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Characterization of the 2-hydroxy-5-methylacetophenone and some aromatıc aldehydes condensation products by NMR and computational methods

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A two-component Claisen-Schmidt condensation between the 2-hydoxy-5-methylacetophenone and some aromatic aldehydes has been carried out for the synthesis of chalcone derivatives at ambient temperature. The products have been obtained with good yields and as a mixture of two compounds or a single product. Piperidine has been used as a catalyst for the *in situ* generation of carbanion from ketone. The possibility of the formation of different products has been investigated on the based PM7 optimization, HMO theory and NMR methods.

Keywords: Ketone, aldehyde, chalcone, chromenone, NMR, molecular modeling

α,β-Unsaturated ketones as products of Claisen-Schmidt condensations of acetophenones with aromatic aldehydes are important intermediates (chalcones) for the synthesis of various heterocycles. Besides it, the pyranone ring (chromenones) is widely present in natural plants. The chalcone, chromenone derivatives are demonstrated various biological activities such as anti cancer, antimicrobial, anti-inflammatory, analgesic, anti-platelet, anti-ulcerative, antimalarial, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulatory, *etc*.[1-17]

In our previous works reported the synthesis, NMR investigations and antimicrobial activity of 2-hydroxy-5-methyacetophenone derivatives[2-13]. The present work devoted to the characterization of the 2-hydroxy-5-methyacetophenone and some aromatic aldehyde condensation products by NMR and computational methods.

Experimental Section

Materials and instrumentation

All the chemicals were obtained from commercial sources (Aldrich) and used as received.

NMR experiments have been performed on a BRUKER FT NMR spectrometer (Ultra ShieldTM Magnet) AVANCE 300(300.130 MHz for ^{1}H and 75.468 MHz for ^{13}C) with a BVT 3200 variable temperature unit in 5 mm sample tubes using Bruker Standard software (TopSpin 3.1). The ^{1}H and ^{13}C chemical shifts were referenced to internal tetramethylsilane (TMS); the experimental parameters for ^{1}H: digital resolution = 0.23 Hz, SWH = 7530 Hz, TD = 32 K, SI = 16 K, 90° pulse-length = 10 μs, PL1 = 3 dB, ns = 1, ds = 0, d1=1 s; for ^{13}C: digital resolution = 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90° pulse-length = 9 μs, PL1 = 1.5 dB, ns = 100, ds = 2, d1 = 3 s (Figure S1-S6).NMR-grade DMSO-d_6(99.7%, containing 0.3% H_2O), acetone-d_6 were used for the solutions of **5**,**6**,**10**,**11**-**13**.

Quantum-chemical calculation have been carried out by the *MOPAC PM7* optimization and HMO theory methods (Figure 1 and S7 and Table I).

The purity of the synthesized compounds was confirmed by thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254), iodine vapor was used as visualizing agent, eluent- 5:2 hexane/ethyl acetate. Melting points were measured on Stuart SMP30 apparatus without correction.

General procedure for preparation of spiropyrrolidinones

A mixture of 0.2 mmol (0.03 g) 2-hydroxy-5-methylacetophenone **1**, 0.2 mmol (0.02 g) benzaldehyde **2** [or 0.2 mmol (0.02 g) 3-pyridinecarboxaldehyde **3**; 0.2 mmol (0.03 g) 4-nitrobenzaldehyde **4**] in 15 mL 96% ethanol, at

Table I — PM7 optimization and HMO calculations data

Compd	Heat of formation, kcal/mol	İonization potential, eV	Dipole moment, D	Bond order C10 and C11		Net charge C10 and C11		Free valance C10 and C11	
5	−26.19	9.18	3.74	1.045	0.911	−0.045	0.089	0.533	0.463
6	−38.29	9.07	2.08	0.907	−	0.093	−	0.396	−
7	−94.96	9.31	5.43	−	−	−	−	−	−
8	−17.05	9.30	4.63	1.002	0.919	−0.002	0.081	0.537	0.464
9	−28.87	9.21	2.42	0.915	−	0.085	−	0.398	−
10	−90.02	9.36	4.95	−	−	−	−	−	−
11	−31.15	9.47	6.89	1.029	0.914	0.019	0.134	0.537	0.462
12	−42.60	9.39	4.92	0.91	−	0.138	−	0.395	−
13	−105.4	9.50	5.29	−	−	−	−	−	−

presence of catalytic amount piperidine were stirred at 25°C for 3 h. The solid formed in the reaction mixture was filtered and to obtain the pure products (chromenone) recrystallized from EtOH. After evaporation of solvent obtained solid (chalcones) recrystallized from methanol.

(2*E*)-1-(2-Hydroxy-5-methylphenyl)-3-phenylprop-2-en-1-one,5: Yellow powder. Yield 33%. m.p.104-106°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.13 (s, 3H, H8), 6.64 (d, ^3J = 15Hz,1H, H11), 7.0-7.42 m (8H, H3, H5, H6, H13-H15), 7.63(d, ^3J = 15Hz,1H, H11), 12.21 (s, 1H, H7); ^{13}C NMR (75. MHz, DMSO-d_6): δ_C 20.76 (C8), 118.70 (C6), 120.22 (C10), 127.6 (C2), 128.59 (C3), 128.89 (C14), 128.96 (C13), 130.47 (C15), 134.97 (C12), 136.96 (C5), 144.81 (C11), 162.15 (C1), 192.44 (C9).

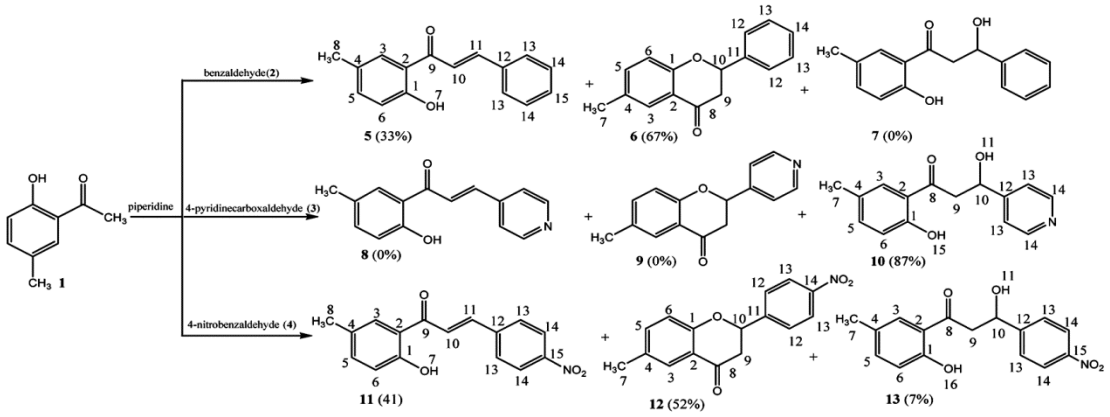
6-Methyl-2-phenyl-2,3-dihydro-4*H*-chromen-4-one, 6: Orange-yellow powder. Yield 67%. m.p.110-112°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.27 (s, 3H, H7), 2.8 and 3.17 (dd, ^2J = 18.0Hz, ^3J = 3.0Hz, ^3J = 12.0Hz, 2H, H9), 5.60 (dd, ^3J = 3.0Hz, ^3J = 12.0Hz, 1H, H10), 6.98 (d, ^3J = 9Hz, 1H, H6), 7.37-7.58 m (8H, H3, H5, H6, H13-H15); ^{13}C NMR (75. MHz, DMSO-d_6): δ_C 20.42 (C7), 44.03 (C9), 79.21 (C10), 118.30 (C6), 120.72 (C2), 123.6 (C3), 123.8 (C13), 128.97 (C14), 128.98 (C15), 130.92 (C4), 137.61 (C5), 139.44 (C11), 159.59 (C1), 192.07 (C8).

3-Hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(pyridin-4-yl)propan-1-one, 10: Light-yellow powder. Yield 90%. m.p.108-110°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.34 (s, 3H, H7), 3.15 and 3.44 (dd, ^2J = 18Hz, ^3J = 3Hz, ^3J = 6.0Hz, 2H, H9), 5.24 (dd, ^3J = 3Hz, ^3J = 6.0Hz, 1H, H10), 5.45 (s, 1H, m, H11), 6.84 (d, ^3J = 6H, 2H, H12), 7.32 (m, 2H, H3, H5), 7.70 (d, ^3J = 6Hz, H6), 8.45 (d, 1H, ^3J = 6Hz, H13), 12.09 (s, 1H, H15); ^{13}C NMR (75. MHz, DMSO-d_6): δ_C 20.63 (C7), 52.02 (C9), 72.91 (C10), 123.00 (C6), 123.90 (C13), 123.91 (C4), 125.79 (C2), 135.31 (C3), 141.40 (C5), 154.44 (C14), 158.34 (C12), 167.01 (C1), 208.79 (C8).

(2*E*)-1-(2-Hydroxy-5-methylphenyl)-3-(4-nitrophenyl)prop-2-en-1-one, 11: Orange-yellow powder. Yield 48%. m.p.213-215°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.36 (s, 3H, H8), 6.84 (d, ^3J = 6Hz,1H, H6), 7.31 (d, ^3J = 6Hz,1H, H5), 7.85 (d, ^3J = 15Hz,1H, H11), 8.1-8.28 m (6H, H3, H10, H13, H14), 12.25 (s, 1H, H7); ^{13}C NMR (75. MHz, DMSO-d_6): δ_C 22.73 (C8), 120.17 (C6), 122.42 (C2), 126.31 (C14), 128.06 (C10), 128.92 (C4), 132.49 (C13), 133.05 (C3), 140.13 (C5), 143.54 (C15), 144.06 (C11), 150.76 (C12), 163.34 (C1), 195.54 (C9).

6-Methyl-2-(4-nitrophenyl)-2,3-dihydro-4*H*-chromen-4-one, 12: Orange-yellow powder. Yield 52%. m.p.143-145°C. ^{1}H NMR (300 MHz, acetone-d_6): δ_H 2.29 (s, 3H, H7), 3.43 and 3.66 (dd, ^2J = 18.0Hz, ^3J = 3.0Hz, ^3J = 9.0Hz, 2H, H9), 5.55 (dd, ^3J = 3.0Hz, ^3J = 9.0Hz, 1H, H10), 6.86 (d, ^3J = 9Hz, 1H, H6), 7.37 (d, ^3J = 9Hz, 1H, H5), 7.81 (s and d, ^3J = 9Hz, 3H, H3, H12), 8.24 (d, ^3J = 9Hz, 2H, H13); ^{13}C NMR (75 MHz, acetone-d_6): δ_C 19.44 (C7), 47.27 (C9), 68.73 (C10), 117.69 (C6), 119.45 (C2), 123.26 (C13), 127.10 (C12), 130.51 (C4), 130.59 (C3), 137.55 (C5), 146.98 (C14), 147.22 (C11), 160.33 (C1), 204.50 (C8).

3-Hydroxy-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)propan-1-one, 13: ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.24 (s, 3H, H7), 3.33 (m, 2H, H9), 5.29 (m, 1H, H10), 5.79 (s, 1H, H11), 6.84 (d, ^3J = 9Hz, 1H, H6), 7.31 (d, ^3J = 9Hz, 1H, H5), 7.69 (d, ^3J = 9Hz, 1H, H14), 8.18 (s and d, ^3J = 9Hz, 3H, H3, H12), 11.68 (s, 1H, H16); ^{13}C NMR (75. MHz, DMSO-d_6): δ_C 20.78 (C7), 46.81 (C9),



Scheme I — Claisen-Schmidt condensation of **1** with some aldehydes

68.94 (C10), 118.83 (C6), 119.34 (C2), 123.90 (C14), 126.60 (C13), 129.76 (C4), 129.88 (C5), 137.32 (C3), 147.46 (C15), 149.87 (C12), 162.63 (C1), 204.65 (C8).

Results and Discussion

The two-component Claisen-Schmidt condensation of 2-hydroxy-5-methylacetophenone **1** with the benzaldehyde **2** (or 4-pyridinecarboxaldehyde **3**; 4-nitrobenzaldehyde **4**) in 96% ethanol have been carried out at RT (Scheme I).

As a result of the reaction between the **1** and **2***two* (**5** and **6**), **1** and **3***one* (**10**), **1** and **4***two* (**11** and **12**) products were obtained. The yield of products was accordingly 33 and 67% (mixture yield 87%) for the first, 90% for the second, 48 and 52% (mixture yield 95%) for the third reactions. At the storing of DMSO solution (containing 0.3% H_2O) of **12** in NMR ampoule during the week the product of **13** was formed. Opening of pyranone ring for the **6** at the same condition was not observed. It is also important to note, that products of **7** for the first, **8** and **9** were not formed for the second reactions. Structure of all known (**5**, **6**, **11** and **12**) and new (**10** and **13**) compounds confirmed by the NMR spectroscopy (Fig. S1-S6).

For the revealing of formation reasons of different products during the condensation of 2-hydroxy-5-methylacetophenone **1** and some aromatic aldehydes (**2**, **3** and **4**) with different electron distribution in a ring, PM7 optimization and HMO theory were applied. Obtained data are given in the Table I. The conformational 3D structure and electrostatic potential for all products were calculated by using of PM7 optimization (Figure 1 and S7).

As seen from Table I more stable 2-hydroxy-5-methylacetophenone chalcone from the **5**, **8** and **11** is

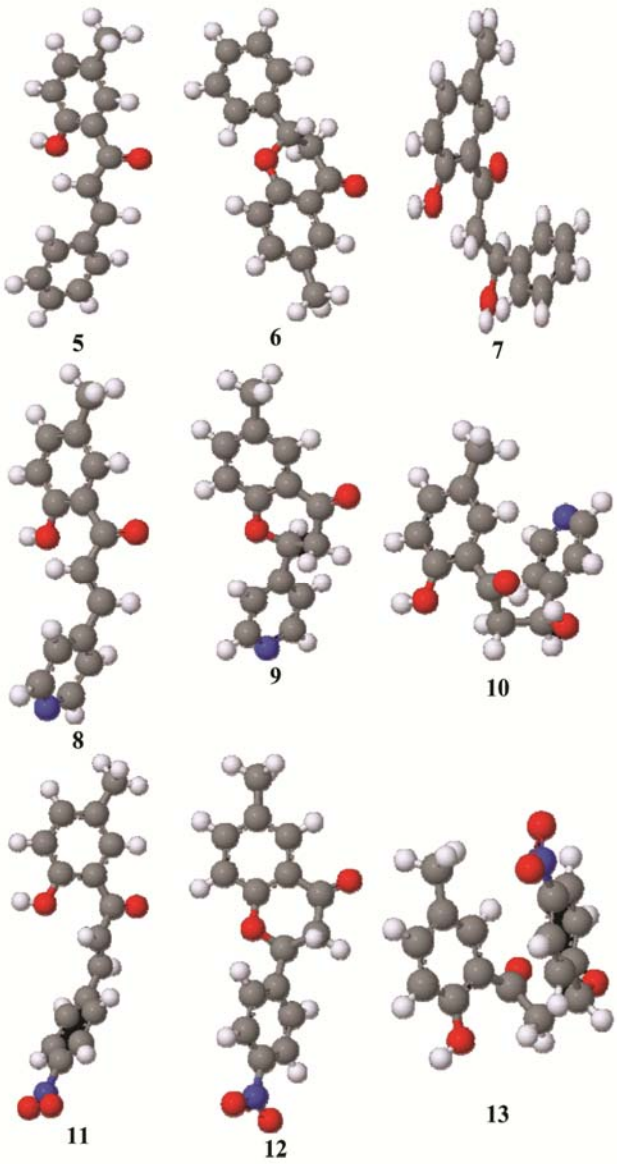


Figure 1 — The conformational 3D structure of all products

(2*E*)-1-(2-hydroxy-5-methylphenyl)-3-(4-nitrophenyl)prop-2-en-1-one**11**with the-31.15 kcal/mol heat of formation energy. Therefore, the yield of this chalcone is higher (52%) than chalcone **5**. The heat of formation energies of **5** and **8** accordingly are -26.19 and -17.05 kcal/mol (yield 33 and 0%). It is important to note, that the 0% yield of the chalcone **8** and chromenone**9** may be connected with the value of net negative charge (-0.002) in compound **8** for the carbon with the number of 10. The values of net charge for the same carbon in compounds **5**, **8**and **11**accordingly are -0.045, -0.002 and 0.019. Considering this fact, we think that at the first stage in the reaction medium taken place formation of chalcone **8**.

At the second stage occurs electrophilic attacking of water proton to the double bond, then nucleophilic attacking of water hydroxyl with the formation of compound **10**.But in the compound of **5** after the formation of chalcone, simultaneously there occurs intramolecular cyclization reaction with the synthesis of compound **6** (without any electrophilic attack of the water molecule).

It is noted that for compound **12**, opening of pyranone ring occurs slowly on storing in DMSO solution for one week.

Conclusions

In conclusion, we report the formation possibility of the different products from the condensation of 2-hydroxy-5-methylacetophenone and some aromatic aldehydes with different electron distribution in a ring. For the characterization of all products NMR and PM7 optimization, HMO theory computational methods were applied.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

Conflict of interest

The authors declare that they have no conflict of interest.

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