*, 1697–1701; (d) Zhou, Z.; Zhao, P.; Huang, W.; Yang, G. *Adv. Synth. Catal.* **2006**, *348*, 63–67; (e) Lamba, M.; Makrandi, J. K. *J. Chem. Res.* **2008**, *2008*, 225–226.
22. (a) Awuah, E.; Capretta, A. *Org. Lett.* **2009**, *11*, 3210–3213; (b) Lorenz, M.; Kabir, M. S.; Cook, J. M. *Tetrahedron Lett.* **2010**, *51*, 1095–1098; (c) Kim, D.; Ham, K.; Hong, S. *Org. Biomol. Chem.* **2012**, *10*, 7305–7312; (d) Kraus, G. A.; Gupta, V. *Org. Lett.* **2010**, *12*, 5278–5280; (e) Kim, K. H.; Lee, H. S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2012**, *53*, 2761–2764; (f) Khoobi, M.; Alipour, M.; Zarei, S.; Jafarpour, F.; Shafiee, A. *Chem. Commun.* **2012**, 2985–2987; (g) Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 1765–1768; (h) Yang, Q.; Alper, H. *J. Org. Chem.* **2010**, *75*, 948–950; (i) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Eur. J.* **2012**, *18*, 12595–12598; (j) Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 6097–6100.
23. (a) Sarda, S. R.; Pathan, M. Y.; Paike, V. V.; Pachmase, P. R.; Jadhav, W. N.; Pawar, R. P. *ARKIVOC* **2006**, *xvi*, 43–48. and references cited therein; (b) Bhosale, R. S.; Sarda, S. R.; Giram, R. P.; Raut, D. S.; Parwe, S. P.; Ardhapure, S. S.; Pawar, R. P. *J. Iran. Chem. Soc.* **2009**, *6*, 519–522. and references cited therein; (c) Du, Z.; Ng, H.; Zhang, K.; Zeng, H.; Wang, J. *Org. Biomol. Chem.* **2011**, *9*, 6930–6933.
24. (a) Lee, J. I.; Son, H. S.; Park, H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1945–1947; (b) Lee, J. I.; Son, H. S.; Jung, M. G. *Bull. Korean Chem. Soc.* **2005**, *26*, 1461–1463; (c) Nagarathnam, D.; Cushman, M. *J. Org. Chem.* **1991**, *56*, 4884–4887; (d) Bennardi, D. O.; Romanelli, G. P.; Jios, J. L.; Autino, J. C.; Baronetti, G. T.; Thomas, H. J. *ARKIVOC* **2008**, *xi*, 123–130; (e) Pérez, M. E.; Ruiz, D. M.; Autino, J. C.; Blanco, M. N.; Pizzio, L. R.; Romanelli, G. P. *J. Porous Mater.* **2013**, *20*, 1433–1440; (f) Zhao, J.; Zhao, Y.; Fu, H. *Org. Lett.* **2012**, *14*, 2710–2713.
25. Maiti, G.; Karmakar, R.; Bhattacharya, R. N.; Kayal, U. *Tetrahedron Lett.* **2011**, *52*, 5610–5612.
26. Yoshida, M.; Fujino, Y.; Saito, K.; Doi, T. *Tetrahedron* **2011**, *67*, 9993–9997.
27. (a) Kumar, P.; Bodas, M. S. *Org. Lett.* **2000**, *2*, 3821–3823; (b) Das, J.; Ghosh, S. *Tetrahedron Lett.* **2011**, *52*, 7189–7194.
28. (a) Yakovenko, V. I.; Oganesyan, É. T.; Dorofeenko, G. N. *Chem. Heterocycl. Compd.* **1981**, *17*, 115–118; (b) Golub, A. G.; Bdzhola, V. G.; Ostrynska, O. V.; Kyshenia, I. V.; Sapelkin, V. M.; Prykhod'ko, A. O.; Kukharenko, O. P.; Yarmoluk, S. M. *Bioorg. Med. Chem.* **2013**, *21*, 6681–6689.
29. Kavala, V.; Lin, C.; Kuo, C.-W.; Fang, H.; Yao, C.-F. *Tetrahedron* **2012**, *68*, 1321–1329.
30. (a) Kálai, T.; Kulcsar, G.; Osz, E.; Jeko, J.; Sumegi, B.; Hidega, K. *ARKIVOC* **2004**, *vii*, 266–276; (b) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626–1632; (c) Khilya, V. P.; Ishchenko, V. V. *Chem. Heterocycl. Compd.* **2002**, *38*, 883–899.
31. Lokhande, P. D.; Sakate, S. S.; Taksande, K. N.; Navghare, B. *Tetrahedron Lett.* **2005**, *46*, 1573–1574.
32. *Typical procedure for the synthesis of flavones:* 2′-Hydroxyacetophenone (1 mmol) and substituted aromatic aldehyde (1 mmol) were mixed together along with pyrrolidine (0.5 mmol) and iodine (0.05 mmol) in DMSO solvent (10 mL). The resulting mixture was then heated at 150 °C for the given time. After completion of reaction (monitored by TLC) the reaction mass was allowed to cool and diluted with ethyl acetate (20 mL). Resulting solution was then washed with water and saturated sodium thiosulfate solution followed by drying over anhydrous sodium sulfate and concentrating under reduced pressure to furnish the crude product. The residue obtained was purified by column chromatography using petroleum ether-ethyl acetate as an eluent to afford flavones (**3a–r**).
33. 1-(2-Hydroxyphenyl)-3-(pyridin-2-yl)propan-1-one was obtained when 2-pyridinecarboxaldehyde was subjected to this protocol due to reduction of the intermediate chalcone by the liberated H_2 along with the corresponding flavanone and flavone.