



Kinetic Investigation of Hydrolysis of Keto Esters Spectrophotometrically

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3-Phenylisocoumarin and 3-(4'-methoxyphenyl)isocoumarin were synthesized. The synthesized compounds were converted into keto acids and subsequently into keto esters. The keto esters were hydrolyzed back into keto acids in presence of aqueous KOH solution. Pseudo first order and second order rate constants for the hydrolysis of reactions were determined spectrophotometrically. Reaction mechanism has been proposed. Rates of reactions at different temperatures were also determined and energy of activation of the reaction was calculated by plotting graph between $\ln k$ and $1/T$. pK_a values of ketoacids were also determined and compared. It is observed that pK_a value of substituted keto acid is less than the unsubstituted one because of presence of electron withdrawing methoxy group in the former keto acid.

Key Words: Isocoumarin, Ketoesters, pK_a values.

INTRODUCTION

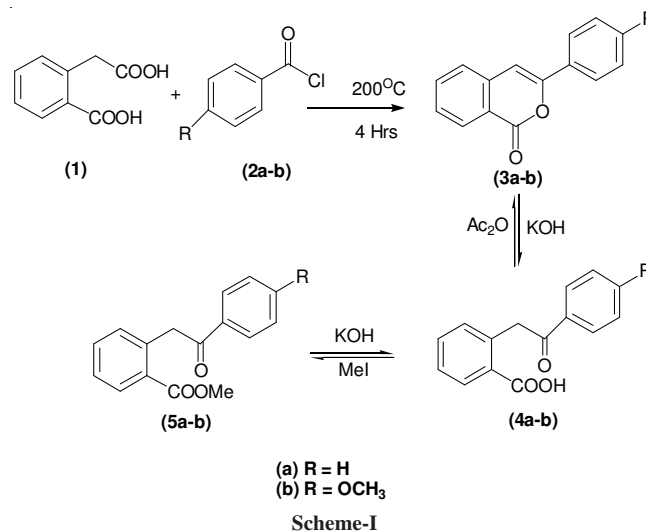
Isocoumarins and 3,4-dihydroisocoumarins are the secondary metabolites of a wide variety of fungi, lichens, molds, bacteria, higher plants and insects. A survey of literature shows that isocoumarins display a wide range of biological activities¹⁻⁵. A wide spectrum of synthetic methods⁶ have been used towards the synthesis of isocoumarins and 3,4-dihydroisocoumarins. A number of new methods⁷ are being developed and reported each year. Some of these methods provide directly the isocoumarins whereas others lead to the 3,4-dihydroisocoumarins. Thus a large number of naturally and non-naturally occurring isocoumarins have been synthesized. Ketoesters are the derivatives of isocoumarins. Upon hydrolysis they are converted into respective ketoacids, which on treating with acetic anhydride regenerate the isocoumarins.

In continuation of our previous work⁸, unsubstituted and substituted isocoumarins were prepared by already available literature method^{9,10} and then converted into ketoesters according to **Scheme-I**.

EXPERIMENTAL

Melting points of the compounds were determined in open capillaries using Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded on Shimadzu, model No IR-460 serial No. 124127 spectrophotometer as KBr disc or neat liquid. ¹H NMR (500 MHz) were recorded on a Bruker AM-500 as CDCl₃ solution using TMS as internal

standard and EIMS were recorded on a MAT-112-S-machine at 70 eV.



Water used in preparation of all the solutions was doubly distilled. Potassium hydroxide and oxalic acid used were obtained from Aldrich. KOH solutions were freshly prepared for all measurements. Fixed volume pipettes with bulb were used for measuring the volumes. Substrate solutions were prepared in Ethanol analaR grade. The reactions were initiated normally by injecting 0.1 cm³ of the substrate solution.

Cecil (Model 3041) UV-Visible spectrophotometers was used for kinetic measurements. It is a single beam spectrophotometer equipped with multicell changer device allowing to monitor the kinetics in four cells at a time. Its wavelength accuracy is ± 1 nm. The reproducibility of this instrument is ± 0.1 nm and photometric accuracy is $\pm 0.005A$.

Reactions were followed at a single wavelength as a trace of absorbance *versus* time (or a printout of absorbance readings against time). In some cases the change in spectrum with time was followed by scanning over an appropriate wavelength range at suitable time intervals. Rate measurements were made by using the conventional UV-Visible spectrophotometer. Initial concentration of the substrate were usually of the order 10^{-4} mol dm^{-3} and were kept at least 20-fold less than the concentration of the most dilute buffer solutions or potassium hydroxide solution to maintain the pseudo-first order conditions. Reactions were followed by monitoring the change in absorbance with time over the appropriate wavelength. Rate coefficients were obtained as the slope of plots of $\ln(A_{\infty}-A_t)$ *versus* time where A_{∞} and A_t are the absorbance at the completion of reaction and that at any time (t) respectively.

Rates of reaction for the hydrolysis of methyl-2-(benzoylmethyl)benzoate were determined at temperatures 30, 40, 45 and 50 °C. In k were plotted against $1/T$. Slope of the plot was multiplied with R (gas constant) to determine energy of activation.

pKa values for keto acids (**4a-b**) were determined by applying Henderson-Hasselbach equation. Buffer solutions of different pH were prepared and a fixed amount of keto acid solutions were added into them. pH of the solutions were determined by pH meter. Ratios of the concentrations of salt to acid were determined by the formula $A-A_a/A_b-A$; where A is the absorbance of buffer solution and A_a and A_b are the absorbances of solution in pure acid and pure base respectively. All the value of absorbance were determined at λ_{max} .

RESULTS AND DISCUSSION

Condensation of benzoyl chlorides (**2a-b**) with homophthalic acid (**1**) at 200 °C afforded isocoumarins (**3a-b**), which showed a characteristic ^1H -singlet at δ 6.80 and 6.83 ppm, respectively for $\text{C}_4\text{-H}$ in ^1H NMR and lactonic carbonyl absorption at 1716 and 1720 cm^{-1} , respectively in IR spectrum. The mass spectra of these compounds showed molecular ion peaks at m/z 222 and 252 respectively, which agreed with their molecular weights. Alkaline hydrolysis of isocoumarins (**3a-b**) yielded the keto-acids (**4a-b**), which showed a 2H-singlet at δ 4.59 and 4.65 ppm, respectively for benzylic $-\text{CH}_2-$ in ^1H NMR while carboxylic carbonyl absorptions in IR spectrum were observed at 1700 cm^{-1} and 1710 cm^{-1} respectively. The mass spectrum of the keto-acids (**4a-b**) showed molecular ion peaks at m/z 240 and 270 respectively. Isocoumarins (**3a-b**) were obtained back on refluxing the keto-acids (**4a-b**) with acetic anhydride. Methylation of (**4a-b**) with excess of methyl iodide yielded methyl keto-esters (**5a-b**) and their structures were confirmed by 3H singlet for OCH_3 at 3.82 and 3.96 ppm, respectively in ^1H NMR while ester carbonyl absorptions in IR spectrum appeared at 1707 and 1702 cm^{-1} , respectively. Mass spectrum of the keto-esters (**5a-b**) showed molecular ion peaks at m/z 254 and 284 respectively.

The compounds (**5a-b**) were hydrolyzed with aqueous KOH solution to afford 2-(benzoylmethyl)benzoic acid (**4a**) and 2-(4'-methoxybenzoylmethyl)benzoic acid (**4b**). The kinetic study of the hydrolysis of keto esters was carried out to investigate the mechanism of the reaction. Pseudo first order conditions were maintained and rate constants were determined by plotting $\ln(A_{\infty}-A_t)$ *versus* time, which is straight line showing the reaction is first order in the substrate. The plot of pseudo first order rate constant k_{obs} against hydroxide ion concentration is 0.022 $\text{dm}^3\text{mole}^{-1}\text{min}^{-1}$, which is the value of second order rate constant. (Fig. 1, Table-1).

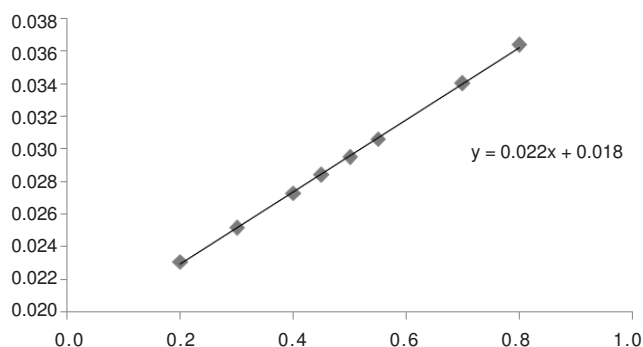
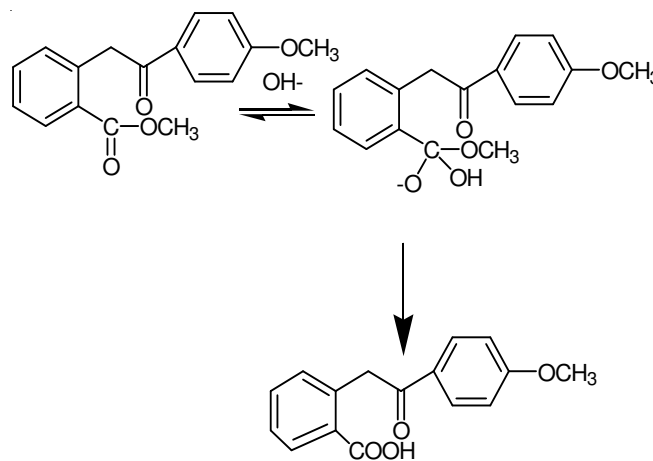


Fig. 1. Plot of pseudo-first order rate constant, k_{obs} against hydroxide ion concentration for the hydrolysis of methyl-2-(4'-methoxybenzoylmethyl)benzoate

TABLE-1
SECOND ORDER RATE CONSTANTS OF THE HYDROLYSIS OF KETO ESTERS WITH AQUEOUS KOH

Name of compound	Temp (°C)	Rate constants ($\text{dm}^3\text{mol}^{-1}\text{min}^{-1}$)
Methyl-2-(4'-methoxybenzoylmethyl)benzoate (5a)	30	0.0220
Methyl-2-(benzoylmethyl)benzoate (5b)	30	0.0213
Methyl-2-(benzoylmethyl)benzoate (5b)	40	0.0218
Methyl-2-(benzoylmethyl)benzoate (5b)	45	0.0221
Methyl-2-(benzoylmethyl)benzoate (5b)	50	0.0224

Intercepts of the plots indicate the role of solvent for the hydrolysis of the reaction. The proposed mechanism of the reaction in the light of spectrophotometric data is given in **Scheme-II**.



Scheme-II Proposed mechanism for the hydrolysis of Keto ester

Rates of reaction for the hydrolysis of (**5a**) was also determined at higher temperatures (40, 45 and 50 °C). The data was used to determine energy of activation for the hydrolysis reaction (30.098 kJ mol⁻¹) (Fig. 2).

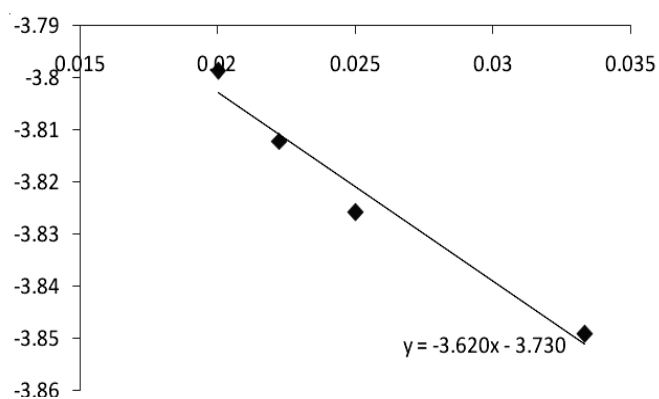


Fig. 2. Plot of $\ln k$ versus $1/T$ for the hydrolysis of methyl-2-(benzoylmethyl)benzoate

pKa values for keto acids (**4a-b**) were determined by applying Henderson-Hasselbach equation. pKa value for (**4a**) (6.23) is slightly greater than that of (**4b**) (6.17). This can be interpreted by presence of electron withdrawing inductive effect of methoxy group which stabilizes carboxylate ion.

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