Regioselectivity and chemoselectivity in the synthesis of flavones

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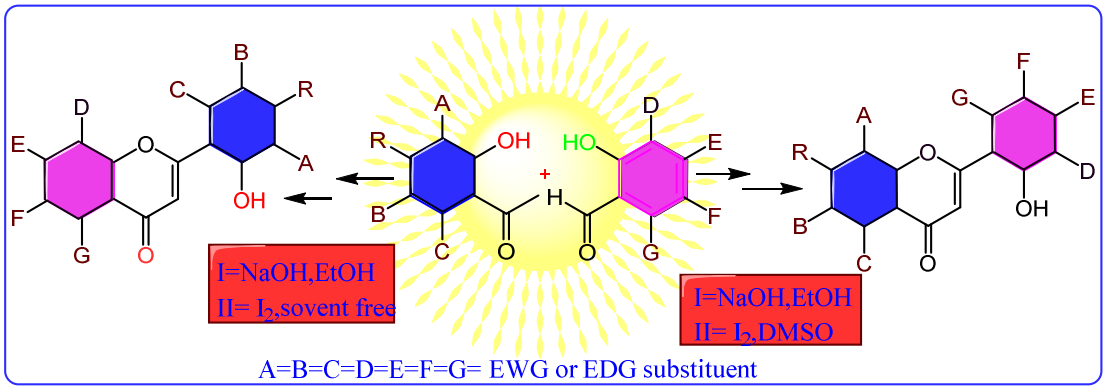
Abstract

In present paper we synthesized flavones regioselectively.Same intermediate chalcone was converted into two flavones stereoselectively.It reduces number of steps for the synthesis as well as two products obtained from single intermediate.Also we can synthesized one product as a major regioselectively.We first time note down that solvent also affect the product formation.So solvent can be used affect chemoselective reactions.We also notified that DMSO acts as a oxidant.It works as a solvent as well as oxidant.



KEYWORDS: Flavone, Claisen-Schmidt, solvent free, chemo selectivity, stereoslectivity, regioselectivity.

INTRODUCTION

Flavones are natural product and attract attention of researchers and scientists of the world, those working on natural products. This skeleton was originated from plant as a secondary metabolite for defence purpose [(1)] & some examples are given in (**Figure1,2**). Food, tea, wine, vegetables and fruit juices are main source of flavonoids [(2)].They contains C_6-C_3-C_6 carbon chain and two oxygen atoms as a ketone and ether in the basic skeleton. Initially it is named as vitamin-But later due to its yellow colour it is named flavonoids (*Flavus*-yellow). Flavonoids are further classified as flavone, flavanone, flavanol, isoflavone & neoflavone [(3)].

At present survey 3900 different flavonoid skeletons are invented from plants as a secondary metabolite[(4)].Due to its wide biological activity like anticancer,antibacterial,antimalerial,antiviral,anti-inflammatory,anti-diabetic etc.[(2,5,6)], it is important to cure various diseases.So many synthetic methodolgies are invented for the synthesis of flavones [(7)].Most common are Claisen-Schmidt[(8-13)],Baker-Venkatraman[(14-15)],Ganguly's method[(7,16)],K.V.Shishdhara's modified method[(4)] etc. are important for the synthesis of flavones.Ram Pratap (Scientist,CDRI-CSIR Lab, Lucknow) write series of review which gives valuble information of flavones[(5)].

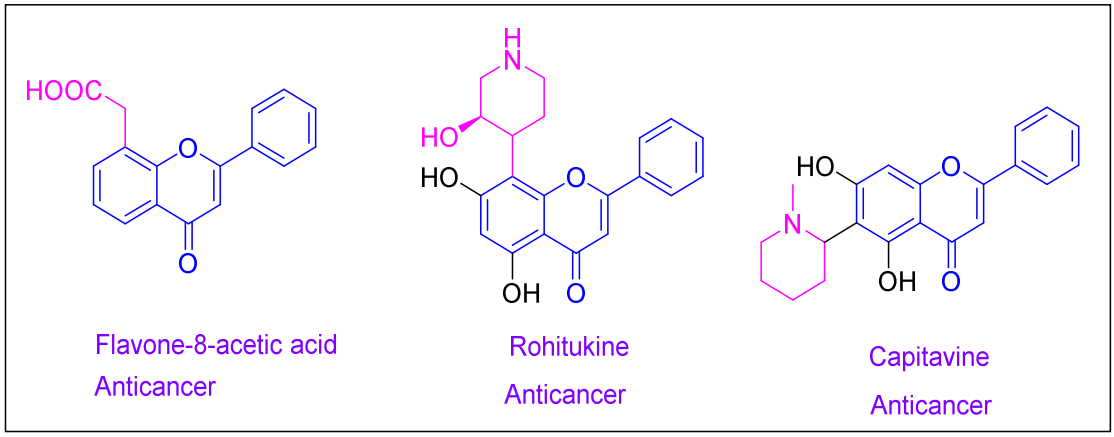


Figure1. Potent&bioactive flavones [6]

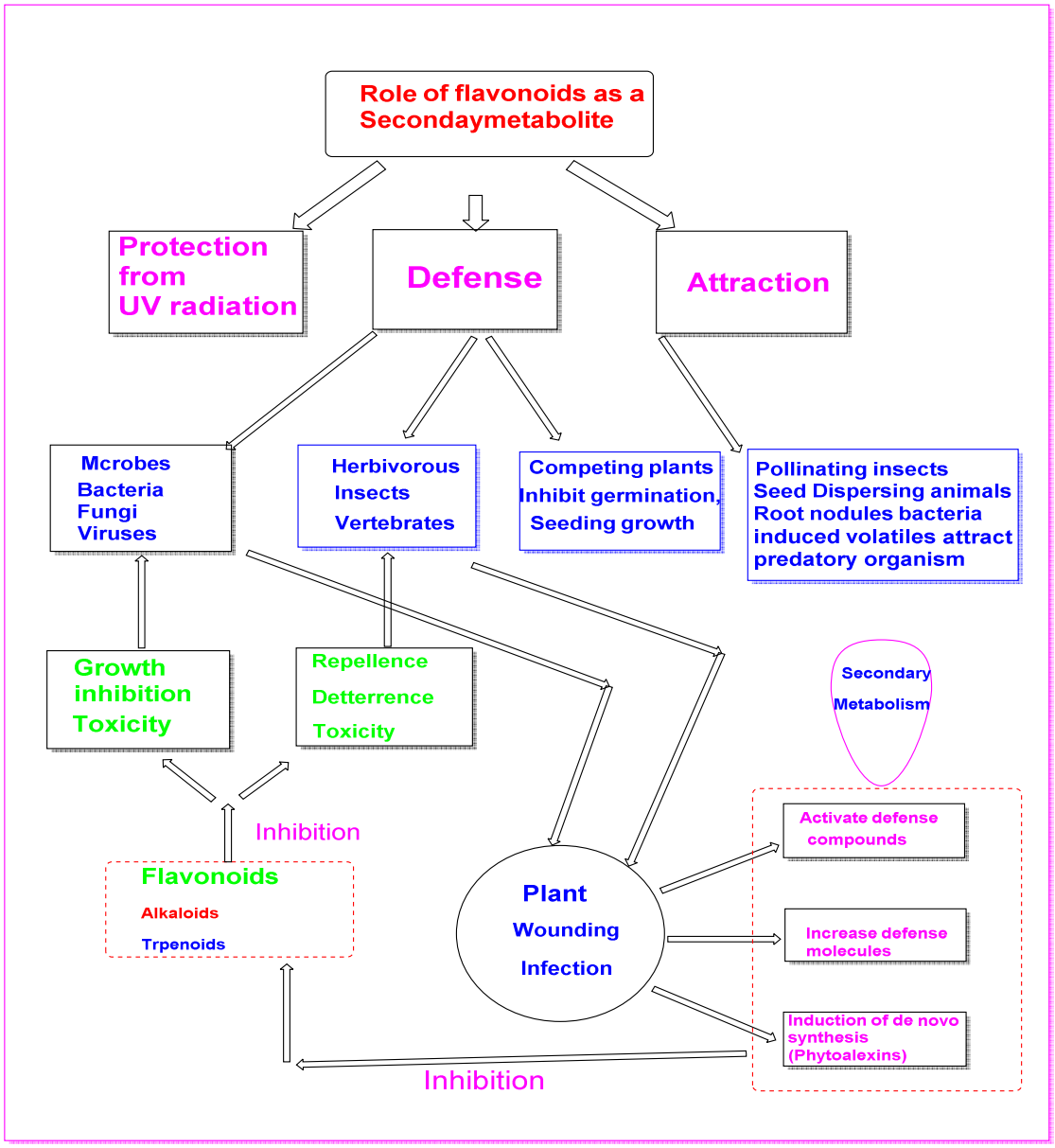
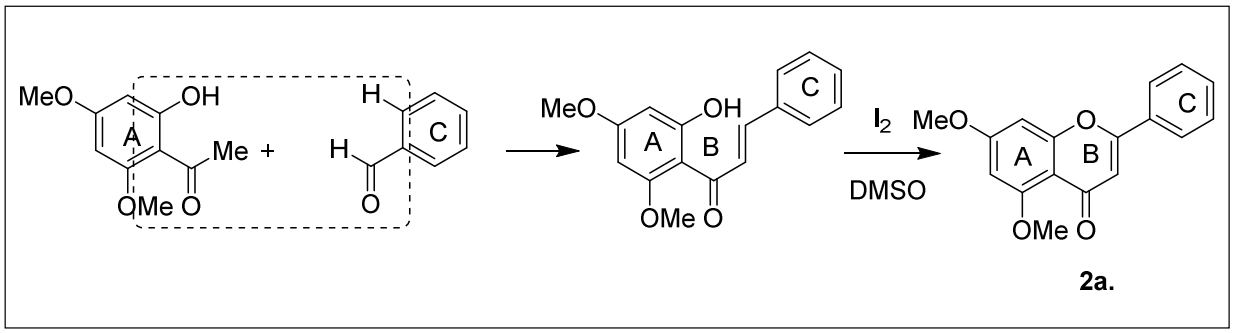


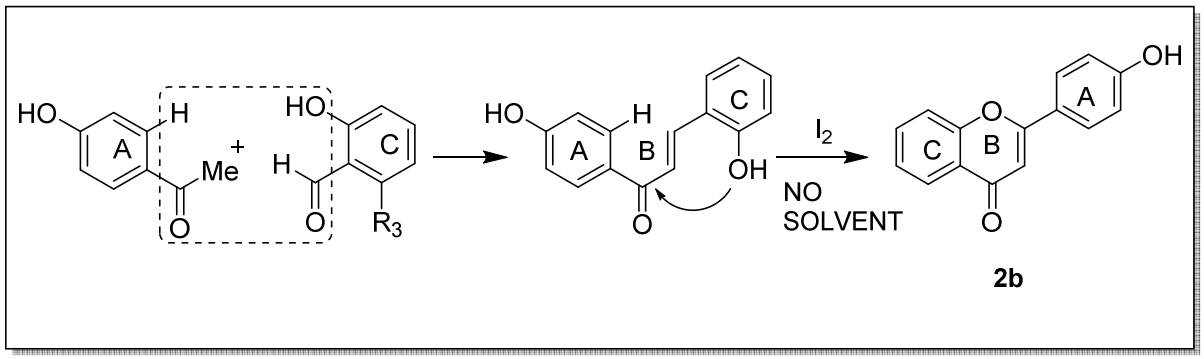
Figure2. Actual role of flavones as defence molecule

Synthetic Methodology

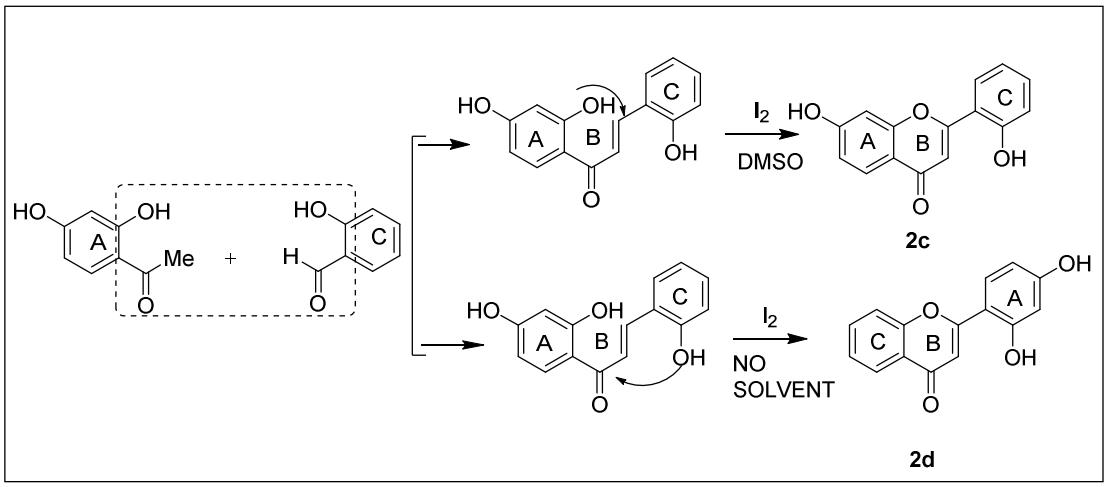
Scheme S_1. Claisen-Schmidt method for the synthesis of flavones [13]



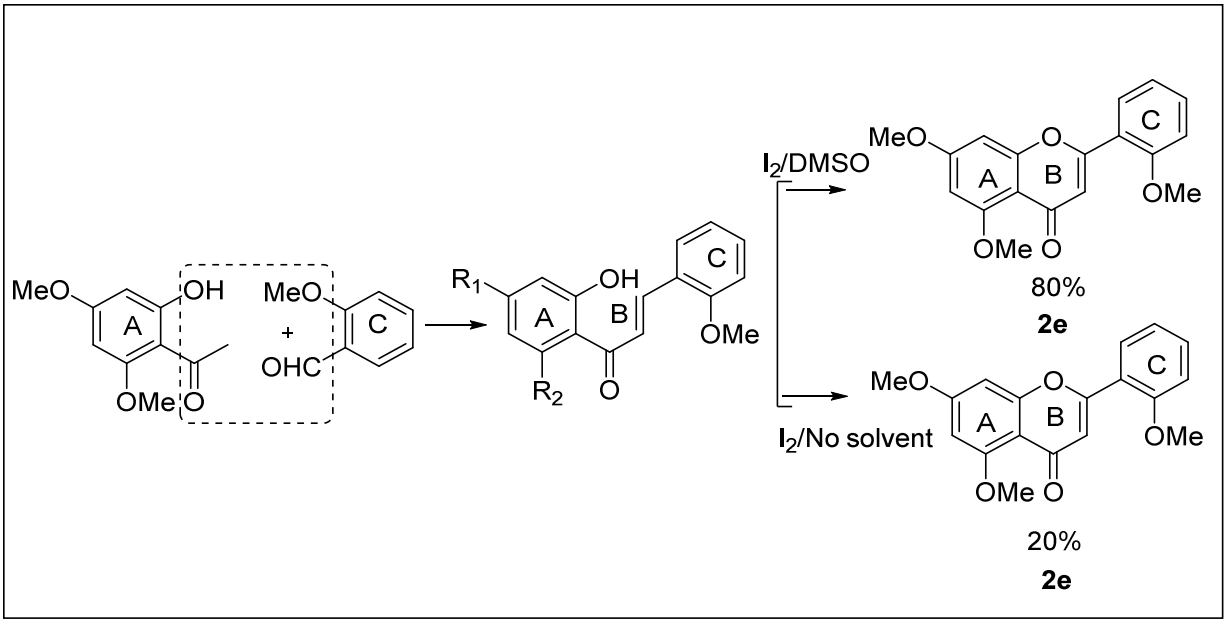
SchemeS_2.K.V. Shashidhara's modified method for the synthesis of flavones[6]



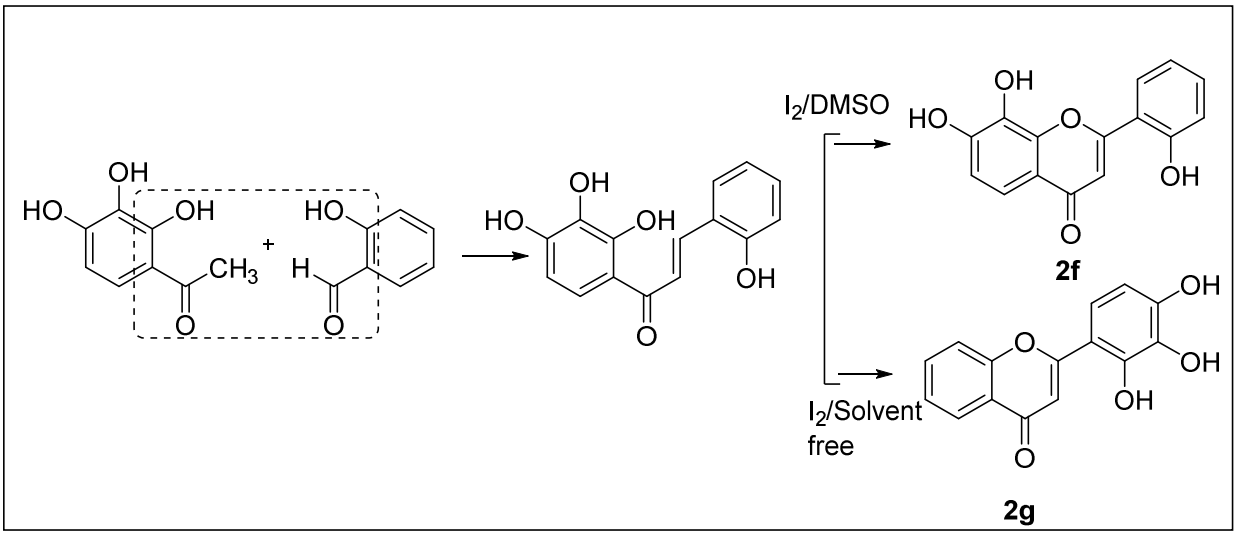
Scheme S_3. Our Regioselective and chemoselective approach for the synthesis of flavones



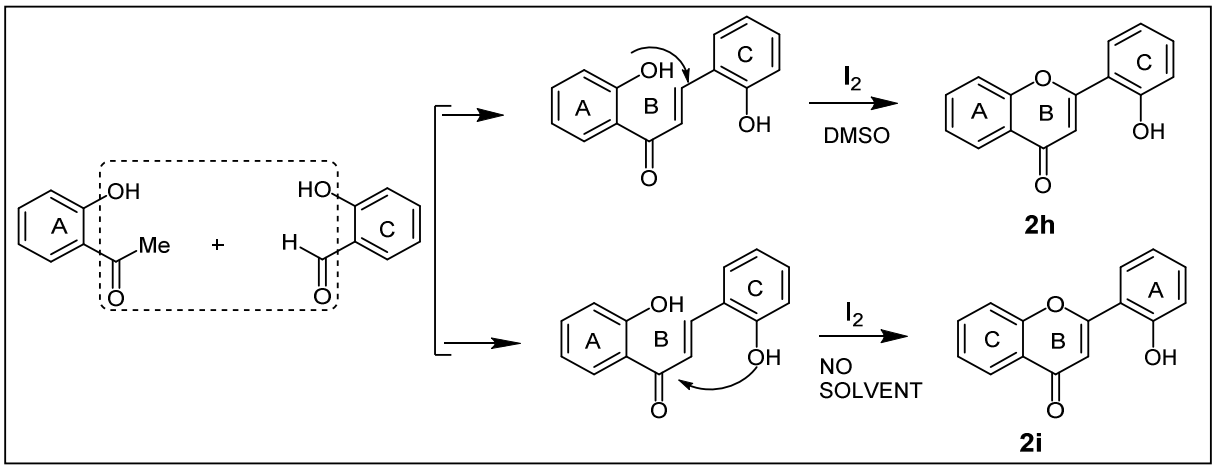
Scheme S_4. Under two different condition reaction is stereo selective



Scheme S_5. Regioselectivity in another flavone synthesis



SchemeS6. Stereoselective and chemoselective synthesis of flavones



RESULTS AND DISCUSSION

We used strategy of regioselectivity in the synthesis of favones.We synthesized flavone molecules by using solvent free and with solvent. In previous methods flavones were synthesized from 2-hydroxyacetophenone and substituted aldehydes (**Scheme 1**).But Koneni V.Shashidhara and his group synthesized flavones from 2-hydroxy aldehyde and substituted acetophenone. He synthesized flavones under solvent free condition. He introduced oxygen of keto group of flavone from water molecule (**Scheme 2**).We carried further research work to obtain flavones from 2,2' dihydroxy chalcone stereo selectively. One flavone by oxidative coupling (**Scheme1**) and second by solvent free method (**Scheme2**).The most important concepts of current synthetic organic chemistry i.e. stereoselectivity,regioselectivity and chemo selectivity was applied here.We first time used 2-hydroxy acetophenone and 2-hydroxy aldehydes for the synthesis of flavones. We used two different reaction conditions (i.e. solvent free and with DMSO as a solvent) for the synthesis of flavones. If 2-hydroxy acetophenone and 2-hydroxy aldehydes are substituted by different group then they gives different flavones under different reaction conditions stereo selectively. One flavone is formed by oxidative coupling [13] via iodinium ion cyclic intermediate and another flavone by nucleophilic reaction of water [6] (via flavynium ion).It was also notified that DMSO acts as oxidant rather than solvent. In Grignard reaction I_2 acts as a initiator, here also acts as a initiator. As per my opinion the mechanism occurs in literatures are not correct. In most cases following mechanism is shown (**Figure1.**) which is not correct as per my opinion.

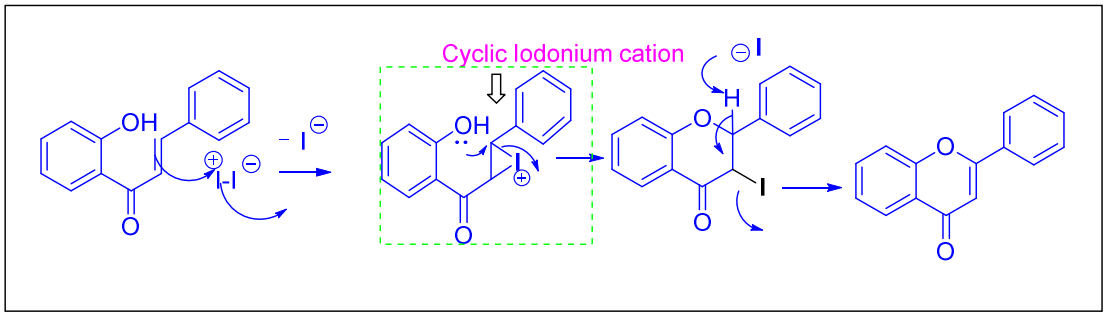


Figure 2. Mechanism of oxidative coupling by iodine & DMSO solvent [13].

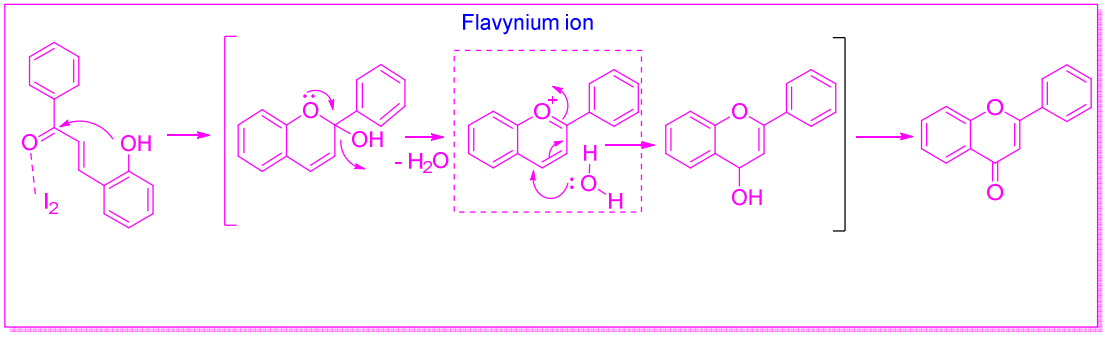


Figure 3. Mechanism of formation of flavone using I_2 & solvent free condition [17].

In (**Figure1.**) mechanism indicates addition of iodine across carbon-carbon double bond followed by attack of of aromatic OH group on cyclic iodonium ring. Then loss of HI takes place to give flavone. But what is role of DMSO? No one explain. As per our opinion iodine first forms bond with oxygen of DMSO.Due to which I^- becomes

free it acts as nucleophile and C=C becomes electrophile (**Figure 3**).Iodine anion attacks C=C forms intermediate as shown in mechanism (**Figure 3**).

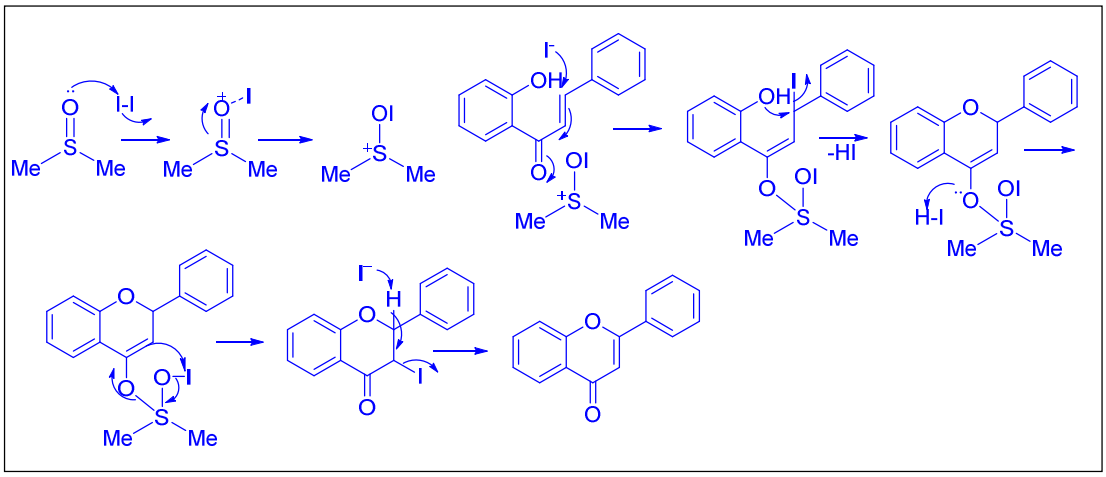


Figure4. Plausible mechanism for the synthesis of flavone with I_2 & DMSO. (Our Approach)

CONCLUSION

We first time concluded that flavones are synthesized chemo selectively and regioselectvely & stereoselectively.With solvent and without solvent affect stereoselectivity of reaction.Steroselectivity, chemoselectivity and regioselectivity are important in the synthesis of natural products. Chemical reagent, solvent changes the percentage of product. One obtained as major and other as minor product this is beauty of stereo selective reaction.DMSO was not only acts as a solvent but also oxidant.

EXPERIMENTAL

All materials are purchased from Sigma, Aldrich and Merck company.^{1}HNMR spectra are recorded on 600MHz spectrometer. Melting points were recorded on melting point apparatus as well as in paraffin oil bath. Compounds were confirmed by NMR spectra as well as IR spectra. But NMR spectra gave correct information and indicate structure of product.

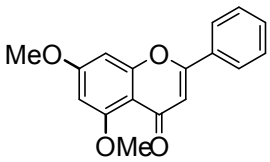
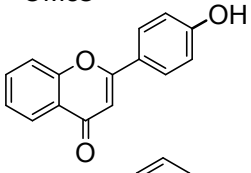
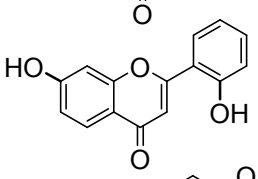
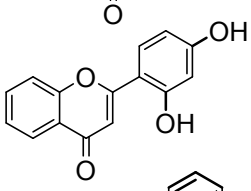
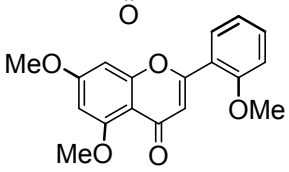
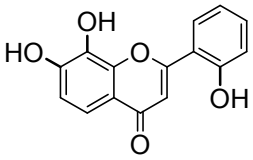
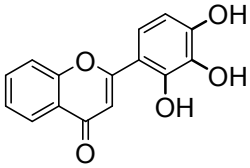
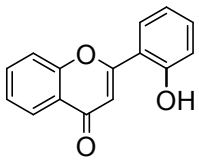
Typical procedure for the synthesis of 5, 7-dimethoxy-2-phenyl-4H-chromen-4-one 2a.

(E)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (1mmole) and I_2 (10 mole %) was taken in RBF. Assembly was kept in oil bath and 110^0C temperature was maintained on hot plate with magnetic stirrer. TLC was checked. If TLC shows reaction was complete then work up was carried out. Reaction mixture was washed with $Na_2S_2O_3$ to remove excess iodine. Reaction mixture also washed with brine to remove inorganic materials. Extracted in suitable solvent. Solvent was distilled out .Recrystallized with suitable solvent if impurity occurred on TLC plate. Yields 80%, yellow solid. Melting point, IR, NMR of sample were taken.

2-(2-hydroxyphenyl)-4H-chromen-4-one (2b)[Procedure to insert oxygen from water]

(E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (0.4 mmol) and I_2 (10 mol-%) were charged in a 2 5mL round bottom flask fitted with a reflux condenser and a calcium chloride guard tube. The mixture was stirred at 100-110 ºC temperature for 1.5 h. If TLC shows completion of reaction then mixture was treated with aq. $Na_2S_2O_3$ solution (5%, 10 mL) to remove excess iodine and the product was extracted with suitable organic solvent (3×20 mL). The combined organic layers were dried with anhydrous sodium sulphate, concentrated and purified by column chromatography (100-200 mesh) (ethyl acetate: hexane) to afford the pure compound.

Table T_1. Flavone molecules synthesized by above method.

Entry	Flavone	Yield	TLC system	M.P. Found	M.P. Reported
2a.		70	$CHCl_3$:MeOH 9.5:0.5	195^0C	201^0C[20]
2b.		72	Hexane:E.A. 1:1	273^0C	270^0C[18]
2c.		70	Hexane:Acetone 9:1	300^0C	300^0C[21]
2d.		75	$CHCl_3$:MeOH 9:1	285^0C	285^0C[23]
2e.		80	$CHCl_3$:MeOH 9:1	178^0C	174^0C[22]
2f.		76	Hexane:E.A. 1:1	219^0C	215^0C[23]
2g.		80	Hexane:E.A. 1:1	300^0C	300^0C[23]
2h.		70	$CHCl_3$:MeOH 9:1	215^0C	210^0C[18]

Spectral data of flavones

5,7-dimethoxy-2-phenyl-4H-chromen-4-one 2a.

Off white powder, MP 146^{0}C, Soluble in $CHCl_3$

FT-IR.-1643, 1610, 1600,1460,1213,1117,790 & 681 cm^{-1}.

^{1}HNMR $CDCl_3$- δ 6.68(s, 1H), 3.91(s, 3H), 3.96(s, 3H), 6.38(d, 1H, J = 1.5Hz),

6.58(d,1H,J = 1.5 Hz),7.88(dd,2H,J = 7.5,1.5 Hz),7.49(dd,2H,J = 7.5,1.5 Hz),

7.50(dd, 1H, J = 7.5, 1.5 Hz).

2-(4-hydroxyphenyl)-4H-chromen-4-one 2b.

Off white powder, MP 273^{0}C, Soluble in DMSO

FT-IR. 3300, 1644 (C=O), 1422, 1129,769 cm $^{-1}$.

^{1}HNMR DMSO – δ 6.87(s, 1H), 10.33(s, 1H, OH), 7.48(dd, 2H, J = 7.5, 1.5 Hz),

6.92(dd,2H,J = 7.5,1.5),8.02(dd,1H,J = 7.5,1.5 Hz),7.47(d,1H,J = 7.5 Hz),

7.81(dd, 1H, J = 7.5, 1.5 Hz), 7.75(dd, 1H, J = 7.5, 1.5).

7-hydroxy-2-(2-hydroxyphenyl)-4H-chromen-4-one 2c.

Cream colour fluffy powder, MP 198^{0}C, Soluble in DMSO

FT-IR- 3250**,** 1635 (C = O), 1600, 830 cm^{-1}

^{1}HNMR , DMSO- δ 6.89(s, 1H), 10.38(s, 1H,-OH),10.27(s, 1H,-OH),

7.86(d,1H,J = 7.5 Hz),6.93(m,1H,J = 7.5,1.5),7.03(m,1H,J = 7.5,1.5 Hz),\

2-(2,4-dihydroxyphenyl)-4H-chromen-4-one 2d.

White powder, MP 285^{0}C, Soluble in DMSO

FT-IR 3300, 1640, 1600, 1100, 840 cm^{-1}.

^{1}HNMR DMSO δ 7.082(s,1H),8.003(dd,1H,J = 7.5,1.5),7.48(m,1H,J= 7.5,7.5,1.5)

7.81(1H,m,J = 7.5,7.5,1.5 Hz),7.75(dd,1H,J = 7.5,1.5 Hz),7.08(dd,1H,J = 7.5,1.5 Hz)

6.44(dd,1H,J = 7.5,1.5 Hz),6.43(d,1H,J = 1.5 Hz),10.10(s,1H,OH),10.27(s,1H,OH)

5, 7-dimethoxy-2-(2-methoxyphenyl)-4H-chromen-4-one 2e.

Yellow powder, MP 178^{0}C, Soluble in $CHCl_3$

FT-IR-1650, 1300,1100,1600,850 cm^{-1}

^{1}HNMR $CDCl_3$- δ 6.53 (s, 1H), 6.36(d, 1H, J=1.5 Hz), 7.02(d, 1H, J = 1.5 Hz)

7.43(m,1H,J = 1.5,7.5,7.5 Hz),7.07(m,1H,J = 1.5,7.5,7.5Hz),7.87(dd,1H,1.5,7.5)

3.95(s, 1H), 3.93(s, 1H), 3.89(s, 1H).

7, 8-dihydroxy-2-(2-hydroxyphenyl)-4H-chromen-4-one 2f.

Light brown crystals, MP 298^{0}C, Soluble in $CHCl_3$

FT-IR -3300, 1640, 1630, 1600, 1100,940 cm^{-1}

^{1}HNMR $CDCl_3$ δ 6.76(s,1H),7.40(d,1H),7.54(d,1H),7.33(dd,1H,J = 7.5,1.5 Hz)

6.94(m,1H,J = 7.5,7.5,1.5 Hz),6.97(m,1H,7.5,7.5,1.5),7.54(dd,1H,J = 7.5,1.5 Hz)

9.47(s, 1H), 9.90(s, 1H), 10.42(s, 1H).

2-(2, 3, 4-trihydroxyphenyl)-4H-chromen-4-one 2g.

Pale yellow powder, MP 252^{0}C, Soluble in DMSO

FT-IR-3300, 3000,1645,1600,100,1100,870 cm^{-1}

^{1}HNMR DMSO δ 7.1(s,1H),8.033(dd,1H,J = 7.5,1.5 Hz),7.46(m,1H,7.5,7.5,1.5 Hz)

7.87(m,1H,J = 7.5,7.5,1.5 Hz),7.74(dd,H,J = 7.5,1.5 Hz),6.52(d,1H,J = 7.5 Hz)

7.38(d, 1H, J = 7.5 Hz).

2-(2-hydroxyphenyl)-4H-chromen-4-one 2h.

Off white powder, MP 245^{0}C, Soluble in DMSO

FT-IR 3200, 1616,1637,1600,1100,960,845 cm^{-1}

^{1}HNMR DMSO δ 7.1(s,1H),8.04(dd,1H,J = 7.5,1.5 Hz),7.47(m,1H,J = 7.5,7.5,1.5 Hz),7.93(m,1H,J = 7.5,7.5,1.5 Hz),7.75(dd,1H,J = 7.5,1.5 Hz),7.38(dd,1H,7.5,1.5),6.99(m,1H J = 7.5,7.5,1.5 Hz),7.008(m,1H,J = 7.5,7.5,7.5 Hz),7.06(dd,1H,7.5,1.5).

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