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(*E*)-2-(2-Pyridinyl)-3-(2-pyridinylmethylene)chromanone, a 1:2 condensation product of 2′-hydroxyacetophenone and pyridine-2-aldehyde, showing some interesting properties

Rina Mondal[†], Nayim Sepay & Asok K Mallik*
Department of Chemistry, Jadavpur University, Kolkata 700 032, India
E-mail: mallikak52@yahoo.co.in

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An efficient synthesis of (*E*)-2-(2-pyridinyl)-3-(2-pyridinylmethylene)chromanone has been done by treatment of 2′-hydroxyacetophenone and pyridine-2-aldehyde in aqueous methanolic KOH. The compound has been obtained as crystalline precipitate from the reaction medium, which was suitable for spectral analysis and X-ray crystallographic study. It possesses an interesting intramolecular hydrogen bonding between the C_2-H and the nitrogen of 2-pyridinylmethylene moiety. At room temperature, it is stable for months in the crystalline state, but in $CDCl_3$ solution it gradually changes to the endocyclic isomer 2-(2-pyridinyl)-3-(2-pyridinylmethyl)chromone. From analysis of the X-ray crystallographic data and DFT studies, possible explanations have been given for the stability of the compound in the crystalline state and its isomerization in solution.

Keywords: Chromanone, 2′-hydroxyacetophenone, pyridine-2-aldehyde, 2-pyridinylmethylene, endocyclic isomer, X-ray, DFT

When flavanones (2-phenylchromanones) (**1**) are condensed with aromatic aldehydes, *E*-3-arylideneflavanones (**3**) are formed and the long-known methods for their synthesis[1-9] involve the use of reaction conditions like dry HCl/EtOH, conc. H_2SO_4/EtOH, pyridine/heat, piperidine/heat, *etc*. A method for synthesis of **3** in alkaline medium reported subsequently by our group[10] involves (i) treatment of flavanones (**1**) or 2′-hydroxychalcones (**2**) with aromatic aldehydes in aqueous methanolic alkali or (ii) treatment of 2′-hydroxyacetophenones with aromatic aldehydes in the same medium (Scheme I). It is interesting to note that since most members of the series **3** are sparingly soluble in the said medium, they are formed as precipitates, and this drives the equilibrium towards the product side.

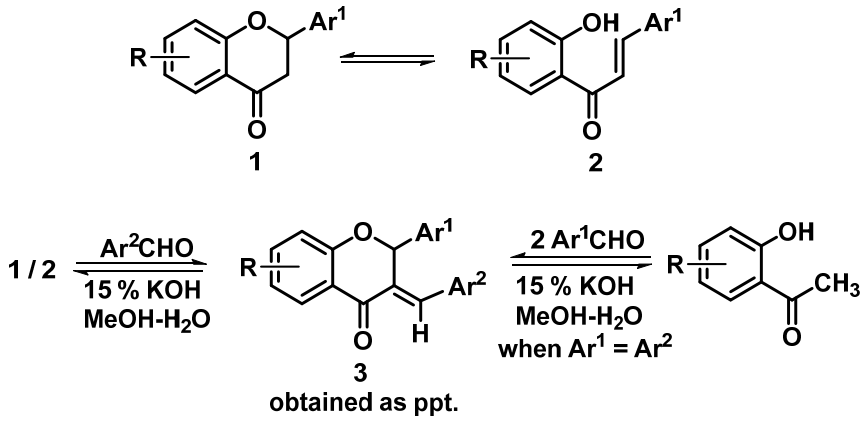
In order to avoid an unfavourable $A^{1,3}$ interaction, *E*-3-arylideneflavanones (**3**) prefer a conformation in which the 2-aryl group is axial[7,11]. Again, an examination of models shows that the aryl group of the arylidene moiety interacts sterically with the equatorial H at C-2 (Scheme II)[12].

In a study of our group on conformational features of **3** and related compounds done by NMR analysis[11], an interesting observation was that when the aryl group of the arylidene moiety was 2-furyl, H-2 appeared at a significantly downfield region (Figure 1). This observation was explained by considering that the oxygen of furan in **4** is involved in intramolecular hydrogen bonding with H-2[11]. It was, therefore, our interest to see whether a replacement of the 2-furyl in **4** by a 2-pyridinyl shows any significant feature in ^{1}H NMR spectrum due to hydrogen bonding of the type shown in **4**. Our interest was also to investigate whether such interaction helps shifting of the enone double bond of the compound from exocyclic to the endocyclic position.

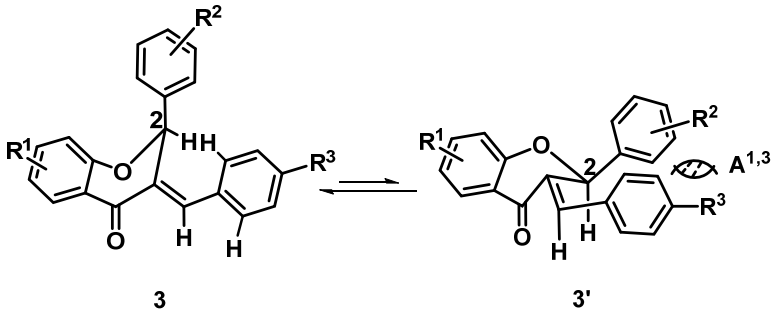
Results and Discussion

Our targeted work was to synthesize *E*-3-(2-pyridinylmethylene)flavanone (**5a**) and (*E*)-2-(2-pyridinyl)-3-(2-pyridinylmethylene)chromanone (**6a**) to study of their ^{1}H NMR spectral features first and then to study their isomerization. It is evident from the literature that recently Arai *et al*.[13] have reported the results of 1:2 condensation of 2′-hydroxyacetophenones with pyridine-2-aldehydes in ethanolic KOH which produced the endocyclic compounds (**7**) and not the exocyclic ones (**6**). This group was, however, successful in getting the exocyclic products (**5b**, **5c**, **6b** and **8**) in some cases by carrying

† Present address: Department of Chemistry, Uluberia College, Uluberia, Howrah 711 315, India



Scheme I — Formation of *E*-3-arylideneflavanones **3** in alkaline medium



Scheme II — Possible conformers of *E*-3-arylideneflavanones **3**

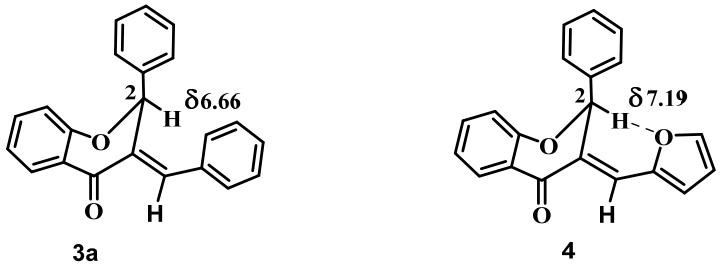


Figure 1 — Different chemical shifts of H-2 in **3a** and **4** explained by C-H…O hydrogen bonding

out K_2CO_3 or Cs_2CO_3 catalyzed reaction in ethanol medium at 40°C. But, they did not report any systematic result about the formation of such compounds. Another publication in this area contained a piperidine catalyzed reaction of two flavanones with pyridine-4-aldehyde which produced *E*-3-(4-pyridylmethylene)flavanones (**9**)[14]. We started our work with the reaction between flavanone and pyridine-2-aldehyde under the piperidine catalyzed condition at 105°C[9,14] when the endocyclic product 3-(2-pyridinylmethyl)flavone (**10**) was obtained. The same result was obtained even at 60°C. The reaction of 6-chlorochromanone and pyridine-2-aldehyde done under these conditions also gave an analogous endocyclic product **11**. All these results are shown in Figure 2.

We then investigated the reaction of each of flavanone (**1a**), 2′-hydroxychalcone (**2a**) and 2′-hydroxyacetophenone with pyridine-2-aldehyde and that of 2′-hydroxyacetophenone with pyridine-3-aldehyde under the condition developed by us[10]. Among these combinations, only the third one (Table I) yielded the desired exocyclic product **6a** as a light yellow crystalline precipitate from the reaction mixture. The other reaction mixtures which failed to yield any precipitated product were worked up by diluting with water and then extracting with ethyl acetate. Chromatography of the crude material thus

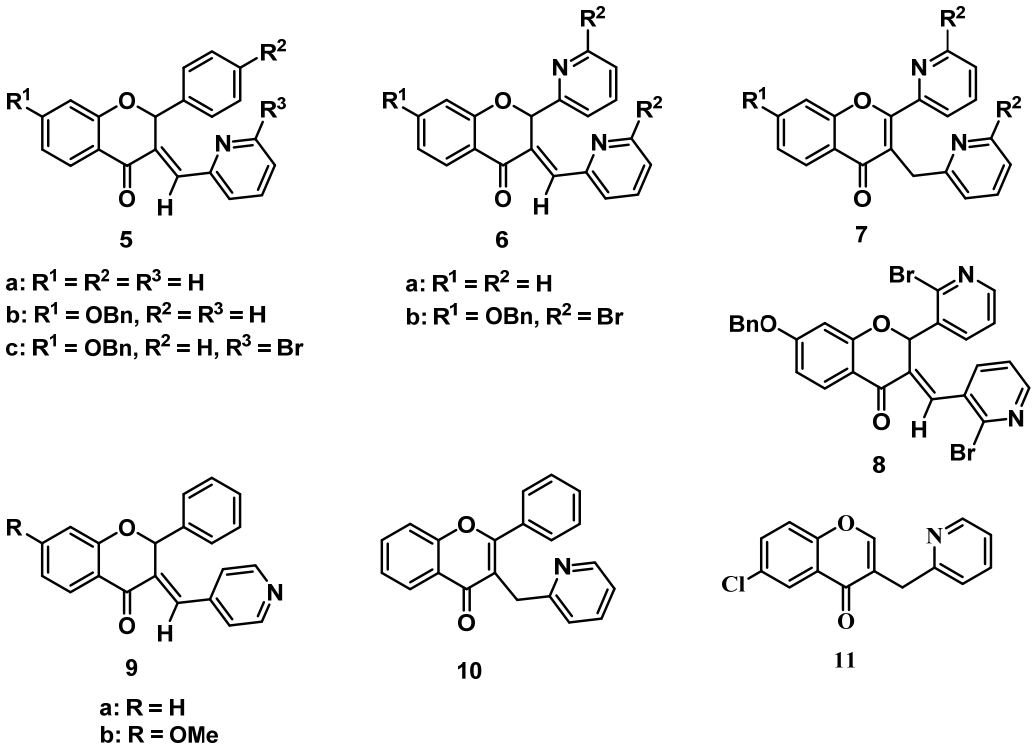
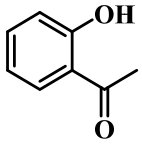
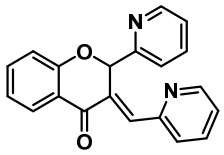
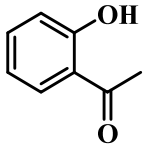
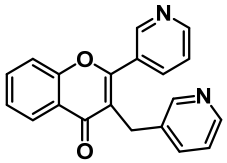


Figure 2 — Condensation products of some flavanones and a chromanone with pyridine aldehydes

Table I — Results of condensation of flavanone, 2′-hydroxychalcone and 2′-hydroxyacetophenone with pyridine aldehydes

Entry	Reactant-1	Reactant-2	Mole ratio	Product [yield (%)]
1	**1a** (**1** with R = H & Ar=Ph)	pyridine-2-aldehyde	1:1	**10** [61]
2	**2a** (**2** with R = H & Ar=Ph)	pyridine-2-aldehyde	1:1	**10** [57]
3		pyridine-2-aldehyde	1:2	 **6a** [67]
4		pyridine-3-aldehyde	1:2	 **12** [59]

obtained over neutral alumina yielded the endocyclic products **10** and **12** (Table I). All these products were characterized from their spectral data. For **6a**, X-ray crystallographic study was also done.

The ^{1}H NMR spectrum of the compound **6a** showed several interesting features. As expected, its H-2 appeared at a significantly downfield position (δ 7.85). It may be mentioned here that this proton in the analogous compounds (**5b**, **5c** and **6b**) synthesized by Arai *et al.* also appeared in the same region (δ 7.78 to 7.88)[13]. This feature is indicative of the presence of an intramolecular hydrogen bond involving H-2 and the nitrogen of the 3-(2-pyridyl)methylene moiety of the molecule. The X-ray crystallographic data of **6a** also suggested the presence of hydrogen bonding as the distance between H-2 and the said pyridine nitrogen was 2.222 Å. This hydrogen bonding possibly facilitates the isomerization of **6a** to **7a** (**7** with $R^1 = R^2$

=H) in $CDCl_3$ solution. The ^{1}H NMR spectrum recorded immediately after preparation of solution was characteristic of a perfectly pure compound **6a**. The ^{13}C NMR spectrum of the compound supported this. However, on keeping the solution, it gradually changed to **7a** and the conversion was complete within 5 days. The ^{1}H NMR spectra given in Figure 3 show the gradual change. It is very interesting to note that the compound **6a** remains unchanged for months at RT in the crystalline state (confirmed by recording ^{1}H NMR spectra of the isolated crystals after 3 and 5 months from their formation). This feature indicates that there is some stabilizing effect for the structure **6a** due to a particular type of crystal packing of the compound.

It is evident from the X-ray crystal structure of **6a** (Figure 4) that the crystals are tightly packed with individual molecules through several favorable weak supramolecular interactions like π-π, π-H, C=O π-aromatic H interactions, *etc*. (Figure 4b). All weak electrostatic interactions play a significant role in stabilizing the crystal lattice. Inside the crystal, enantiomers of the compound **6a** exist in a unit cell having 'P -1' space group. The compound **7a** is achiral and almost planar. A substantial structural transformation is needed in the isomerization of **6a** to **7a**. Again, the above-mentioned supramolecular interactions are also changed during this process. Therefore, the isomerization is energetically quite difficult in the solid state, which may be the reason for the solid state stability of **6a**. Absence of such interactions and no requirement of compact arrangement of molecules in the solution phase facilitate the observed isomerization.

To understand the mechanism of isomerization of **6a** to **7a**, detailed DFT calculations have been performed. These calculations suggested that above mentioned C-H…N hydrogen bonding plays a key role in the isomerization of **6a** in the solution phase. The reaction proceeds through an intermediate **6a*** having 2.38 kcal/mol more Gibbs free energy than **6a** (Figure 5). A high energy transition state **6a**$^{\neq}$ (ΔG = 22.89 kcal/mol) is involved in this transformation. The intermediate **6a*** can easily get aromatized to generate the product **7a** which is 10.03 kcal/mol more stable than **6a**. On the other hand, the conversion of **7a** to **6a** through **6a**$^{\neq}$ needs high Gibbs free energy change (ΔG = 32.92 kcal/mol), which indicates that the backward reaction is quite difficult. Thus, once **7a** is formed from **6a**, it is not re-isomerized to give back the starting material.

Experimental Section

Melting points were recorded on a Köfler block and are uncorrected. Column chromatography was done on neutral alumina (Marck, India). Thin-layer chromatography plates (alumina) were visualized by exposure to ultraviolet light and/ or iodine vapor. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker 300 MHz NMR spectrometer. Chemical shifts

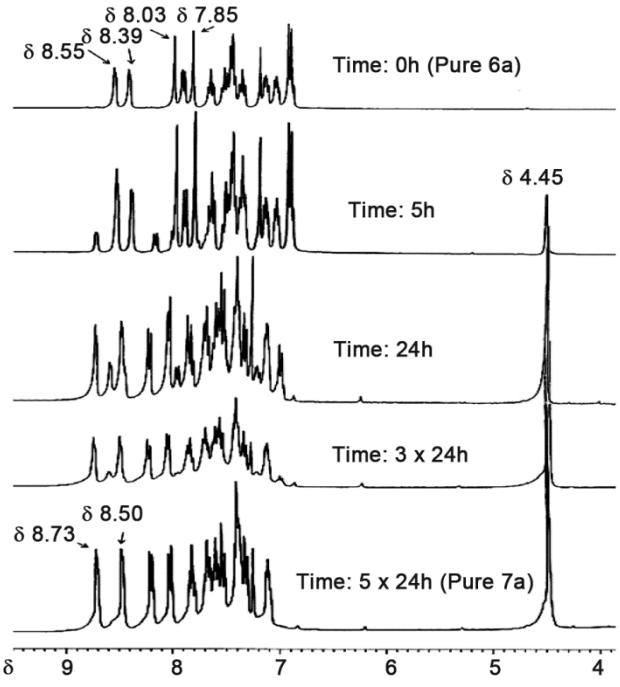


Figure 3 — Gradual change of **6a** to **7a** as observed from ^{1}H NMR spectral study in $CDCl_3$

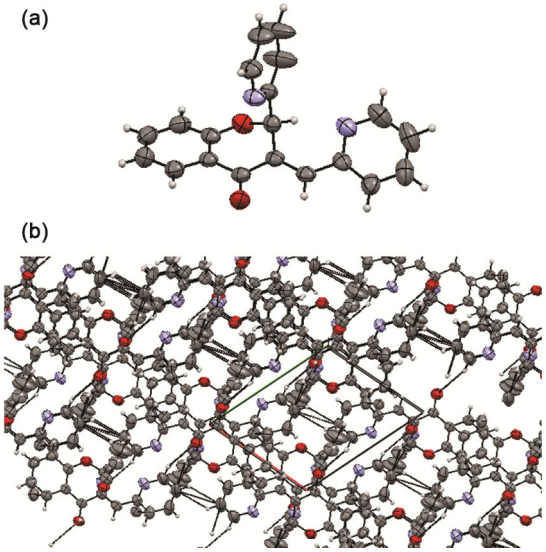


Figure 4 — (a) ORTEP diagram (50% thermal probability) and (b) crystal packing of **6a** (CCDC 1835003)

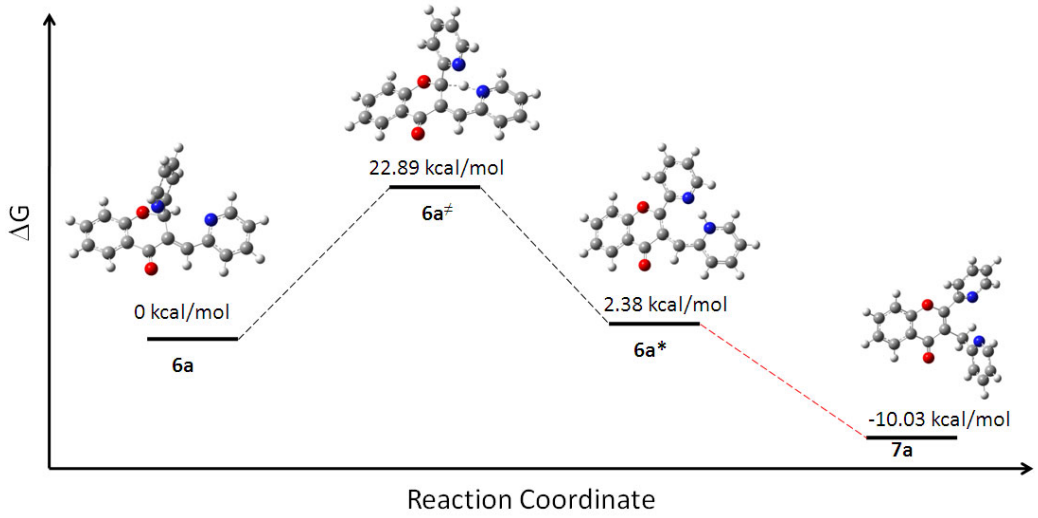


Figure 5 — Conversion of **6a** to **7a**: a DFT study

(δ) were reported in parts per million (ppm) taking $CHCl_3$ peak at δ 7.26. HRMS were recorded on a Waters Xevo G2QT mass spectrometer. Elemental analyses were done using Perkin-Elmer 2400 Series II C, H, N analyzer. Single-crystal X-ray diffraction data were collected on a Bruker-AXS SMART APEX II diffractometer, using graphite monochromatized Mo*K*α radiation (λ = 0.71073 Å). DFT calculations given in this paper were performed using a GAUSSIAN 09 program package[15]. For these Becke three parameter hybrid exchange[16] and the Lee–Yang–Parr correlation functionals[17] (**B3LYP**) were used as functionals. The 6-311G basis set was used for geometry optimization and transition state calculation for the isomerization of **6a**.

Synthesis of 6a

To a mixture of 2′-hydroxyacetophenone (1 mmol) and pyridine-2-aldehyde (2 mmol) a warm solution of (15%) KOH in aqueous methanol (1:1) was added drop-wise with stirring until a clear solution resulted. On cooling to RT, the reaction mixture became somewhat turbid and then a few drops of methanol were added to remove the turbidity. After *ca*. 1 h at RT, a liquid began to be deposited at the bottom. The reaction mixture was kept under stoppered condition for 24 h. The solid crystalline material obtained as precipitate from the reaction mixture was collected by filtration and washed carefully with aqueous methanol (1:1) (5 × 3 mL).

3-(2-Pyridinylmethyl)flavone, 10: Light yellow crystals. m.p.126-128°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.41 (br. s, 2H), 7.41-7.55 (m, 7H), 7.71-7.75 (m, 3H), 7.94 (br. s, 1H), 8.20 (d, 1H, J = 7.7 Hz), 8.59 (d, 1H, J = 4.7 Hz). Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.63; H, 4.66; N, 4.30%.

6-Chloro-3-(2-pyridinylmethyl)chromone, 11: Light yellow crystals. m.p.114-116°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94 (br. s, 2H), 7.12 (br. t, 1H, J = 6.3 Hz), 7.34-7.42 (m, 2H), 7.54 (dd, 1H, J = 9 and 2.5 Hz), 7.60 (dt, 1H, J = 7.6 and 1.4 Hz), 7.96 (br. s, 1H), 8.11 (d, 1H, J = 2.3 Hz), 8.48 (br. d, 1H, J = 3.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 119.9, 121.7, 122.8, 123.9, 124.8, 125.2, 130.9, 133.7, 136.9, 149.1, 153.8, 154.8, 158.3, 176.2. Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16. Found: C 66.51; H, 3.54; N, 5.28%.

(*E*)-2-(2-Pyridinyl)-3-(2-pyridinylmethylene) chromanone, 6a: Light yellow crystals. m.p.134-136°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (t, 1H, J = 7.2 Hz), 6.95 (d, 1H, J = 8.4 Hz),7.06 (br. t, 1H, J = 6.3 Hz), 7.13 (br. t, 1H, J = 7.5 Hz), 7.38 (dt, 1H, J = 8.4 and 1.6 Hz), 7.45-7.56 (m, 3H), 7.66 (dt, 1H, J = 7.7 and 1.7 Hz), 7.85 (br. s, 1H, H-2), 7.94 (dd, 1H, J = 7.6 and 1.2 Hz), 8.03 (br. s, 1H, H-β), 8.39 (d, 1H, J = 4.7 Hz), 8.55 (d, 1H, J = 4.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.2, 118.4, 121.4, 122.2, 122.6, 122.9, 123.4, 127.5, 128.0, 134.9, 135.5, 135.9, 136.4, 136.6, 149.3, 149.6, 153.8, 158.4, 159.7, 182.6; HRMS: *m/z* Calcd for $C_{20}H_{14}N_2O_2$: 337.0953 $[M+Na]^+$. Found: 337.0989. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.22; H, 4.28; N, 8.62%.

2-(3-Pyridinyl)-3-(3-pyridinylmethyl)chromone, 12: Light yellow semisolid. ^{1}H NMR (300 MHz,

$CDCl_3$): δ 3.98 (br. s, 2H), 7.24 (t, 1H, *J* = 7.5 Hz), 7.44-7.52 (m, 3H), 7.59 (d, 1H, *J* = 7.6 Hz), 7.75 (dt, 1H, *J* = 8.4 and 1.4 Hz), 7.83 (d, 1H, *J* = 7.8 Hz), 8.25 (dd, 1H, *J* = 7.8 and 1.1 Hz), 8.31 (br. s, 1H), 8.42 (d, 1H, *J* = 4.2 Hz), 8.78 (d, 1H, *J* = 3.6 Hz), 8.83 (br. s, 1H); HRMS: *m/z* Calcd for $C_{20}H_{14}N_2O_2$: 337.0953 $[M+Na]^+$. Found: 337.0972.

2-(2-Pyridinyl)-3-(2-pyridinylmethyl)chromone, 7a: Light yellow semisolid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.45 (br. s, 2H), 7.70 (t, 2H, *J* = 6.5 Hz), 7.31-7.43 (m, 3H), 7.54 (d, 1H, *J* = 8.4 Hz), 7.62 (dt, 1H, *J* = 7.6 and 1.6 Hz), 7.70 (dt, 1H, *J* = 8.3 and 1.5 Hz), 7.84 (dt, 1H, *J* = 7.7 and 1.6 Hz), 8.22 (d, 1H, *J* = 7.9 Hz), 8.50 (d, 1H, *J* = 4.2 Hz), 8.73 (d, 1H, *J* = 3.1 Hz); HRMS: *m/z* Calcd for $C_{20}H_{14}N_2O_2$: 337.0953 $[M+Na]^+$. Found: 337.0877.

Conclusion

In summary, we have synthesized (*E*)-2-(2-pyridinyl)-3-(2-pyridinylmethylene)chromanone **6a** by condensation of 2′-hydroxyacetophenone and pyridine-2-aldehyde in aqueous methanolic KOH. The compound was obtained as crystalline precipitate from the reaction mixture and it was found to be stable for months at room temperature in the solid state. It possesses an interesting intramolecular hydrogen bonding between the C_2-H and the nitrogen of 2-pyridinylmethylene moiety. It slowly isomerizes in solution in $CDCl_3$ yielding 2-(2-pyridinyl)-3-(2-pyridinylmethyl)chromone **7a**. The results of X-ray crystallographic and DFT studies on **6a** have been discussed.

Acknowledgements

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