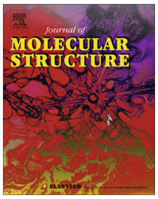
Journal of Molecular Structure 1076 (2014) 600–605

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstruc



X-ray diffraction and VT-NMR studies of (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one

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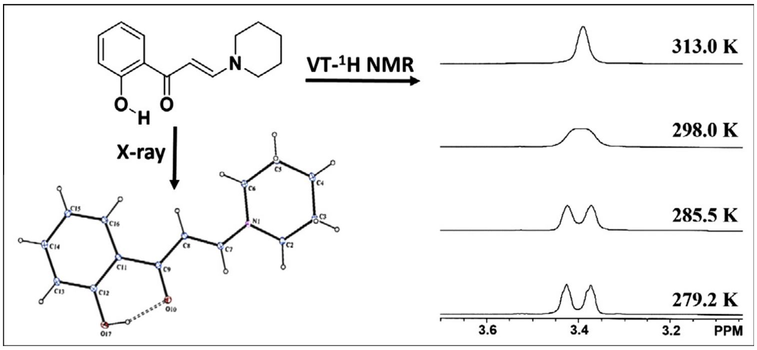
HIGHLIGHTS

- (E)-Selective synthesis of 3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one.
- 3D structure determination of the compound by X-ray diffraction.
- Spectroscopic characterization of the compounds by 1D and 2D NMR.
- Flexible rotation of the compound along the C—N bond explained by VT-NMR studies.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 29 May 2014
Received in revised form 5 August 2014
Accepted 5 August 2014
Available online 12 August 2014

Keywords:
Enaminones
X-ray diffraction
VT-NMR
Flexible rotation

ABSTRACT

A series of 1-aryl-3-(cyclicamino)-prop-2-en-1-one analogs was synthesized from commercial acetophenones in 2 or 3 steps. Compound **6**, (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)-prop-2-en-1-one, exhibited the unique shape and intensity of the C_{sp2}—N—CH_2 peaks in the ^{1}H and ^{13}C NMR spectra. Variable temperature (VT) nuclear magnetic resonance (NMR) and X-ray diffraction (XRD) studies of **6** revealed that the piperidine ring has a lower energy barrier to rotation than the 5-membered pyrrolidine **9** due to the less effective π electron delocalization along the C_{sp2}—N bond.

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Introduction

Enaminones, consisting of the conjugated N—C=C—C=O system, are attractive functional groups in the field of medicinal chemistry because of their versatile utilization as intermediates for the synthesis of pharmacologically active agents [1–3]. They have been widely used as important intermediates and building blocks for preparing heterocyclic moieties, including quinolones, indoles, isoxazoles, and pyridines, because they can act not only as nucleophiles but also as electrophiles in a variety of chemical reactions [4–9]. Some of the enaminone-containing molecules were used as key intermediates for the synthesis of FDA-approved drugs such as ciprofloxacin and imatinib [10,11]. Despite the importance of enaminone systems in synthetic chemistry and

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http://dx.doi.org/10.1016/j.molstruc.2014.08.016
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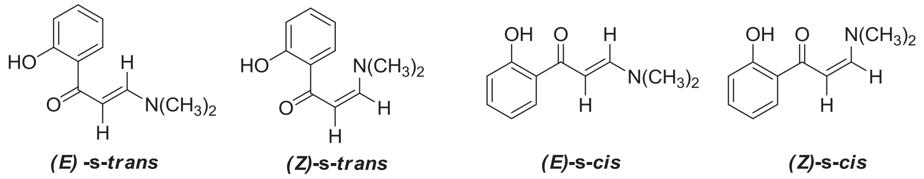

(E) -s-trans **(Z)-s-trans** **(E)-s-cis** **(Z)-s-cis**

Fig. 1. Geometrical and conformational isomers of 3-(dimethylamino)-1-(2′-hydroxyphenyl)prop-2-en-1-one.

medicinal chemistry, few reports have been published on the structural analysis of enaminone systems by X-ray crystal analysis and variable-temperature (VT)-nuclear magnetic resonance (NMR) experiments [12–16].

In general, substituted enaminones are classified into (*E*) and (*Z*) geometrical isomers based on the relative position of substituents with higher priorities of the carbon–carbon double bond. They are also classified into s-*cis* and s-*trans* conformational isomers based on the relationship of alkene and carbonyl groups around the central single C—C bond. For example, 3-(dimethylamino)-1-(2′-hydroxyphenyl)prop-2-en-1-one (Fig. 1) has four possible isomeric forms: (*E*)-s-*trans*, (*Z*)-s-*trans*, (*E*)-s-*cis*, and (*Z*)-s-*cis*. In this study, we synthesized 1-aryl-3-(cyclicamino)-prop-2-en-1-one analogs and fully analyzed the chemical structure of (*E*)-3-(piperidinyl)-1-(2′-hydroxyphenyl)prop-2-en-1-one, one of the analogs, by means of X-ray crystallography and VT NMR spectroscopy.

Experimental

General

Chemicals and solvents were purchased from Aldrich and Acros. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BRUKER Biospin AVANCE 600 MHz and 300 MHz spectrometer. Chemical shifts are reported as δ values downfield from internal TMS in appropriate organic solvents. Mass spectra were recorded on Agilent 6530 Accurate mass Q-TOF LC/MS spectrometer. HPLC were recorded on Agilent HPLC 1260 Infinity. Silica gel column chromatography experiments were performed using Merck Silica Gel F_{254}. VT NMR experiments were carried out by cooling and heating the probe. For VT NMR studies the sample was placed in the probe and allowed to equilibrate to the required temperature for 30 min.

Synthesis of compounds *6* and *9*

*(E)-3-(Dimethylamino)-1-(2′-hydroxyphenyl)-prop-2-en-1-one (**5**)*

To a solution of 2′-hydroxyacetophenone (2.73 g, 20 mmol) in *p*-xylene (20 mL) was added dimethylformamide-dimethylacetal (DMF-DMA) (2.34 g, 20 mmol). The reaction mixture was stirred under reflux for 2 h. After monitoring the progress of the reaction by TLC, the excessive solvent was removed under reduced pressure. The precipitate solid was collected by filtration and washed with ethanol. Crystallization from ethanol afforded the compound **5** (hexane/ethyl acetate = 1.5:1, R_f = 0.22) in 79% yield as orange–red solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 (s, 3H, NCH_3), 3.19 (s, 3H, NCH_3), 5.78 (d, 1H, *J* = 12.2 Hz, =CH—), 6.82 (m, 1H, *J* = 1.2, 8.1 Hz, Ar—H), 6.93 (dd, 1H, *J* = 1.0, 8.3 Hz, Ar—H), 7.32–7.38 (m, 1H, *J* = 1.6, 7.3, 8.7 Hz, Ar—H), 7.69 (dd, 1H, *J* = 1.6, 8.0 Hz, Ar—H), 7.90 (d, 1H, *J* = 12.1 Hz, =CH—), 13.93 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.39 (NCH_3), 45.33 (NCH_3), 90.13 (=CH—), 117.95, 118.24, 120.36, 128.21, 133.94, 154.71, 162.98, 191.56 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_{14}NO_2$ (*m*/*z*): 192.1025, found: 192.1018.

*3-Acetyl-4H-chromen-4-one (**8**)*

To a solution of compound **5** (1.90 g, 10 mmol) in acetonitrile (30 mL) was added pyridine (25 mL) and acetic anhydride (4.8 g, 40 mmol). The reaction mixture was refluxed for 4 h. After monitoring the progress of the reaction by TLC, the excessive solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (100 mL) and washed with 1 N HCl solution (100 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica-gel chromatography (hexane/ethylacetate = 5:1, R_f = 0.33) afforded the compound **8** in 52% yield as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (s, 3H, $COCH_3$), 7.28–7.50 (m, 2H, *J* = 0.9, 7.1 Hz, Ar—H), 7.53 (d, 1H, *J* = 8.4 Hz), 7.72–7.77 (m, 1H, *J* = 1.4, 8.5 Hz, Ar—H), 8.31 (d, 1H, *J* = 7.9 Hz, Ar—H), 8.63 (s, 1H, Ar—H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.54 ($CO\underline{C}H_3$), 118.27, 122.86, 125.43, 126.29, 126.47, 134.33, 155.88, 161.67, 175.32, 196.68 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_9O_3$ (*m*/*z*): 189.0552, found: 189.0504.

*(E)-1-(2′-Hydroxyphenyl)-3-(piperidin-1-yl)-prop-2-en-1-one (**6**)*

To a solution of compound **8** (0.262 g, 1.4 mmol) in chloroform (30 mL) was added piperidine (14 mmol). The reaction mixture was stirred under reflux for 6 h. After monitoring the progress of the reaction by TLC, the excessive solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (50 mL) and washed with 1 N HCl solution (50 mL × 2). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate = 5:1, R_f = 0.26) provided compound **6** in 32% yield in white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 6H, $N(CH_2)_2(\underline{CH_2})_3$), 3.41 (s, 4H, $N(\underline{CH_2})_2(CH_2)_3$), 5.88 (d, 1H, *J* = 12.3 Hz, =CH—), 6.81 (dd, 1H, *J* = 7.6 Hz, Ar—H), 6.93 (d, 1H, *J* = 8.3 Hz, Ar—H), 7.27–7.37 (m, 1H, *J* = 1.1, 7.1, 8.3 Hz, Ar—H), 7.67 (d, 1H, *J* = 1.1, 8.0 Hz, Ar—H), 7.86 (d, 1H, *J* = 12.3 Hz, =CH—), 14.02 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.97, 30.89, 44.81, 89.09, 117.89, 118.25, 120.51, 128.08, 133.83, 153.44, .162.93, 191.81 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_{14}NO_2$ (*m*/*z*): 232.1338, found: 232.1346.

*(E)-1-(2′-Hydroxyphenyl)-3-(pyrrolidin-1-yl)-prop-2-en-1-one (**9**)*

Compound **9** was prepared according to the procedure described for compound 6 using pyrrolidine instead of piperidine.

Yield: 22% R_f = 0.37 (hexane/ethyl acetate = 3:2), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.93–2.01 (m, 2H, $NCH_2C\underline{H_2}$), 2.03–2.12 (m, 2H, $NCH_2C\underline{H_2}$), 3.33 (t, 2H, *J* = 6.9 Hz, $NC\underline{H_2}CH_2$), 3.61 (t, 2H, *J* = 6.6 Hz, $NC\underline{H_2}CH_2$), 5.74 (d, 1H, *J* = 12.1 Hz, =CH—), 6.79–6.84 (m, 1H, *J* = 1.2,7.3, 8.0 Hz, Ar—H), 6.93 (d, 1H, *J* = 1.0, 8.3 Hz, Ar—H), 7.32–7.38 (m, 1H, *J* = 1.6, 7.3, 8.5 Hz, Ar—H), 7.69 (dd, 1H, *J* = 1.5, 8.0 Hz, Ar—H), 8.10 (d, 1H, *J* = 12.1 Hz, =CH—), 14.03 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.17 ($NCH_2\underline{C}H_2$), 47.17 ($N\underline{C}H_2CH_2$), 52.69 ($N\underline{C}H_2CH_2$), 90.92, 117.90, 118.21, 120.38, 128.21, 133.84, 150.42, 162.97, 191.23 (C=O). HRMS (ESI): $[M+H]^+$, calcd for $C_{11}H_{14}NO_2$ (*m*/*z*): 218.1181, found: 218.1180.

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