Asian Journal of Green Chemistry 7 (2023) 70-84

Asian Journal of Green Chemistry

Original Research Article

View Article Online | View Journal

Effect of Solvents on Kinetics and Mechanistic Investigation of Highly Substituted Piperidines: Spectrometry Approaches

Younes Ghalandarzehi[a,*], Halime Kord-Tamandani[b]

[a]Faculty of Industrial & Mining, University of Sistan and Baluchestan, P. O. Box 98135-674, Zahedan, Iran

[b]Department of Chemistry, University of Sistan and Baluchestan, P. O. Box 98135-674, Zahedan, Iran

ARTICLE INFORMATION

Submitted: 2023-01-09
Revised: 2023-02-05
Accepted: 2023-02-09

Manuscript ID: AJGC-2301-1366
Checked for Plagiarism: Yes
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Sami Sajjadifar

DOI: 10.22034/ajgc.2023.380483.1366

KEYWORDS

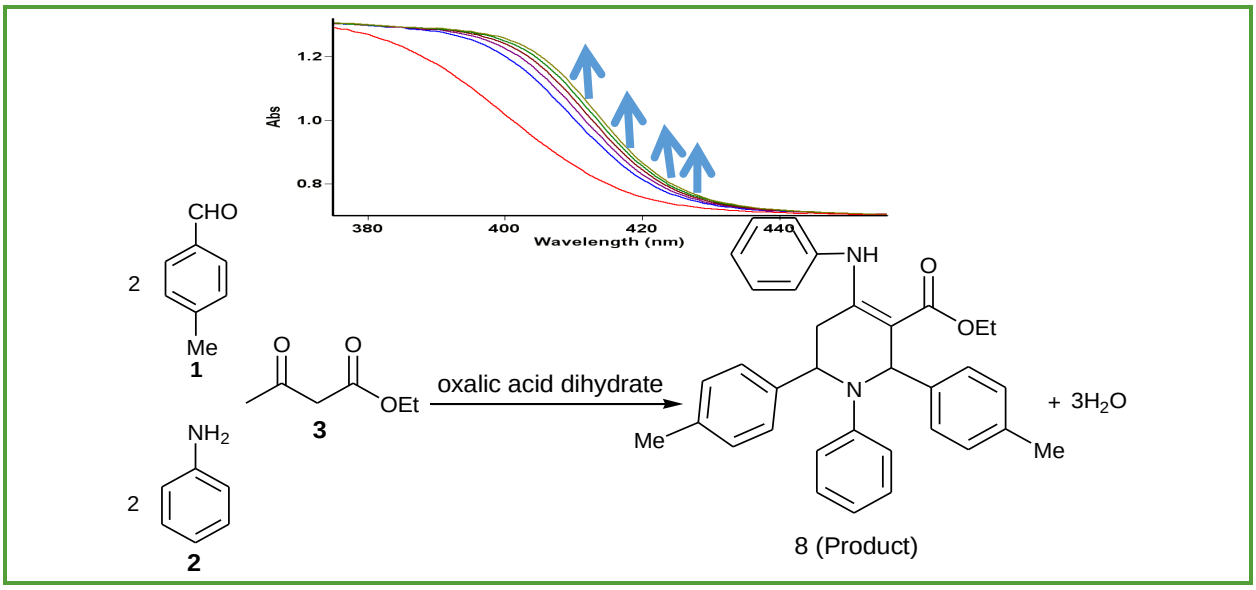
Kinetic and Mechanistic Investigation
Catalyst
Oxalic acid dehydrate
Multicomponent Reaction
UV-vis spectrophotometry
Piperidine

ABSTRACT

On the basis of reaction rates, chemical equilibrium positions, competitive reaction mechanisms, chemoselectivity, and stereoselectivity, various solvent effects can be categorized. Most organic reactions fall into one of several categories, including dipolar transition state, isopolar transition state, nonpolar transition state, and others, depending on how sensitive to solvents they are. In this instance, kinetic considerations were made for the formation of substituted piperidine **8** from the reaction between 4-methylbenzaldehyde **1**, aniline **2**, and ethyl acetoacetate **3** in the presence of oxalic acid dihydrate at room temperature in both methanol and ethanol media. In addition to being an excellent catalyst, oxalic acid dihydrate is a substance that is kind to the environment. To investigate the kinetics and mechanism of the aforementioned reaction, UV-vis spectrophotometry was used. The data from the experiment indicate that there are two steps in the reaction overall. The reaction was carried out multiple times at various temperatures and the relationship between the overall rate constant, Ln k_{ove}, or (Ln k_{ove}/T), and the reciprocal temperature was well supported by the Arrhenius and Eyring equations, respectively. This gave the necessary plots to calculate the reaction's parameters (E_a, $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta G^{\ddagger}$). Methanol was previously recognized as a desirable solvent in the synthesis of piperidine. However, in a kinetic investigation, ethanol had good effects on accelerating the reaction rate compared with methanol. Ethanol is classified as an environmentally preferable green solvent because it is available by fermenting renewable sources, including sugars, starches, and lingo cellulosics, while, methanol is a toxic alcohol. Herein, we have shown ability of ethanol as a solvent to synthesis of substituted piperidines. The outcomes demonstrated that step k_1 is a rate-determining step (RDS) in the reaction mechanism. The obtained results and the steady state approximation supported the proposed mechanism.

Corresponding authors, email: Younes.Ghalandarzehi@chem.usb.ac.ir (Y. Ghalandarzehi).
Tel.: 05433723561.

Graphical Abstract



Introduction

In recent years, one-pot multicomponent reactions involving domino processes with three different starting materials such as 1,3-dicarbonyl compounds, aldehydes, and nucleophilic compounds have received special attention owing to their potential in providing different condensation products depending on the specific conditions and structures of the building blocks [1]. Therefore, the high synthetic efficiency of these accessible reagents has seen many applications, especially for the synthesis of complex heterocyclic molecules [2]. Poly functionalized piperidines are widely distributed in naturally occurring monocyclic and bicyclic alkaloids and synthetic drugs [3]. Naturally occurring and synthetically produced piperidines, are characterized by a wide range of structural properties, many of which display important biological properties including anti-HIV, anti-carcinogenic, antimycobacterial, antimicrobial, antimalarial, anti-inflammatory, and anti-septic properties of inhibitors of many biological systems [4-8]. Therefore, the synthesis of highly substituted piperidines has been widely studied [9], and several methods have been developed using various methods [10-26]. However, some of these methods have disadvantages such as long reaction times and the use of expensive catalysts. It appears that, the development of a simple and high-performance eco-friendly protocol is essential for one-pot multicomponent synthesis of piperidines without the above problems. It is known that homogeneous catalysts have attracted interesting attention in recent years due to operational simplicity, low cost, ease preparation and handling, high stability, lack of toxicity, economic, and environmental aspects. One of these homogeneous is oxalic acid dehydrate. Oxalic acid dihydrate a homogenous catalyst has many applications in the food, pharmaceutical, and textile industries [27]. It is relatively microbiologically stable compared with other naturally occurring organic acids, such as malic and citric acids [28]. Hence, it is used in this work. As part of the present study, thorough kinetic and mechanistic investigations were carried out for the development and mechanistic investigation of dynamic multi-component reactions and the

production of interesting bioactive molecules [29-41]. In addition, ethanol is classified as an environmentally preferable green solvent because it is available by fermenting renewable sources, including sugars, starches, and lignocellulosics, while methanol is a toxic alcohol. Herein, we have shown ability of ethanol as a solvent to synthesis of substituted piperidines. Next reaction by UV-vis spectrophotometry technique. The synthesis of this reaction was described previously [42] (Figure 1).

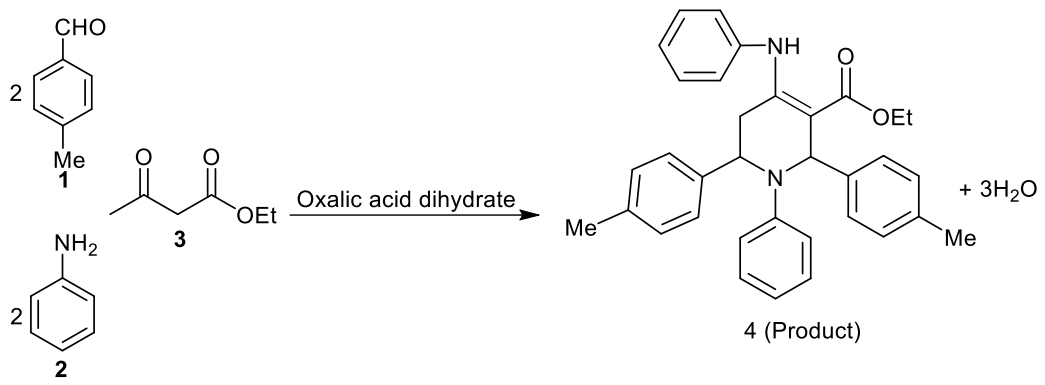


Figure 1. 4-methylbenzaldehyde **1** (2 mmol), aniline **2** (2 mmol), and ethyl 3-oxobutanoate **3** (1 mmol) are reacted with oxalic acid dehydrate as a catalyst

Experimental

Materials and methods

The 4-methylbenzaldehyde **1**, aniline **2**, ethyl 3-oxobutanoate **3**, and oxalic acid dihydrate were obtained from Merck (Darmstadt, Germany), Acros (Geel, Belgium), and Fluka (Buchs, Switzerland), and used without further purification. All extra pure solvents including the methanol and tetrahydrofuran were further obtained from Merck (Darmstadt, Germany). A Cary UV-vis spectrophotometer model Bio-300 with a 10 mm light-path quartz cell was employed throughout the current work. Optimization concentration of catalyst was chosen, 8×10^{-3} M, in each experiment on the basis of the report in synthesis section.

Kinetics

Using the UV-vis spectrophotometric technique, a kinetic study of the reactions was carried out to learn more about the mechanism underlying the reaction between 4-methylbenzaldehyde **1**, aniline **2**, and ethyl acetoacetate **3** in the presence of oxalic acid dihydrate as a catalyst.

First, the relevant spectrum of each compound was recorded over the wavelength range 190-600 nm. Then, the reaction mixture was started into a 1 mm quartz spectrophotometer cell with 2×10^{-2}, 2×10^{-2}, and 1×10^{-2} M solutions of compounds **1**, **2**, and **3**, respectively along with 8×10^{-3} M oxalic acid dihydrate with respect to stoichiometry of each compound in the overall reaction. The absorbance changes of mixed solution were recorded until the reaction was finished (Figure 2). The reaction was monitored by recording scans of the entire spectrum every 5 minute during the whole reaction time at ambient temperature. The ultra-violet spectra depicted in Figure 2 are typical. Herein, the upward of direction of the arrow indicate that the progress of product versus times. Therefore, the

appropriate wavelength was found to be 420 nm (corresponding mainly to product **8**). Since at this wavelength, compounds **1**, **2**, **3**, and oxalic acid dihydrate have relatively no absorbance value, provided the opportunity to fully investigate the kinetics of the reaction and also to find the practical conditions that allows a kinetics study of the reaction. Herein, in all the experiments, the UV-vis spectrum of compound **8** (product) was measured over the concentration range (10^{-3} M ≤ M product ≤10^{-2} M) to check for a linear relationship between absorbance values and concentrations. In the next experiment, under same concentration with the previous experiment, we observed an increasing in absorbance during the formation of product against time at 20 °C and wavelength 420 nm (Figure 3A). As can be seen in Figure (3B), the original experimental absorbance curve versus time (dotted line) is exactly fitted to the second-order fit curve (solid line). The second-order rate constant (k_{obs} = 92.4 $min^{-1}.M^{-1}$) is then automatically calculated using the standard equations within the program at 20 °C [43]. It is obvious that the reaction is the second-order.

In this case, overall order of rate law can be written as:

$$\alpha+\beta+\gamma= 2$$

$$\text{rate} = k_{ovr}[\mathbf{1}]^{\alpha}[\mathbf{2}]^{\beta}[\mathbf{3}]^{\gamma}[\text{Cat}] \quad (1)$$

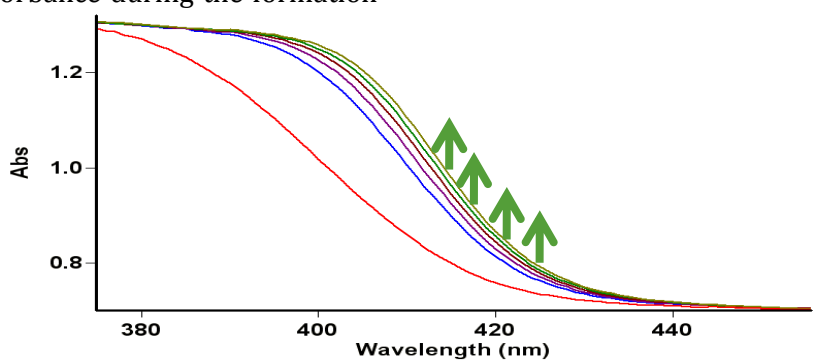


Figure 2. The UV-vis spectra of the 4-methylbenzaldehyde **1** (2×10^{-2}), aniline **2** (2×10^{-2}), and ethyl acetoacetate **3** (1×10^{-2}) reaction in ethanol in the presence of the catalyst oxalic acid dihydrate (8×10^{-3}) at wavelength 375–455 nm. The upward direction of the arrow in this instance denotes the product progression over time

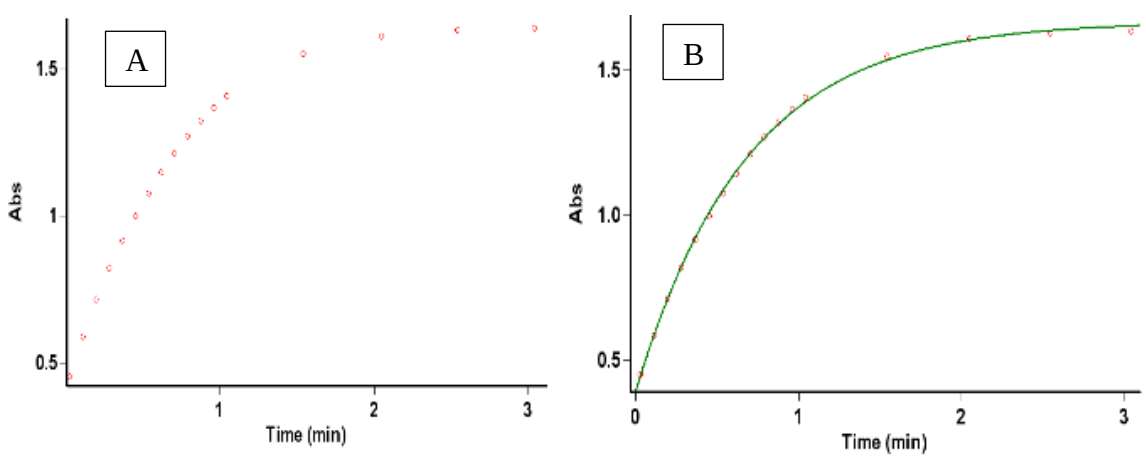


Figure 3. A) The original experimental absorbance versus time. B) A second-order fit curve (solid line) and the original experimental curve (dotted line) for the reaction between **1** (2×10^{-2}), **2** (2×10^{-2}), and **3** (1×10^{-2}) in the presence of oxalic acid dihydrate (8×10^{-3} M) at 20 °C and 420 nm in ethanol

Results and Discussion

Effect of concentration

The pseudo-order conditions were applied to the reaction to obtain a partial order of the reaction for ethyl acetoacetate (3). In the other experiment, we therefore tracked the kinetics of the reaction between (**1**) (2×10^{-2} M), (**2**) (2×10^{-2} M), and (**3**) (5×10^{-3} M) in the presence of oxalic acid dihydrate (8×10^{-3} M) at 20 °C in ethanol. Under a pseudo-order condition, the rate law is conceivable in this scenario.

$$\text{rate} = k_{\text{ovr}}[3]^{\alpha}[2]^{\beta}[1]^{\gamma}[\text{cat}]$$
$$\text{rate} = k_{\text{obs}}[3]^{\alpha}$$
$$k_{\text{obs}} = k_{\text{ovr}}[2]^{\beta}[1]^{\gamma}[\text{cat}] \quad (2)$$

Figure 4A can be used to determine the infinity absorbance (A^{∞}), or the absorbance at reaction completion (Figure 4A when t=3 minutes). The UV-vis instrument's software [43] could automatically draw the reaction's zero, first, or second curves in relation to this value. Using the initial experimental data on absorbance vs. time (Figure 4A) offered a pseudo-second-order fit curve at 420 nm that flawlessly matches the experimental curve (dotted line) in Figure 4B). In relation to ethyl acetoacetate **3**, α=0, it is clear that the reaction is of zero order. Observation rate constant (k_{obs} = 93.1 $\text{min}^{-1}.\text{M}^{-1}$) is used here was calculated automatically using the predefined standard equations in the software [43]. As is evident k_{obs}=93.1 $\text{min}^{-1}.\text{M}^{-1}$, k_{obs} = 92.4 $\text{min}^{-1}.\text{M}^{-1}$ are roughly equivalent, which was discovered through earlier research.

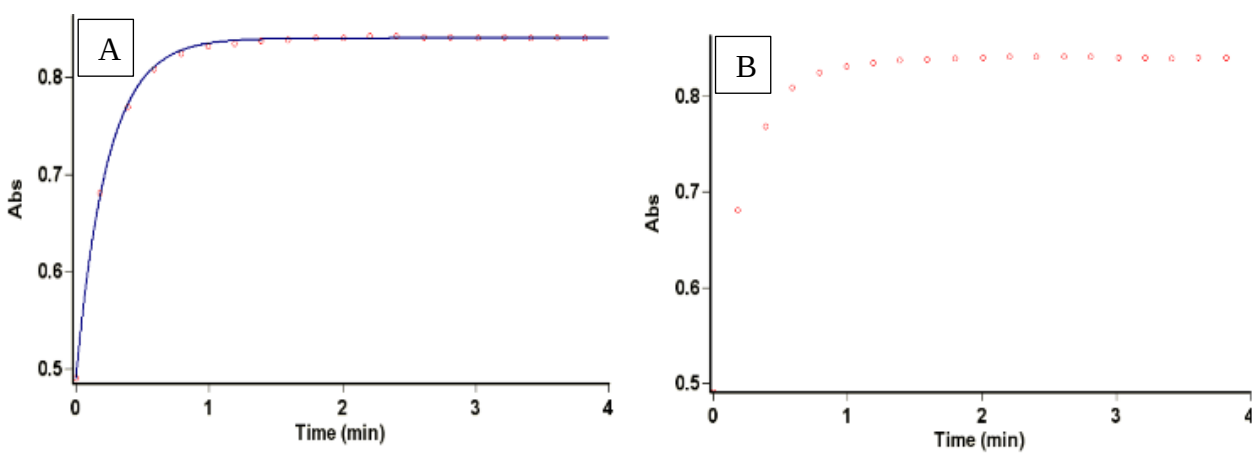


Figure 4. A) The original experimental absorbance curve versus time (dotted line). B) The second pseudo order fit curve (solid line) accompanied by the original experimental curve (dotted line), for the reaction between **1** (2×10^{-2}), **2** (2×10^{-2}), and **3** (5×10^{-3}) in the presence of oxalic acid dihydrate (8×10^{-3} M) at 20 °C proceeded in ethanol

The same procedure was used with concentrations of (2×10^{-2} M, reactant **1**), (2×10^{-2} M, reactant **2**), and (10^{-3} M, reactant **3**) in the presence of oxalic acid dihydrate (8×10^{-3} M) to confirm the previous result using a different concentration of ethyl acetoacetate **3**. The identical findings are presented in Table 1 together (The comparison of the rate constants (k_{obs}) in both scenarios). This experiment shows that the rate of reaction is unaffected by the amount of ethyl acetoacetate present **3**.

Because the stoichiometry of the two reactants change when the concentrations are changed under pseudo-order conditions, it is

impossible to determine the partial order of the reaction with respect to reactants **1** and **2**.Thus, the second-order kinetics governs the reaction between 4-methylbenzaldehyde **1**, aniline **2**, and ethyl acetoacetate **3** in the presence of oxalic acid dihydrate.

The rate law can be written:

From the second experiment: $\alpha+\beta+\gamma= 2$

From the third experiment: $\alpha = 0$

Hence,

rate = $k_{ovr}[2]^{\beta}[1]^{\gamma}[cat] = k_{obs}[2]^{\beta}[1]^{\gamma} = k_{obs}[2][1]$

if

$k_{obs} = k_{ovr}[cat]$

And partial orders with respect to reactants **1** and **2** being one and one, respectively.

Table 1. Rate constant (k_{obs}) for the reaction between reactants **1, 2, 3,** and oxalic acid dihydrate in ethanol measured at wavelength 420 nm and 20.0 °C

Number	Concentration (1)	Concentration (2)	Concentration (3)	Oxalic acid dehydrate	k_{obs} ($min^{-1}.M^{-1}$)
1	(2×10^{-2} M)	(2×10^{-2} M)	(10^{-2} M)	(8×10^{-3} M)	92.4
2	(2×10^{-2} M)	(2×10^{-2} M)	(5×10^{-3} M)	(8×10^{-3} M)	93.1

Table 2. Values of the rate constants k_{obs} ($min^{-1}.M^{-1}$) for the reaction between **1** (2×10^{-2}), **2** (2×10^{-2}), and **3** (1×10^{-2}) with oxalic acid dihydrate as a catalyst in the presence of different solvents at all temperatures investigated and 420 nm

(λ) (nm)	Solvent	ε(D)	k_{obs} ($min^{-1}.M^{-1}$)				
			20.0 °C	25.0 °C	30.0 °C	35.0 °C	40.0 °C
420	Methanol	32.70	24.5	36.8	43.7	65.9	85.1
420	Ethanol	24.55	92.2	176.4	347.5	698.1	1420.3

Effect of solvent and temperature

Important variables that affect rate constants include polarity and the solvent dielectric constant. The relative stabilization of the initial materials and associated transition state through solvation determine how a solvent affects the rate of reaction [44, 45]. Various experiments were set up with various temperatures and solvents under the same conditions as the prior experiment to ascertain the impact of these changes on the reaction rate. The second-order rate constants for reactions were obtained after all experiments were performed five times at various temperatures, including 25, 30, 35, and 40 °C for each reaction. Compared with reactions occurring at other temperatures, the reaction at 20 °C lasts longer to complete. Compared with other temperatures, the reaction at 20 °C lasts longer to complete. According to Table 2, the rate rises as the temperature rises from 20 to 40 °C. The stability of the reactant and activated complex is actually significantly impacted by changing the solvent. Methanol and ethanol were therefore used in the experiment to determine the solvent effect. The findings revealed that, at all temperatures examined, the rate of reaction in methanol (ε = 32.70, 25 °C) is lower than that in ethanol (ε = 24.55, 25 °C), a solvent with a lower dielectric constant. As can be seen, at higher temperatures, each solvent's reaction rate quickens. The reaction's second-order rate constant, or ln k1, was found to be inversely proportional to the temperature in the studied temperature range, supporting the Arrhenius Equation (3).

The solvent dielectric constant and polarity are important parameters that influence the rate constants. Solvent effects on the rate of reaction depend on the relative stabilization of the starting materials and the corresponding

transition state through solvation [44, 45]. To determine the effect of change in temperature and solvent environment on the reaction rate, various experiments were arranged with different temperatures and solvent under the same conditions with the previous experiment. All the experiments were repeated at four different temperatures, including 25, 30, 35, and 40 °C for each reaction and the second-order rate constants of reactions were obtained. The reaction at 20 °C needs more time to complete when compared with other temperatures. From the Table 2, it was realized that the rate increases as temperature goes up from 20 to 40 °C. In fact, changing the solvent has a considerable effect on stability of the reactant and activated complex. Thus, to find the solvent effect, methanol and ethanol have been used in the experiment. The results, showed that the rate of reaction in a solvent with high dielectric constant [methanol (ε = 32.70 , 25 °C)] are lower than solvent with lower dielectric constant [ethanol (ε = 24.55, 25 °C)] at all temperatures investigated (Table 2). As can be seen, the rate of reaction increases in each solvent at higher temperatures. In the studied temperature range, the second-order rate constant (ln k_1) of the reaction was inversely proportional to the temperature, which is consistent with the Arrhenius Equation (3):

$$lnk = lnA - \frac{E_a}{RT} \quad (3)$$

In ethanol and methanol, rate constants were measured for the reaction between (**1**), (**2**), and (**3**) at five different temperatures, and they were plotted against 1/T. The Arrhenius plot's slope, which is depicted in Figure 5, shows a good straight line with the slope of $-\frac{E_a}{R}$, as illustrated in Equation (3), and this allowed the activation energy (Ea) to be calculated. The outcomes are compiled in Table 3. The highest activation energy (E_a = 104.2 kJ. mol^{-1}), whereas the solvent for ethanol was smaller (E_a = 46.9 kJ. mol^{-1}, indicating that the reactants need high energy for the non-polar transition state.), which indicates that the reaction will be simpler.

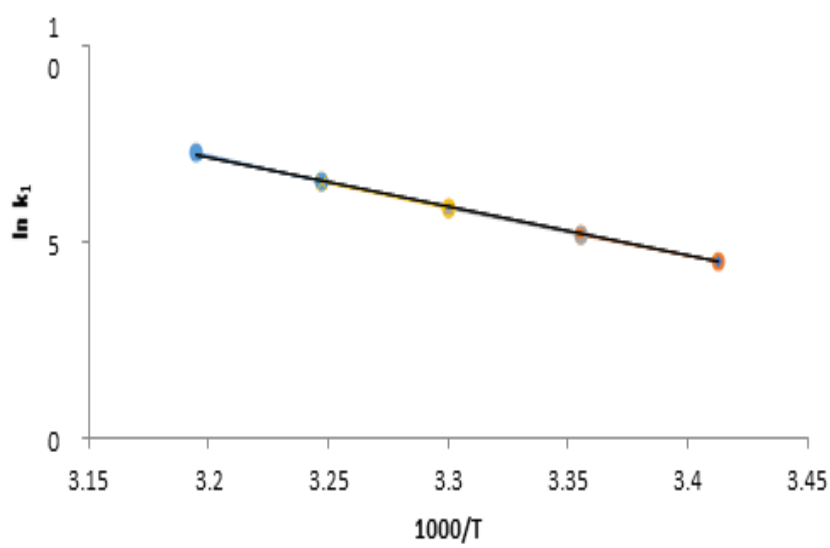


Figure 5. Dependence of the second-order constant (ln k_{obs} = ln k_1) on reciprocal temperature for the reaction between compounds **1**, **2**, and **3** in the presence of Oxalic acid dihydrate as catalyst in methanol measured at wavelength 420 nm in accordance with Arehenius equation

On the basis of Eyring Equation (4):

$$ln\frac{k}{T} = -\frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R} + ln\frac{k_B}{h} \quad (4)$$

That k_B = Boltzmann's constant, T = temperature, h = Planck's constant, and R = universal gas constant.

Figure 6A was plotted and kinetic parameters were estimated. The activation parameters $\Delta H^{\ddagger}$ (activation enthalpy), $\Delta S^{\ddagger}$ (activation entropy), and $\Delta G^{\ddagger}$ (activation Gibbs energy) were determined using the intercept and slope of the corresponding lines, respectively. The obtained activation parameters for both solvents are listed in Tables 3.

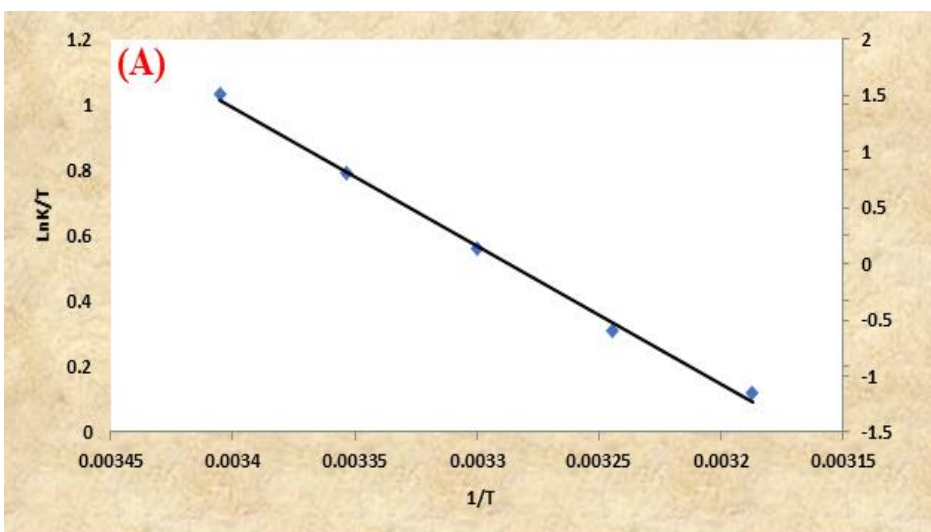
In addition, a different linearized form of Eyring Equation [Tln (k_{ovr}/T) versus T] were examined (Figure 6B) to check the results obtained by both methods (Tables 4).

$$Tln\frac{k}{T} = -\frac{\Delta H^{\ddagger}}{R} + T(\frac{\Delta S^{\ddagger}}{R} + ln\frac{k_B}{h}) \quad (5)$$

As can be seen, there is a good agreement between the results obtained by both methods. Although, the reaction is enthalpy controlled in both solvent, in ethanol the non-polar transition state of step 1 in reaction mechanism is more highly ordered than methanol ($\Delta S^{\ddagger}$ = 142.5 in comparison with $\Delta S^{\ddagger}$ = -66.6). This is a good advantage for ethanol to provide a better environment for the perfect reaction's progressing. The positive value of $\Delta H^{\ddagger}$ means that energy consumes in its process. The entropy of activation gives a measure of the inherent probability of transition state, apart from energetic considerations, formation of the transition state requires the reacting molecules to adopt precise conformations and approach one another at a precise angle [46]. If $\Delta S^{\ddagger}$ is large and negative, it indicates a transition state that is more highly ordered than the reactants. The activation Gibbs free energy was determined using Equation (6):

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad (6)$$

The highest activation Gibbs free energy was obtained for methanol solvent that means the reaction will occur harder.



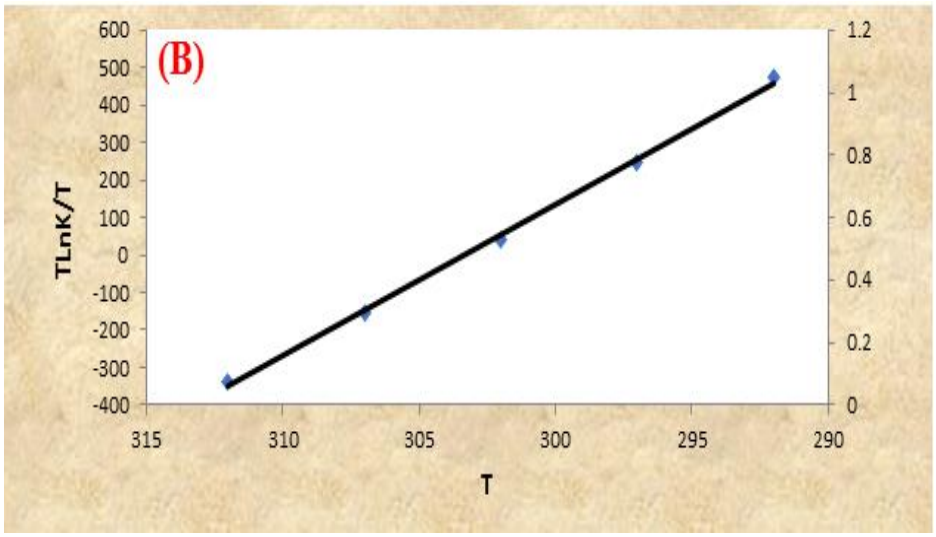


Figure 6. Eyring plots according to equations (4) and (5) for the reaction between **1**, **2**, **3,** and oxalic acid dihydrate in ethanol

Table 3. Activation parameters ($\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and E_a) using the Arrhenius equation (3) and Eyring Equation (4)

Solvent	$\Delta H^{\ddagger}$ (kJ.mol^{-1})	$\Delta S^{\ddagger}$ (J.mol^{-1}K^{-1})	$T\Delta S^{\ddagger}$ (kJ.mol^{-1})	$\Delta G^{\ddagger}$ (kJ.mol^{-1})	Ea^a(kJ.mol^{-1})	Ea^b(kJ.mol^{-1})
Ethanol	44.3	-66.6	-19.5	63.8	46.9	41.8
Methanol	102.6	142.5	41.8	60.7	104.2	100.2

[a]Obtained by the Arrehnius Equation
[b]Obtained from $\Delta H^{\ddagger}$ = Ea + RT

Table 4. Activation parameters ($\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$, and E_a) using different linearized form of Eyring Equation (5)

Solvent	$\Delta H^{\ddagger}$ (kJ.mol^{-1})	$\Delta S^{\ddagger}$ (J.mol^{-1}K^{-1})	$T\Delta S^{\ddagger}$ (kJ.mol^{-1})	$\Delta G^{\ddagger}$ (kJ.mol^{-1})
Ethanol	44.3	-66.6	-19.5	63.8
Methanol	101.8	139.8	41.0	60.8

On the basis of experimental data and report on literature [42], the above mechanism was suggested.

Further study

A new set of experiments (two component reaction) with three categories were performed to determine which steps of the suggested mechanism (Figure 7) might be a rate-determining step:

i) The reaction between 4-methylbenzaldehyde 1 and aniline 2 [Re.1 or step 1 in Figure 7],

ii) The reaction between ethyl acetoacetate 3 and aniline 2 [Reation 2 or step 2 in Figure 7],

iii) The reaction between 4-methylbenzaldehyde 1 and ethyl acetoacetate 3 (Reation 3).

The Reation 1 at 20 °C in methanol, using the same concentration (10^{-2} M) of each reactant. Here, the rate constants for these two-component reactions were determined as k_{obs} = 435 $M^{-1}.S^{-1}$ monitored by recording scans of the entire spectra (Figure 8A) and Figure 9A, respectively) with the 1.5 minute intervals, (Figure 8B) and k_{obs} = 1420 $M^{-1}.S^{-1}$ (Figure 9B) for Reation 1 and Reation 2 in that order.

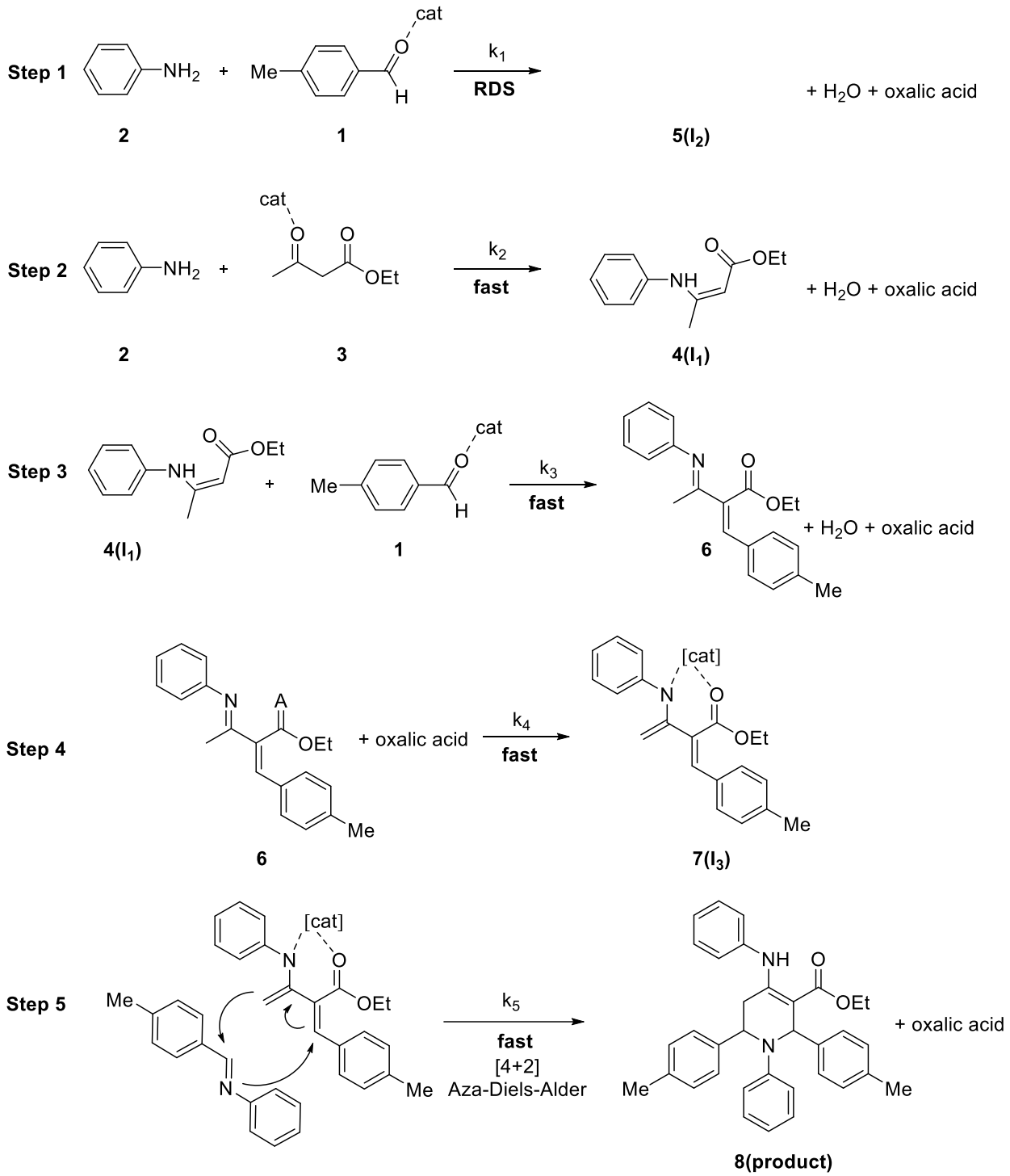


Figure 7. The proposed mechanism for the reaction between 4-methylbenzaldehyde **1**, aniline **2** and ethyl acetoacetate **3** in the presence of oxalic acid dihydrate

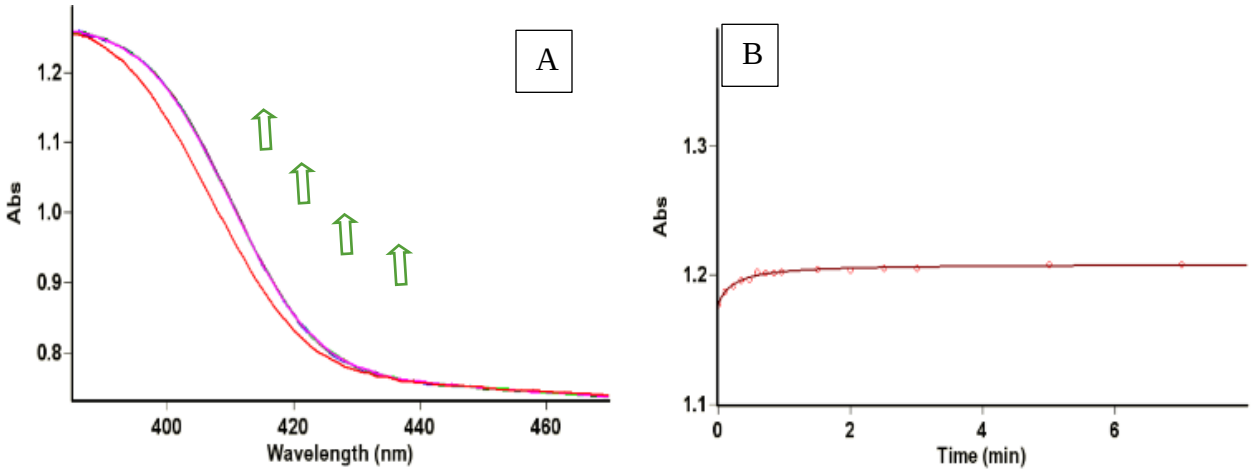


Figure 8. A) The UV-vis spectra of reaction between and B) the second order fit (solid **1** and solid **2** at 20 °C in ethanol line) accompanied by the original experimental curve (dotted line) for the reaction between **1** and **2** at 20 °C in ethanol

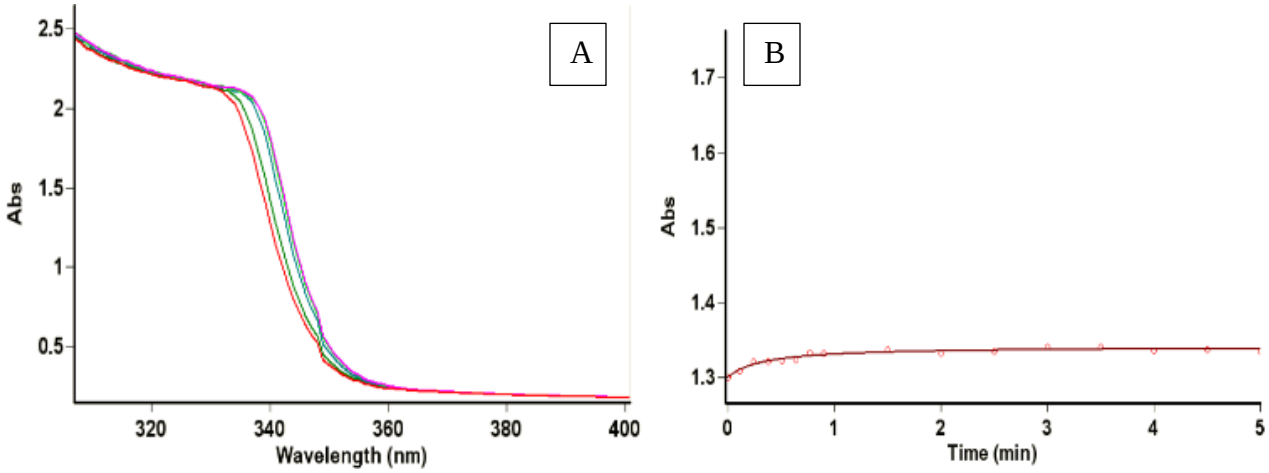


Figure 9. A) The UV-vis spectra of reaction between and B) the second order fit (solid **2** and **3** at 20 °C in ethanol line) accompanied by the original experimental curve (dotted line) for the reaction between **2** and **3** at 20 °C

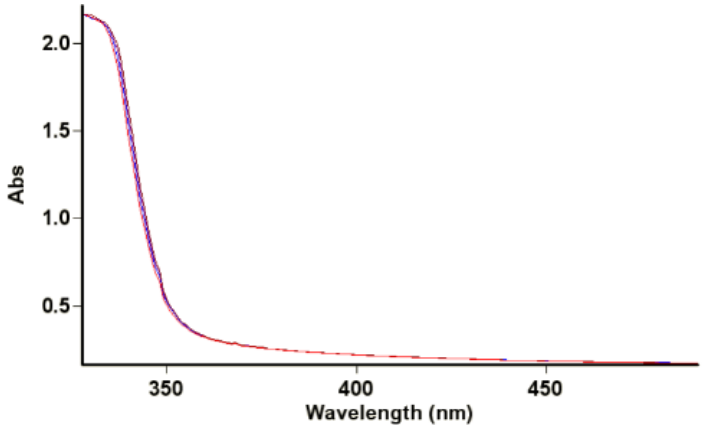


Figure 10. The UV-vis spectra of reaction between **5I**$_2$ and **7I**$_3$ at 20 °C in ethano

As a result, Reation 1 is much slower than Reation . The results are well consistent with the report on literature [46]. At pH range near or above neutrality (herein, methanol or ethanol), this dehydration and the imine–forming elimination reaction undergoes E_2 (concerted reaction) (not E_1) mechanism as a rate determining step [47]. Therefore, it makes sense to accept that this is why the reaction speeds up in ethanol rather than methanol. Likewise, ethanol has shown no reaction between **1** and **3** (Reation was not observed). In another separate experiment, the product of step 2 ($4I_1$, Figure 7) in liquid phase was added to the same concentration of 4-methyl benzaldehyde **1** (both starting reactants of step 3 in Figure 7) for generation of **6** or a corresponding to $7I_3$ in step 4. As expected, the reaction was too fast and detailed analysis by the UV-vis spectrophotometry was impossible. In further experiment, the product of step 4 ($7I_3$) in a liquid phase was added to product of step 1 ($5I_2$) [both reactants in final (step 5) of Figure 7]. UV-vis spectra are depicted in Figure 10.

As can be seen, cycloaddition reaction [4 + 2] between $\mathbf{5I_2}$ and $\mathbf{7I_3}$ is very fast. Thus, the analysis of this spectrum was impossible using UV-vis technique. As a result of these entire investigations and the experimental observations, a speculative mechanism containing five steps with starting reaction between **1** and **2** as a rate-determining step along with the other more rapidly accruing steps have been proposed in Figure 7, as presented previously. Now, we can use steady state approximation for conformation of the rate-determining step (experimental result proved that step 1 is a rate-determining step). Therefore, the rate law is written using the final step of reaction (step 5) to generate product (**8**):

$$rate = k_5[I_2][I_3] \tag{11}$$

The steady state assumption can be applied to obtain the concentration of $[I_2]$ which is generated from the following equations:

$$\frac{d[I_2]}{dt} = k_1[2][1] - k_5[I_2][I_3] = 0 \tag{12}$$

$$k_5[I_2][I_3] = k_1[2][1] \tag{13}$$

The value of Equation (3) can be replaced in Equation (1) so the rate equation becomes:

$$rate = k_1[2][1] \tag{14}$$

Equation (14) shows that the overall order of reaction is two and indicates that the first step of the reaction is *RDS* (since k_1 is the only rate constant which appeared in the equation (14)). Previously, this equation was confirmed by the UV-vis experimental data ($rate = k_1[2][1]$). It means that k_{obs} is identical with k_1 ($k_{obs} = k_1$).

Conclusion

Oxalic acid dihydrate has been employed as an effective and capable catalyst with environmentally friendly character. In kinetics, it was found that ethanol had more effects on the reaction rate than methanol. It was recognized that step 1 of reaction mechanism is a rate-determining step (RDS). In step 1, dehydration process for the generation of imine-forming proceeds through the E_2-elemination (concerted reaction) with a non-polar transition state that is more consistent with ethanol than methanol. Although, the reaction is enthalpy controlled in both solvent, but the non-polar transition state of step 1 has more highly ordered in relation to ethanol than methanol ($\Delta S^{\ddagger}$ = -66.6 in comparison with $\Delta S^{\ddagger}$ = 142.4). This is a good advantage for ethanol to provide a better environment for the reaction's progressing. The large negative value of $\Delta S^{\ddagger}$ in the case of ethanol express the activated

complex has a more ordered or more rigid structure in the transition state, which indicates an associative mechanism. Experimental data indicated that the second step of the reaction is a fast step. High value of activation Gibss free energy indicated that the reaction is a chemically, controlled process.

Acknowledgments

The authors would like to extend our gratitude of Sistan and Baluchestan University for providing the financial protection of this work.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Orcid

Younes Ghalandarzehi
https://orcid.org/0000-0002-6051-4906
Halime Kord-Tamandani
https://orcid.org/0000-0001-9823-3715

References

[1]. Simon C., Constantieux T., Rodriguez J. *Eur J Org Chem*., 2004, 4957 [Crossref], [Google Scholar], [Publisher]

[2]. Liéby-Muller F., Simon C., Constantieux T., Rodriguez J. *QSAR Comb Sci.*, 2006, **25**:432 [Crossref], [Google Scholar], [Publisher]

[3]. Watson P.S., Jiang B., Scott B. *Org Lett*., 2000, **2**:3679 [Crossref], [Google Scholar], [Publisher]

[4]. Imamura S., Nishikawa Y., Ichikawa T., Hattori T., Matsushita Y., Hashiguchi S., Kanzaki N., Iizawa Y., Baba M., Sugihara Y. *Bioorg Med Chem*., 2005, **13**:397 [Crossref], [Google Scholar], [Publisher]

[5]. Weis R., Schweiger K., Faist J., Rajkovic E., Kungl A.J., Fabian W.M.F., Schunack W., Seebacher W. *Bioorg Med Chem*., **2008**, **16**:10326 [Crossref], [Google Scholar], [Publisher]

[6]. Ishikawa M., Furuuchi T., Yamauchi M., Yokoyama F., Kakui N., Sato Y. *Bioorg Med Chem*., 2010, **18**:5441 [Crossref], [Google Scholar], [Publisher]

[7]. Zhang J., Zhang P., Liu X., Fang K., Lin G. *Bioorg Med Chem Lett*., 2007, **17**:3769 [Crossref], [Google Scholar], [Publisher]

[8]. Srinivas C., Kumar C.N.S.P., Raju B.C., Rao V.J., Naidu V.G.M., Ramakrishna S., Diwan P.V. *Bioorg Med Chem Lett*., 2009, **19**:5915 [Crossref], [Google Scholar], [Publisher]

[9]. Esquivias J., Arrayas R.G., Carretero J.C. *J Am Chem Soc*., 2007, **129**:1480 [Crossref], [Google Scholar], [Publisher]

[10]. Lebold T.P., Leduc A.B., Kerr M.A. *Org Lett*., 2009, **11**:3770 [Crossref], [Google Scholar], [Publisher]

[11]. Takasu K., Shindoh N., Tokuyama H., Ihara M. *Tetrahedron*, 2006, **62**:11900 [Crossref], [Google Scholar], [Publisher]

[12]. Murty M.S.R., Ram K.R., Yadav J.S. *Tetrahedron Lett*., 2008, **49**:1141 [Crossref], [Google Scholar], [Publisher]

[13]. Fustero S., Jimenez D., Moscardo J., Catalan S., del Pozo C. *Org Lett*., 2007, **9**:5283 [Crossref], [Google Scholar], [Publisher]

[14]. Davis F.A., Chao B., Rao A. *Org Lett*., 2001, **3**:3169 [Crossref], [Google Scholar], [Publisher]

[15]. Misra M., Pandey S.K., Pandey V.P., Pandey J., Tripathi R., Tripathi R.P. *Bioorg Med Chem*., 2009, **17**:625 [Crossref], [Google Scholar], [Publisher]

[16]. Clarke P.A., Zaytzev A.V., Whitwood A.C. *Tetrahedron Lett.*, 2007, **48**:5209 [Crossref], [Google Scholar], [Publisher]
[17]. Clarke P.A., Zaytzev A.V., Whitwood A.C. *Synthesis*, 2008, **21**:3530 [Crossref], [Google Scholar], [Publisher]
[18]. Khan A.T., Parvin T., Choudhury L.H. *J Org Chem.*, 2008, **73**:8398 [Crossref], [Google Scholar], [Publisher]
[19]. Khan A.T., Lal M., Khan M.M. *Tetrahedron Lett.*, 2010, **51**:4419 [Crossref], [Google Scholar], [Publisher]
[20]. Khan A.T., Khan M.M., Bannuru K.K.R. *Tetrahedron*, 2010, **66**:7762 [Crossref], [Google Scholar], [Publisher]
[21]. Wang H.J., Mo L.P., Zhang Z.H. *ACS Comb. Sci.*, 2011, **13**:181 [Crossref], [Google Scholar], [Publisher]
[22]. Mishra S., Ghosh R. *Tetrahedron Lett.*, 2011, **52**:2857 [Crossref], [Google Scholar], [Publisher]
[23]. Sajadikhah S.S., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., Shams-Najafi S. *J. Monatsh. Chem.*, 2012, **143**:939 [Crossref], [Google Scholar], [Publisher]
[24]. Brahamachari G., Das S. *Tetrahedron Lett.*, 2012, **53**:1479 [Crossref], [Google Scholar], [Publisher]
[25]. Ramachandran R., Jayanthi S., Jeong Y.T. *Tetrahedron*, 2012, **68**:363 [Crossref], [Google Scholar], [Publisher]
[26]. Sajadikhah S.S., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., Willis A.C. *Chin Chem Lett.*, 2012, **23**:569 [Crossref], [Google Scholar], [Publisher]
[27]. Zhang K., Wang M., Wang D., Gao C. *J Membrane Sci.*, 2009, **341**:246 [Crossref], [Google Scholar], [Publisher]
[28]. Clark A.C., Prenzler P.D., Scollary G.R. *Food Chem.*, 2007, **102**:905 [Crossref], [Google Scholar], [Publisher]
[29]. Maghsoodlou M.T., Yavari I., Nassiri F., Dajahanian H., Razmjoo Z. *Monatsh Chem.*, 2003, **134**:1585 [Crossref], [Google Scholar], [Publisher]
[30]. Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., Heydari R., Marandi G., Lashkari M., Bagherpour K., Gharechaei Z. *Monatsh Chem.*, 2010, **141**:351 [Crossref], [Google Scholar], [Publisher]
[31]. Marandi G., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., Akbarzadeh-Torbati N., Rostami-Charati F., Skelton B.W., Makha M. *Mol Divers.*, 2011, **15**:197 [Crossref], [Google Scholar], [Publisher]
[32]. Hazeri N., Marandi G., Maghsoodlou M.T., Habibi-Khorassani S.M. *Lett Org Chem.*, 2011, **8**:12 [Crossref], [Google Scholar], [Publisher]
[33]. Sajadikhah S.S., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M. *Lett Org Chem.*, 2011, **8**:743 [Crossref], [Google Scholar], [Publisher]
[34]. Shahraki M., Habibi-Khorassani S.M., Dehdab M. *RSC Advances,* 2015, **5**:52508 [Crossref], [Google Scholar], [Publisher]
[35]. Shahraki M., Habibi-Khorassani S.M., Ebrahimi A., Maghsoodlou M.T., Ghalandarzehi Y. *Structural Chemistry*, 2013, **24**:623 [Crossref], [Google Scholar], [Publisher]
[36]. Ghodsi F., Habibi-Khorassani S.M., Shahraki M. *Molecules,* 2016, **21**:1514 [Crossref], [Google Scholar], [Publisher]
[37]. Asheri O., Habibi-Khorassani S.M., Shahraki M. *RSC Advances,* 2016, **6**:111239 [Crossref], [Google Scholar], [Publisher]
[38]. Ghalandarzehi Y., Shahraki M., Habibi-khorassani S.M., Kordi-Tamandani H. *American Journal of Chemistry and Application*, 2015, **2**:91 [Google Scholar], [Publisher]
[39]. Ghalandarzehi Y., Habibi-Khorassani S.M., Shahraki M. *Oriental Journal of Chemistry*, 2016, **32**:2735 [Google Scholar], [Publisher]
[40]. Asheri O., Habibi-Khorassani S.M., Shahraki M. *Current Organocatalysis*, 2016, **3**:52 [Google Scholar], [Publisher]
[41]. Shahraki M., Habibi-Khorassani S.M., Maghsoodlou M.T., Zarei T., Kazemidoost M.S.

American Journal of Chemistry and Applications, 2015, **2**:10 [Publisher]

[42]. Sajadikhah S.S., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., Willis A.C. *Chinese Chemical Letters*, 2012, **23**:569 [Crossref], [Google Scholar], [Publisher]

[43]. Schwartz L.M., Gelb R.I. *Anal Chem*., 1978, **50**:1592 [Crossref], [Google Scholar], [Publisher]

[44]. Lerveny C., Ruzicka V. *Adv Catal*., 1981, **30**:335 [Crossref], [Google Scholar], [Publisher]

[45]. Mortimer M., Taylor P. *Chemical Kinetics and Mechanism*, *The Royal Society of Chemistry, homas Graham House, Science Park, Milton Road, Cambridge, CB4 OWF, UK,* 2002 [Google Scholar], [Publisher]

[46]. Azab H.A., Ahmed I.T., Mahmoud M.R. *J Chem Engineering Data*, 1997, **42**:593 [Crossref], [Google Scholar], [Publisher]

[47]. Chester W.S., Alberto V., Wiebe H. A., Julian H. *Journal of the American Chemical Society*., 1973, **95**:13 [Crossref], [Google Scholar], [Publisher]

How to cite this manuscript: Younes Ghalandarzehi*, Halime Kord-Tamandani. Effect of solvents on kinetics and mechanistic investigation of highly substituted piperidines: spectrometry approaches. *Asian Journal of Green Chemistry*, 7(2) 2023, 70-84. DOI: 10.22034/ajgc.2023.380483.1366