



## Original Research Article

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

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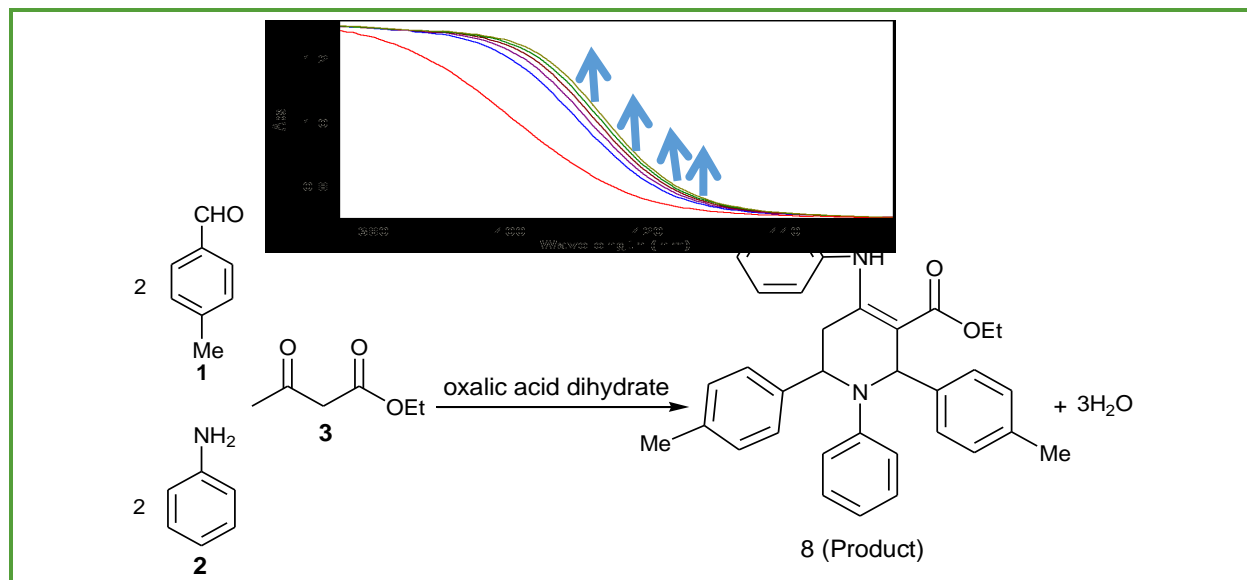
Piperidine

## 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 cellulose, 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.

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## Graphical Abstract



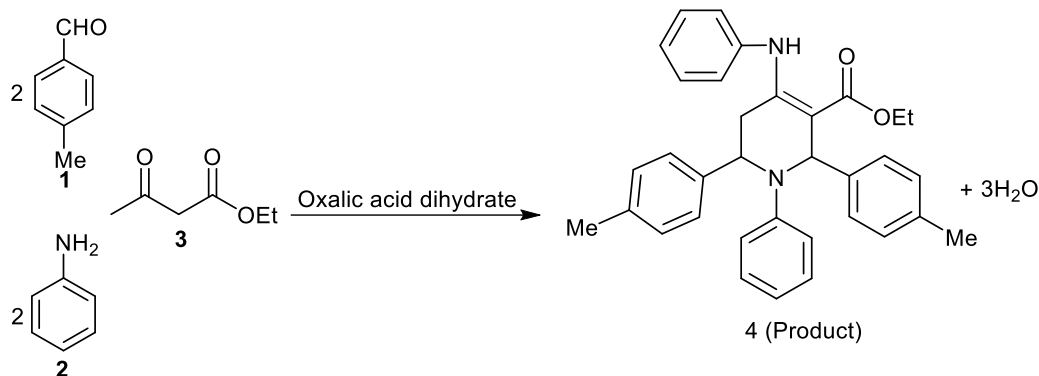
## Introduction

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 dihydrate. 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 dihydrate 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,  $8 \times 10^{-3}$  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  $2 \times 10^{-2}$ ,  $2 \times 10^{-2}$ , and  $1 \times 10^{-2}$  M solutions of compounds **1**, **2**, and **3**, respectively along with  $8 \times 10^{-3}$  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

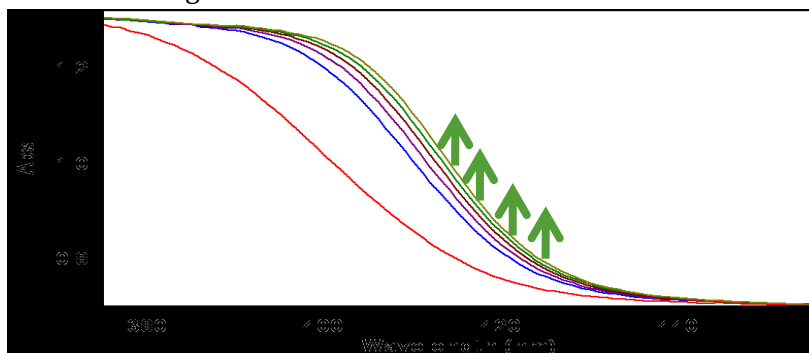
appropriate wavelength was found to be 420 nm (corresponding mainly to product **8**). Since at this wavelength, compounds **1**, **2**, **3**, and oxalic acid dihydrate have relatively no absorbance value, provided the opportunity to fully investigate the kinetics of the reaction and also to find the 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 ( $10^{-3} \text{ M} \leq \text{M product} \leq 10^{-2} \text{ M}$ ) 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 ( $k_{\text{obs}} = 92.4 \text{ min}^{-1} \cdot \text{M}^{-1}$ ) 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.

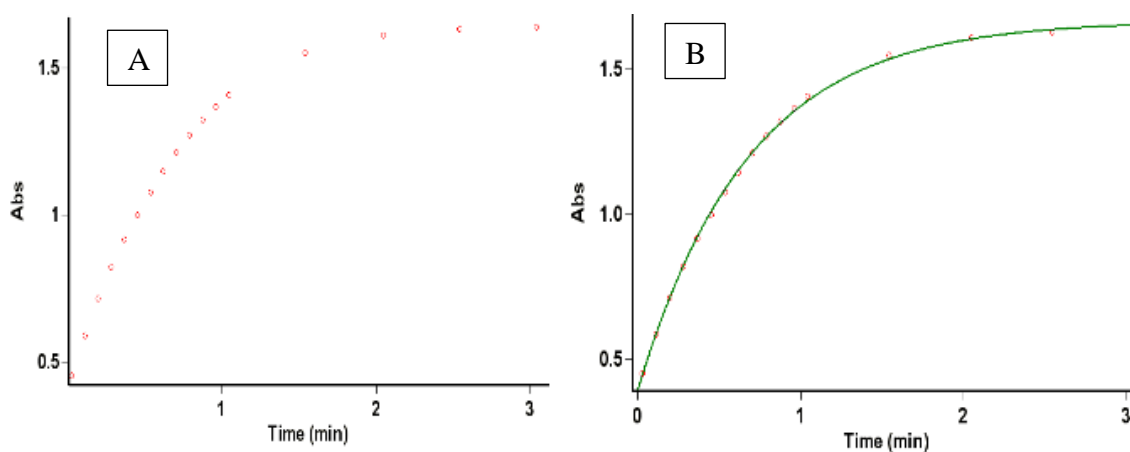
In this case, overall order of rate law can be written as:

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

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



**Figure 2.** The UV-vis spectra of the 4-methylbenzaldehyde **1** ( $2 \times 10^{-2}$ ), aniline **2** ( $2 \times 10^{-2}$ ), and ethyl acetoacetate **3** ( $1 \times 10^{-2}$ ) reaction in ethanol in the presence of the catalyst oxalic acid dihydrate ( $8 \times 10^{-3}$ ) 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** ( $2 \times 10^{-2}$ ), **2** ( $2 \times 10^{-2}$ ), and **3** ( $1 \times 10^{-2}$ ) in the presence of oxalic acid dihydrate ( $8 \times 10^{-3} \text{ M}$ ) at 20 °C and 420 nm in ethanol

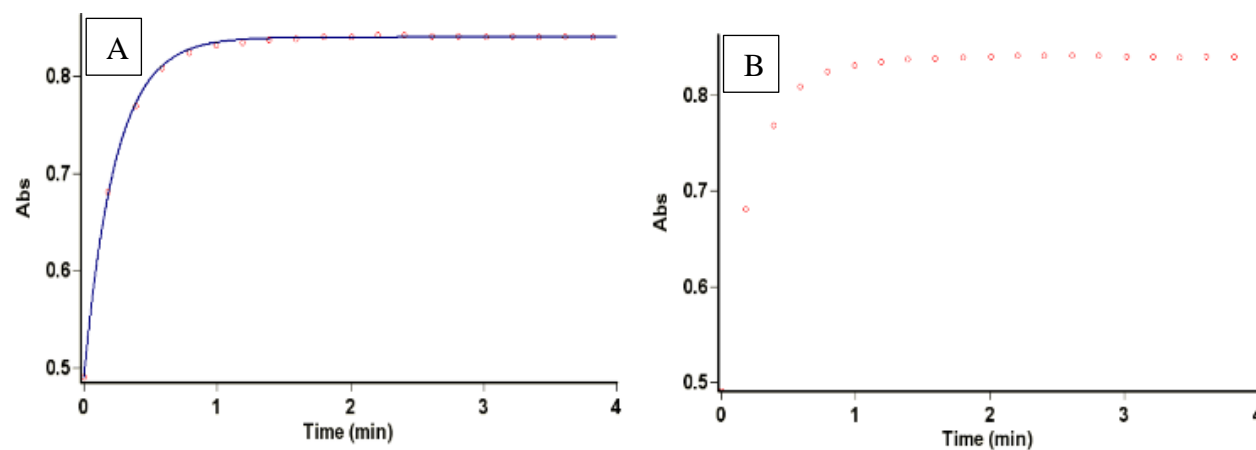
## Results and Discussion

### 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**) ( $2 \times 10^{-2}$  M), (**2**) ( $2 \times 10^{-2}$  M), and (**3**) ( $5 \times 10^{-3}$  M) in the presence of oxalic acid dihydrate ( $8 \times 10^{-3}$  M) at 20 °C in ethanol. Under a pseudo-order condition, the rate law is conceivable in this scenario.

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

Figure 4A can be used to determine the infinity absorbance ( $A^{\infty}$ ), or the absorbance at



**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** ( $2 \times 10^{-2}$ ), **2** ( $2 \times 10^{-2}$ ), and **3** ( $5 \times 10^{-3}$ ) in the presence of oxalic acid dihydrate ( $8 \times 10^{-3}$  M) at 20 °C proceeded in ethanol

The same procedure was used with concentrations of ( $2 \times 10^{-2}$  M, reactant **1**), ( $2 \times 10^{-2}$  M, reactant **2**), and ( $10^{-3}$  M, reactant **3**) in the presence of oxalic acid dihydrate ( $8 \times 10^{-3}$  M) to confirm the previous result using a different concentration of ethyl acetoacetate **3**. The identical findings are presented in Table 1

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**,  $\alpha=0$ , it is clear that the reaction is of zero order. Observation rate constant ( $k_{\text{obs}} = 93.1 \text{ min}^{-1} \cdot \text{M}^{-1}$ ) is used here was calculated automatically using the predefined standard equations in the software [43]. As is evident  $k_{\text{obs}}=93.1 \text{ min}^{-1} \cdot \text{M}^{-1}$ ,  $k_{\text{obs}} = 92.4 \text{ min}^{-1} \cdot \text{M}^{-1}$  are roughly equivalent, which was discovered through earlier research.

together (The comparison of the rate constants ( $k_{\text{obs}}$ ) 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 =  $k_{\text{ovr}} [2]^\beta [1]^\gamma [\text{cat}] = k_{\text{obs}} [2]^\beta [1]^\gamma = k_{\text{obs}} [2] [1]$   
if

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

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

**Table 1.** Rate constant ( $k_{\text{obs}}$ ) 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 dihydrate	$k_{\text{obs}}$ (min <sup>-1</sup> .M <sup>-1</sup> )
1	(2×10 <sup>-2</sup> M)	(2×10 <sup>-2</sup> M)	(10 <sup>-2</sup> M)	(8×10 <sup>-3</sup> M)	92.4
2	(2×10 <sup>-2</sup> M)	(2×10 <sup>-2</sup> M)	(5×10 <sup>-3</sup> M)	(8×10 <sup>-3</sup> M)	93.1

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

$(\lambda)$ (nm)	Solvent	$\epsilon(D)$	$k_{\text{obs}}$ (min <sup>-1</sup> .M <sup>-1</sup> )				
			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 ( $\epsilon = 32.70$ , 25 °C) is lower than that in ethanol ( $\epsilon = 24.55$ , 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  $\ln k_1$ , 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



















