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

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Received 28 April 2018; accepted (revised) 23 January 2019

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 C2-H and the nitrogen of 2-pyridinylmethylene moiety. At room temperature, it is stable for months in the crystalline state, but in CDCl3 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-arylideneflavonones (3) are formed and the long-known methods for their synthesis1-9 involve the use of reaction conditions like dry HCl/EtOH, conc. H2SO4/EtOH, pyridine/heat, piperidine/heat, etc. A method for synthesis of 3 in alkaline medium reported subsequently by our group10 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 A1,3 interaction, E-3-arylideneflavonones (3) prefer a conformation in which the 2-aryl group is axial7,11. 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 analysis11, 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-211. 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 1H 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 1H 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...
out K₂CO₃ or Cs₂CO₃ 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°C⁹,¹⁴ 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 us¹⁰. 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
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 ($\delta$ 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 ($\delta$ 7.78 to 7.88). 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 2.22 Å. This hydrogen bonding possibly facilitates the isomerization of 6a to 7a (7 with $R^1 = R^2$).
-H) in CDCl₃ solution. The ¹H NMR spectrum recorded immediately after preparation of solution was characteristic of a perfectly pure compound 6a. The ¹³C 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 ¹H 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 ¹H 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≠ (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≠ 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. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker 300 MHz NMR spectrometer. Chemical shifts

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Figure 3 — Gradual change of 6a to 7a as observed from ¹H NMR spectral study in CDCl₃

Figure 4 — (a) ORTEP diagram (50% thermal probability) and (b) crystal packing of 6a (CCDC 1835003)
(δ) were reported in parts per million (ppm) taking CHCl₃ 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 MoKα 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 stopped 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; ¹H NMR (300 MHz, CDCl₃): 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 C₂₁H₁₅NO₂: 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; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 C₁₅H₁₀ClNO₂: 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; ¹H NMR (300 MHz, CDCl₃): 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-β), 8.03 (br. s, 1H, H-β), 8.39 (d, 1H, J = 4.7 Hz), 8.55 (d, 1H, J = 4.3 Hz); ¹³C NMR (75 MHz, CDCl₃): 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 C₂₀H₁₄N₂O₂: 337.0953 [M+Na]+. Found: 337.0989. Anal. Calcd for C₂₀H₁₄N₂O₂: 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. ¹H 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), 7.83 (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$_{2}$O$_{2}$: 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$_{2}$O$_{2}$: 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
Financial support and spectral facilities from the PURSE and FIST programs of the DST and CAS program of the UGC, New Delhi to the Department of Chemistry, Jadavpur University is gratefully acknowledged. The UPE-II program of the UGC is also thanked for financial assistance. RM and NS are thankful to the UGC, New Delhi for their Research Fellowships.

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