Synthesis and Kinetic Investigations for the Isomerization Process of 2–Hydroxy Chalcone Derivatives

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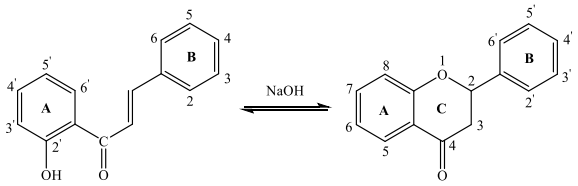
Summary: The wide biological activities of flavanones are mainly depends on their physical and chemical properties, thus a number of substituted 2-Hydroxy chalcones have been synthesized, and their isomerization to their corresponding flavanones was studied. In order to determine the rate constant, kinetic experiments were performed using HPLC technique in (9:1) (CH_3CN:H_2O) medium at different temperature (298-318) K. The obtained results were interpreted by four steps mechanism, which considered the existence of phenoxide ion as the key intermediate.
This study performed with a pseudo first order (reaction in which the rate for the studied compounds follow the sequence 5 > 2 > 1 > 4 > 3, the activation energy have the same sequence for these compounds .The effect of substituents on the rate showed that electronic and steric factors play reasonable role on the stability of the product .

Key words: Isomerization, Flavanones, 2-Hydroxy chalcones, Phenoxide ion.

Introduction

Claisen–Schmidt condensation of 2-hydroxyacetophenone and substituted aromatic aldehydes results in the formation of substituted 2-hydroxychalcones, which on isomerization produce flavanones (Fig. 1). Chalcones and flavanones display a wide range of applications [1]. Flavanones are subclass of flavonoid family, which are ubiquitous group of polyphenolic substances [2] that are present in most plants [3], in the last years, this family of natural products has received large attention due to their health-related properties [4], such as antibacterial [5, 6], cytotoxic [7], antioxidant [8], both of enzyme inhibition and induction [9] activities in addition to many other therapeutic [10, 11]. It is well known that an important relationship exists between the acidity constant, the solubility of lipid and the adsorption characteristics of many pharmaceutical [12], furthermore, the knowledge of the acid base properties plays an important role in the development of pharmaceutical formations and studies in medicaments stability [13, 14], this shows the importance of establishing the acid-base behavior of biologically active flavanones.

In order to get further information about acid base behavior of flavanone of chemical and biological interest [15], we report in the present work, the formation of phenoxide ion as an intermediate for the conversion of 2-hydroxy-chalcones to their corresponding isomers flavanones. The rate constant for these reactions were also studied which affected by different substituents at ring B. Furthermore the chalcone – flavanone ratio have been determined during (0.5-1) and after 48 hs.



1=H, 2= 2-Cl, 3= 4-OCH_3, 4= 2,4- Di-OCH_3, 5=3,4 Di-Cl

Fig. 1: General equation for 2-hydroxy chalcone-flavanone isomerization.

Experimental

Instrumentation

Melting points were determined on an electrothermal IA 9300 Digital – Series (1998) apparatus , and they were uncorrected .

Infrared spectra were recorded on a Bruker, FT_IR Spectrophotometer Tensor 27, Germany, and a Biotech Engineering Management, FT - IR – 600, U.K., using KBr and NaCl discs.

Ultra –Violet spectra were recorded on a Shimadzu UV–1650 pc, UV–Visible spectrophotometer, Japan, using chloroform as a solvent

Reaction temperature controlled by means of water bath (Haake NK22) ± 0.15 ^oC, Germany.

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HPLC experiments were conducted on a Shimadzu LC2010 AHT liquid chromatograph. Acetonitrile was used as solvent while the mobile phase was acetonitrile and water (9:1) (v/v) with suitable flow rate 1 mL/min at 12 Mpa as pressure into column to insure separation of all components. The separation has been performed with column (type C8 block heating Shim-pack 4.6 mm interior and 150 mm long) with particles size of 5 mm. The analyte have been detected by means of UV-visible detector which was thermally controlled by internal heater. The kinetic study was carried out in a special cell, which was placed in the HPLC apparatus in order to determine retention time (t_R) for all compounds.

Procedures

Synthesis of substituted -2- hydroxychalcones [16, 17]

In a (100 mL) round bottomed flask, equimolar amounts of 2-hydroxyacetophenone (25 mmole) and appropriate aromatic aldehydes (25 mmole) in (40 mL.) of ethanol were stirred and slowly treated with aqueous solution of sodium hydroxide (2 g. in 5 mL of water). Stirring was continued for (3-4) hs until the mixture was so thick that stirring was no longer affective, since a deep yellow solid mass of the chalcones sodium salt has been formed. After completion of the stirring, the mixture was kept overnight at room temperature. The precipitate was then filtered off and washed with a little amount of ether. The solid compound was treated with (100 mL.) of ice – cold water and acidified with (10 %) of hydrochloric acid to give the chalcones. The product was filtered and washed thoroughly with cold water and recrystallized from ethanol to give chalcones (1–5). The physical properties are listed in Table-1.

Synthesis of unsubstituted flavanone [21, 22]

In a (100 mL.) round bottomed flask, 2-hydroxychalcone (8.93 mmole) was dissolved in (10 mL.) of absolute ethanol by heating the mixture on steam bath. When the entire solid was dissolved, the mixture was removed from the steam bath and with gentle shaking, dilute aqueous sodium hydroxide solution (30 mL. of 1.5 %) was added. The mixture turned red and became cloudy. The mixture was kept overnight at room temperature. The resulting solid was then filtered off and washed thoroughly with cold aqueous ethanol (80: 20, water: ethanol) then recrystallized from ethanol to give white crystals of flavanone (6), m.p. 77 – 78°C in (60%) yield

Kinetic experiments

Reaction rate were preliminary estimated using HPLC technique at the appropriate λ_{max} which was curtained by scanning the components using UV-Visible spectrophotometer. These experiments was performed by mixing 1 mL ($1x10^{-3}$ M) 2-hydroxychalcone with 1 mL of NaOH ($1x10^{-2}$ M) in the reaction cell which kept thermostated then take 20 µL of the mixture into HPLC apparatus to start the measurements inorder to study the isomarization process. Kinetic measurements were carried out at different temperatures between (25-45 ^{o}C) for each reaction, which always followed up to 75-85% completion of reaction.

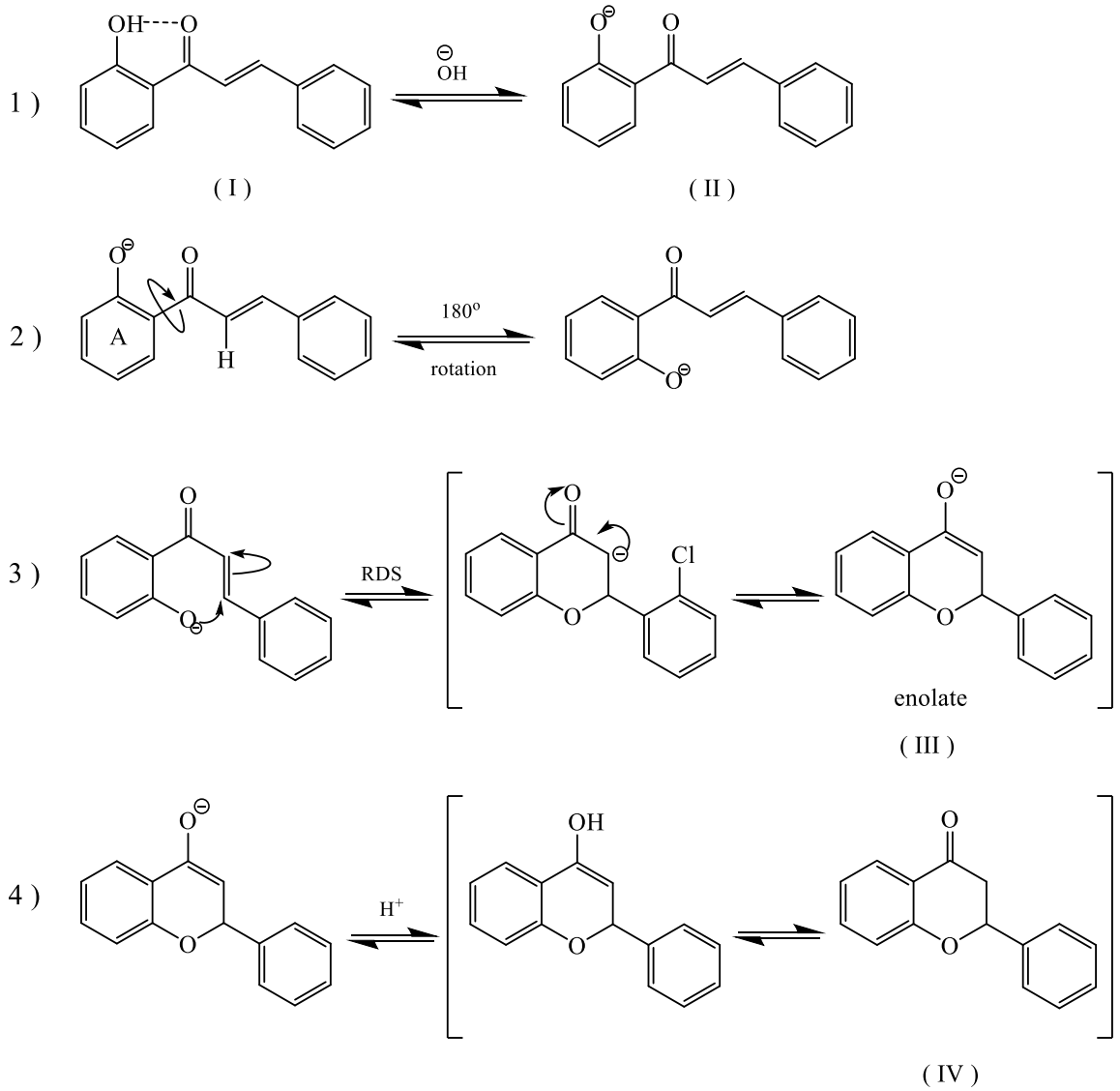
Results and Discussion

Flavanones represent valuable and attractive compounds due to their wide applications as mentioned previously. A synthetic approach for these compounds can be accomplished by two steps reaction , the first step involve the formation of substituted 2-hydroxychalcones (1-5) via Claisen–Schmidt condensation of 2- hydroxy acetophenone and aromatic aldehydes in basic medium, the structures of the synthesized compounds were confirmed by means of physical and spectroscopic methods Table-1 and 2.

The second step in involves the formation of flavanone which was achieved through base catalyzed intramolecular 1, 4–addition of the phenoxide ion at the β–carbon of chalcone as shown in the following scheme:

Table-1: Physical properties for compounds (1-5).

Comp. No.	R	Molecular Formula	m.p. °C	m.p. °C lit.	Yield %	Color	Purity % of chalcone calculated from area under peak(HPLC)
1	H	$C_{15}H_{12}O_2$	89 – 90	88-89 [18]	75	Yellow	98.5
2	2- Cl	$C_{15}H_{11}ClO_2$	100 – 102	88-92 18,19]	20	Deep yellow	98
3	4- OCH_3	$C_{16}H_{14}O_3$	92 – 94	90-92 [18]	60	Deep yellow	99
4	2,4- (OCH_3)$_2$	$C_{17}H_{16}O_4$	102 – 104	111 [20]	59	yellow	97.5
5	3,4- (Cl)$_2$	$C_{15}H_{10}Cl_2O_2$	133 – 136	142 [20]	20	Deep yellow	98



Scheme-1: General scheme for the isomerization process of (2-hydroxychalcone-flavanone).

As we can see , the 2- hydroxy chalcones exist in the more stable formula (I) in which the phenolic hydroxyl group tend to form an intramolecular hydrogen bonding with the carbonyl oxygen atom [23, 24] .

The suggested mechanism is consist of four steps, the first one involve the formation of phenoxide ion (II) which exist on an equilibrium state with the starting chalcone .The second step involve 180° rotation of ring A of (II) about ($C_8 - C_{aromatic}$) single bond Fig. 2, due to the repulsive forces between the phenoxide ion and the carbonyl oxygen, which mean that the ion will be in a perfect position for ring closure.

In the third step, ring closure take place via intramolecular 1,4 – addition of the phenoxide ion at β position of the conjugated system that afforded anion (III). The structure of the latter anion is a resonance hybrid between the keto form (the negative charge on the carbon atom) and predominantly the enol in which the charge on the oxygen atom of the carbonyl group [25, 26]. This step is thought to be the rate-determining step (RDS) in which the substituents on ring B play an important rule in this rate, since the electron withdrawing groups (EWG) enhance the reaction rate, thus compounds 5 and 2 react faster than the other noticing that compound 2 react slower than 5 due to steric hindrance of the substituent in the ortho position that affect on reaction center. On the other hand electron donating groups (EDG) decrease the reaction rate as shown in Table-3.

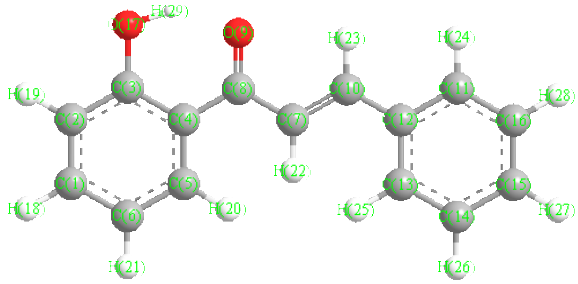


Fig. 2: 3-D structure of 2-hydroxy chalcone.

The final step involves abstraction of proton from the reaction medium of the enolate ion to give the enol form that tautomerize to the more stable keto form, *i.e*. flavanone (IV).

The rate equations

Typical reaction runs toward the conversion of (2-hydroxy chalcone to flavanone), the reaction proceeds via a four steps pathway involving the formation and disappearance of the intermediate phenoxide ion, so that r = k_{obs} [2-hydroxy chalcone], and the observed rate constant k_{obs}, corresponded to k[flavanone], was calculated.

In this case the disappearance of one mole of Chalcone corresponded to the formation of one mole of intermediate and if the transformation is complete then it will converted to the flavanone, and the maximum absorbance of the intermediate A_M will be either or at least proportional to the initial absorbance A_o of chalcone if the reaction is complete.

The rate constants were evaluated by fitting the absorbance time data to appropriate pseudo first order rate equation using linear regression programmer.

$$Ln\frac{[2-hydroxy\ chalcone]0}{[2-hydroxy\ chalcone]t} = Ln\frac{[Intermediate]0}{[Intermediate]t} = Ln\frac{[flavanone]0}{[flavanone]t} \quad (1)$$

$$Ln\left(\frac{A_M - A_0}{A_M - A_{t_1}}\right) = k_1\, t \quad (2)$$

(For intermediate formation process rate. enolate formation)

This step consider rate determining step

A_M Maximum absorbance of intermediate.
A_t Absorbance for formation of intermediate at any time.
A_0 Absorbance of intermediate at zero time (zero time base line).
K Rate constant for formation of intermediate.

In this case, the disappearance of the 2-Hydroxychalcone will be equivalent to the formation of the intermediate (A_M-A_t) at any time

$$Ln\left(\frac{A_M - A_\infty}{A_{t_2} - A_\infty}\right) = k_2\, t \quad (3)$$

For intermediate disappearance and its conversion to the corresponding flavanone.

A_t Absorbance for disappearance of intermediate at any time.
A_∞ Absorbance at infinite time for disappearance of intermediate.
A_M-A_∞ Equivalent to initial concentration of intermediate.
A_t-A_∞ Equivalent to intermediate concentration at any time.
K Rate constant for disappearance of intermediate.

Kinetic results came with a good agreement with the suggested mechanism; these results have been summarized in Table-3, which influenced by the substituents nature.

Table-2: Some spectral data for compounds (1–6).

Compd. No.	IR (KBr) υ(cm^{-1}) O-H	C=O	C=C	C-O-C	UV ($CHCl_3$) λ max (nm)	^{1}H-NMR (d_6 – DMSO) δ (ppm)
1	3444	1639	1572	----	316	----
2	3444	1641	1584	----	312	----
3	3444	1640	1607	----	364	----
4	3444	1640	1573	----	324	3.81(s,3H,OMe–3);3.84(s,3H,OMe -2);7.00(d,2H,Ar–H4,6);7.13(d,1H,Ar–H–3`);7.17(d,1H,Ar–H–6`);7.53–7.63(m,2H,Ar–H–5`,H–α);8.20(d,1H,H–β);12.4(bs,1H,OH).
5	3444	1644	1572	----	324	----
6	----	1690	----	1148 , 1228	320	----

Table-3: Rate constant for compound (1-5).

Temp. K	Com. 1 10^2 k/min	Com. 2 10^2 k/min	Com. 3 10^2 k/min	Com. 4 10^2 k/min	Com. 5 10^2 k/min
298	6.31	6.25	3.31	5.46	8.35
303	8.86	11.81	6.23	7.98	12.52
308	10.24	13.77	7.36	9.53	15.92
313	13.34	14.72	9.78	10.86	19.54
318	17.89	19.24	13.95	15.56	27.62

Table-4: Correlation coefficient & Standard deviation.

Temp.K	Com. 1		Com. 2		Com. 3		Com. 4		Com. 5	
	R	σ/min	R	σ/min	R	σ/min	R	σ/min	R	σ/min
298	0.988	0.114	0.968	0.189	0.982	0.071	0.974	0.177	0.971	0.274
303	0.990	0.152	0.996	0.119	0.978	0.147	0.989	0.155	0.989	0.175
308	0.977	0.267	0.962	0.457	0.965	0.189	0.988	0.196	0.991	0.525
313	0.963	0.476	0.989	0.184	0.942	0.144	0.991	0.165	0.984	0.362
318	0.983	0.466	0.985	0.306	0.975	0.165	0.984	0.309	0.979	0.587

It is obviously that the reaction is reversible, since an equilibrium state between chalcone and flavanone was observed during kinetic runs.

The reactions between chalcone and NaOH toward the formation of flavanone were found to obey unimolecular pseudo first order, leading to linear relationship Figs. 3-7. Table-4 shows the R values and standard deviation **(**σ) of the slope of plot represent simply the uncertainly which is due to the scatter of points about the regression line , and is thus a measure of reproducibility of the result rather than its absolute accuracy, furthermore plots demonstrate very good agreement between repeated runs .

Effect of Activation energy and Entropies activation

The values of activation energy are of great importance to discern the mechanism under all circumstance studied here.

Our observations were concentrated on the ring closure process of the phenoxide in order to produce the flavanone; this process was found to be a first order unimolecular reaction.

A unimolecular reaction is in principle of the simplest kind of elementary reaction, since it involves the isomarization (including intramolecular ring closure) or decomposition of a single isolated reactant molecule well known that this type of reactions are first order process in the high concentration (or pressure) region of reactant [27].

For the isomarization reaction with different substituent, it can be noticed that all of their E_a vary in line as we obtained.

A fast reaction requires low E_a and vice versa, this observation is explicable with formation of enolate which leads to decreasing the repulsive forces during cyclization that lead to a higher chance for the formation of flavanone, since (EWG) stabilize the intermediate (III) in contrast with (EDG), thus activation energy for compounds under study were found to vary in the following order (5 > 2 > 1 > 4 > 3) as shown in Table-5.

Other factors that have an important role in managing the reactions rate are the frequency factor (the A-factor) and its corresponding entropy of activation $\Delta S^{\neq}$. These factors determine the rigidity of the cyclic transition state that produced through the ring closure process.

Lower values of A-factor or $\Delta S^{\neq}$, means the formation of more rigid cyclic transition state that lead to a faster process.

These factors are related to each other by the following equation [28].

$$A=\frac{ekT}{h}e^{\Delta S/R}$$ *k:Boltzman constant, h=Plank constant, T=mean temperature*

From the above equation, a value of $A=10^{13.5}$ s^{-1} correspond to $\Delta S^{\neq}=0$, the decrease in this value results in a negative entropy of activation, this noted that all of A-factors obtained $\Delta S^{\neq}$. Values are negative.

Negative value of $\Delta S^{\neq}$ for the cyclization process; indicate the formation of restricted enolate which suffers from lack of certain degree of freedom compared to chalcone.

A valuable indication about the intermediate stability can be obtained from the A-factor values which provide good support for elucidation the reason of the differences in the rate constant values, since the decrease in both A-factor and $\Delta S^{\neq}$ values lead to the same goal. The order of $\Delta S^{\neq}$ (5 > 2 > 1 > 4 > 3).

We can notice that; electron withdrawing groups decrease the $\Delta S^{\neq}$ values causing a more rigid and aligned T.S that lead to faster cyclization process while electron donating group caused a relative increase $\Delta S^{\neq}$ values but still with same order.

Table-5: Arrhenius parameters and entropies of activation.

Comp. No.	E/kJ.mol-1	A-factor/min-1	ΔS≠JK-1mol-1 at 308 k	ΔG≠ kJ.mol-1
1	1290.2	-231.47	184.7 *105	5.9219
2	1162.8	-232.58	138.0 *104	5.0770
3	1622.4	-229.47	634.6*105	6.6811
4	1468.6	-230.08	283.2*105	6.0195
5	1121.1	-232.79	183.5*103	4.7055

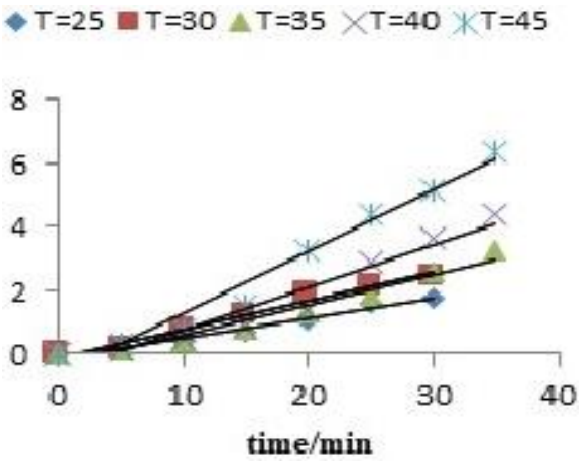


Fig. 3: Pseudo 1st order plot for decreasing of compound 1 at different temperatures.

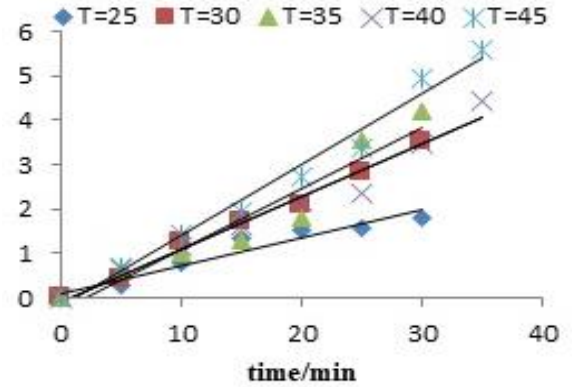


Fig. 4: Pseudo 1st order plot for decreasing of compound 2 at different temperatures.

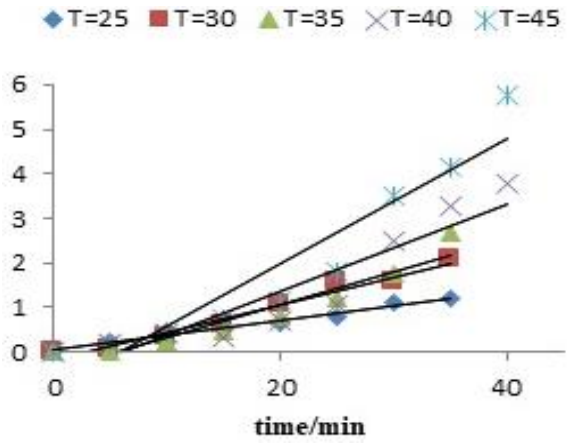


Fig. 5: Pseudo 1st order plot for decreasing of compound 3 at different temperatures

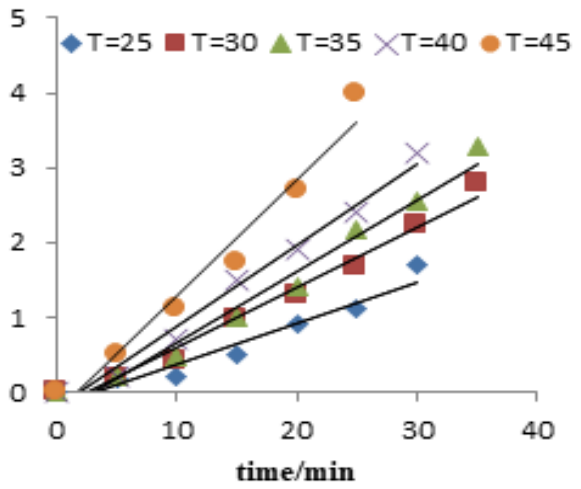


Fig. 6: Pseudo 1st order plot for decreasing of compound4 at different temperatures.

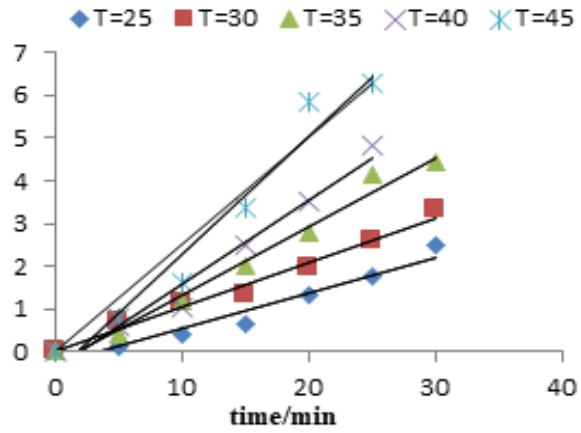
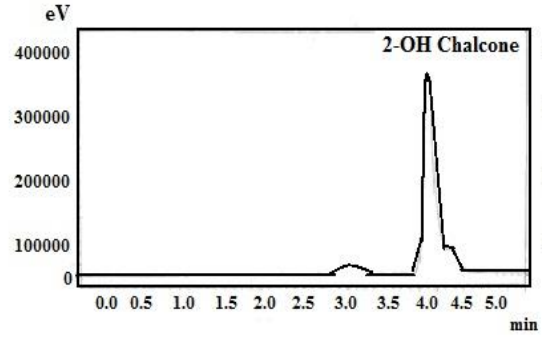


Fig. 7: Pseudo 1st order plot for decreasing of compound5 at different temperatures.

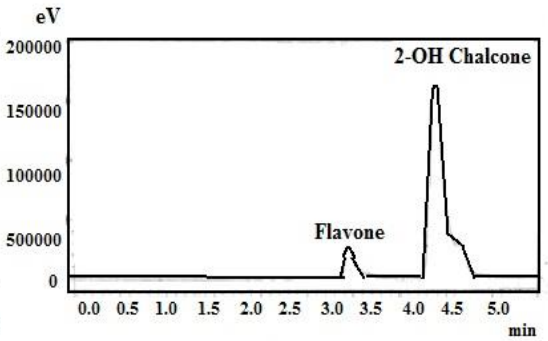
Finally, from Table-6 we can note that there is an equilibrium state between flavanone and chalcone after 1 h of the reaction, but after 48 hs the equilibrium tend to proceed toward flavanone formation as shown in Fig. 8.

Table-6:

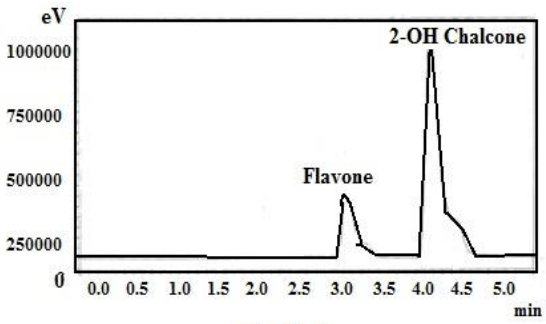
Comp. No.	R.time (flavanon) min	R.time (chalcone) min	Ratio (flavanone: chalcone)% After 1 h	Ratio (flavanone: chalcone)% After 48 hs
1	2.86	3.92	(47.63:52.37)	(67.55:32.45)
2	3.43	4.19	(55.80:44.19)	(73.92:26.08)
3	2.76	3.34	(41.62:58.38)	(58.49:41.51)
4	2.87	3.36	(44.72:55.28)	(62.74:37.26)
5	3.78	4.88	(61.64:38.36)	(80.74:19.26)



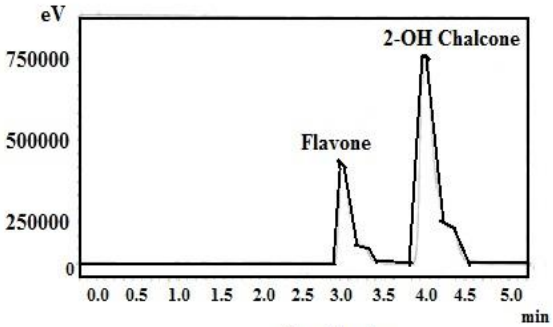
Chalcone only



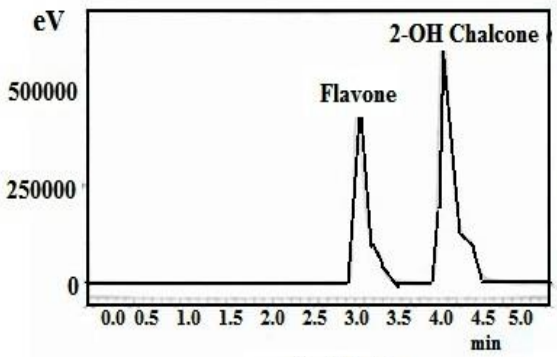
at the begining of reaction



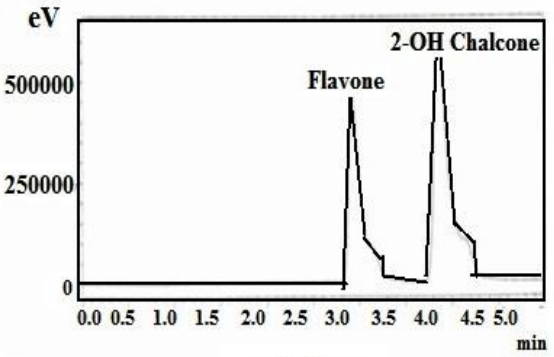
after 5 min



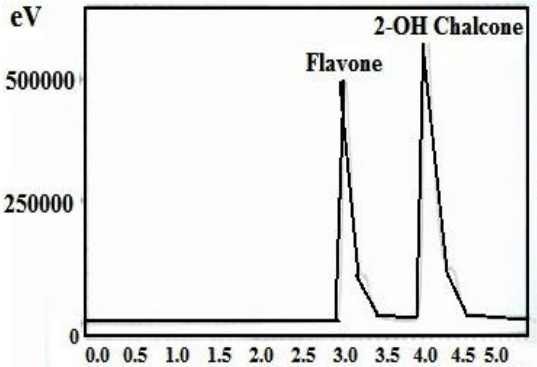
after 10 min



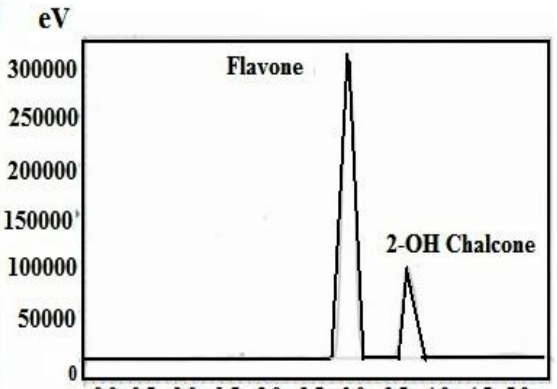
after 15 min



after 20 min



after 30 min



after 48 hs

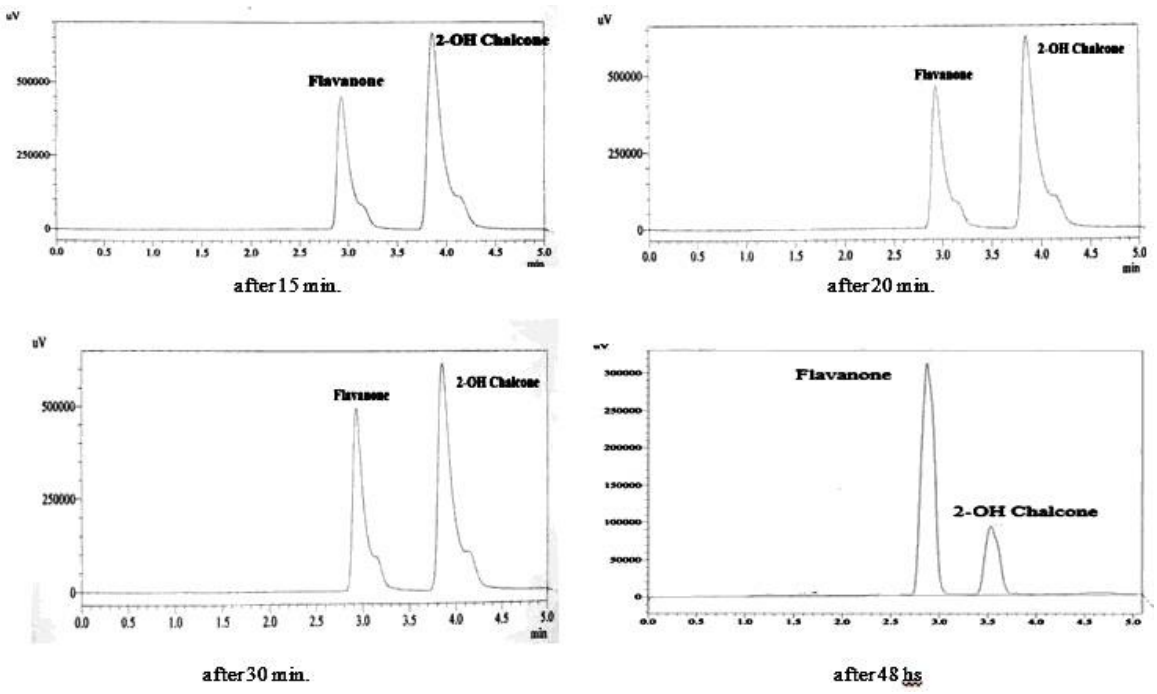


Fig. 8: Chalcone-Flavanone isomerization HPLC-Chromatograms at different times.

Finally, from Fig. 9 clearly we can notice that all substituted flow the same mechanism.

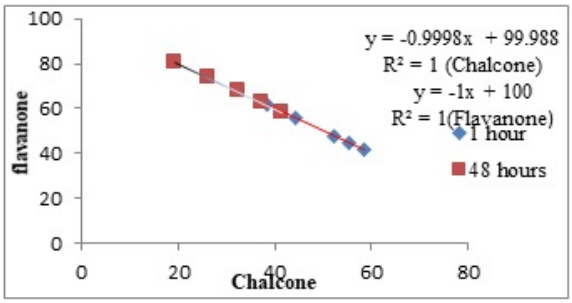


Fig. 9: The relationship between chalcone-flavanone isomerization

Conclusion

From the data presented in our work which involve the synthesis of 2-hydroxychalcones and their transformation to the corresponding flavanones , we can note that the isomerization process proceed throughout a four step mechanism in which the RDS was the ring closure process of the phenoxide ion that results in the formation of the enolate ion (3rd step) , the reaction was influenced by the type and the position of substituents at ring B of the synthesized chalcones , since the reaction rate was enhanced by electron withdrawing groups which stabilize the intermediate and this in contrast with the electron donating groups that decrease the rate due to the destabilization of the intermediate (enolate ion) . Furthermore, we can note that the equilibrium was shifted toward the more stable flavanone after 48 hs

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