Letters in Organic Chemistry, 2014, *11*, 413-421

Full Kinetics and a Mechanistic Investigation of the Synthesis of Tetrahydrobenzo[b]pyrans in the Presence of Sodium Acetate as a Catalyst by a One-pot Three-component Reaction

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Received May 20, 2013: Revised October 04, 2013: Accepted October 15, 2013

Abstract: Sodium acetate effectively catalyzes the three component reaction between 4-nitrobenzaldehyde, malononitrile and dimedone for the formation of corresponding pyran annulated heterocyclic systems. This method offers the advantages of proceeding in neutral and mild environmental conditions, lack of toxicity, short reaction time, giving high to excellent yields of the products and simple work-up. Moreover, for the first time, an investigation of the kinetics and mechanism was made for the reaction between 4-nitrobenzaldehyde **2**, malononitrile **3** and dimedone **1** compounds in the presence of sodium acetate as a catalyst. For determining the kinetics parameters of the reactions, they were monitored using UV/Vis spectrophotometery. The second order rate constant (k_1) was automatically calculated by the standard equations contained within the program. In the studied temperature range, the second order rate constant depended (Lnk_1, Lnk_1/T) on reciprocal temperature was in good consistency with Arrhenius and Eyring equations, respectively. This data provided the suitable plots for calculating the activation energy and parameters (Ea, $\Delta G^{\neq}$, $\Delta S^{\neq}$ and $\Delta H^{\neq}$) of the reaction. Furthermore, from studying the effect of solvent, concentration and catalyst on the reaction mechanism, useful information was obtained. The results showed that the first step of the reaction mechanism is a rate determining step (RDS). The mechanism which we proposed was confirmed in accordance with experimental data form UV/Vis experiment and also the steady state assumption.

Keywords: Dimedone, tetrahydrobenzo[b]pyran, Sodium acetate, 4-nitrobenzaldehyde, malononitrile, Kinetics and Mechanistic Investigation, UV/Vis spectrophotometery.

1. INTRODUCTION

Tetrahydrobenzo[b]pyrans are an important class of organic compounds that attract considerable attention because of their wide range of biological activities. These compounds show anticoagulant, anticancer, spasmolytic, diuretic, and anti-ancaphylactia activities [1-3]. Polysubstituted tetrahydrobenzo[b]pyrans constitute a structural unit of a series of natural products [4]. They can also be used as cognitive enhancers for the treatment of neurodegenerative diseases such as Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [5]. Recently, there have been many methods reported for the preparation of chromenes and their derivatives three-component condensations including the use of microwave [6] and ultrasonic [7] irradiation, as well as catalysis by tetrabutylammonium bromide (TBAB) [8, 9], Tetra-methyl ammonium hydroxide (TMAH) [10], rare earth perfluorooctanoate [11], and ZnO-beta zeolite [12]. However, most of these methods have drawbacks, such as toxic catalysts, environmental pollution, and expensive catalyst, difficulty of preparation, unavailable reagents, prolonged reaction times, unsatisfactory yields, and harsh reaction conditions. Therefore, it is necessary to further develop an efficient one-pot multi-component synthesis of tetrahydrobenzo[b]pyrans which is devoid of these problems. It is well known that homogeneous catalysts have gained increasing attraction in recent years due to their operational simplicity, low cost, ease of preparation and handling, stability, lack of toxicity, and economic and environmental advantages. As a part of our current studies on the development of efficient multi-component reactions for the preparation of interesting bioactive molecules [13-16], herein, we present a simple and efficient method for the synthesis of tetrahydrobenzo[b]pyrans *via* a one-pot three-component reaction between 4-nitrobenzaldehyde, malononitrile and dimedone in the presence of sodium acetate in a mixture of solvent H_2O: EtOH at 50 °C (Scheme **1**). Kinetics studies of these reactions are therefore important, but they have not yet been investigated. Hence, we now describe full kinetics and mechanistic of mentioned reaction in later section. Numerous kinetic investigations over a large area of different reactions have previously been reported using the UV/Vis technique [17-29].

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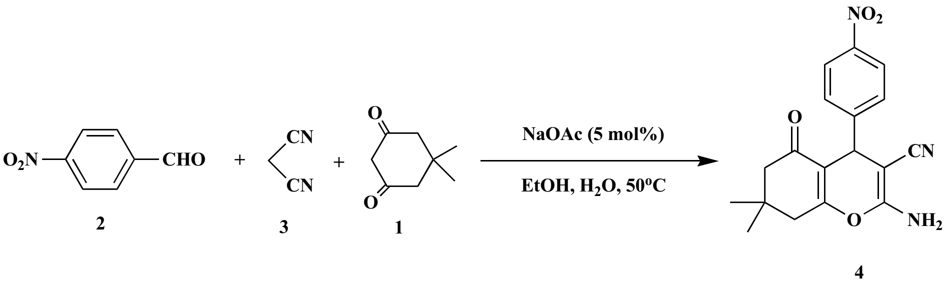
1875-6255/14 $58.00+.00



Scheme 1. Synthesis of tetrahydrobenzo[b]pyransin **4**.

Table 1. Syntheses of Tetrahydrobenzo[b] pyran 4 using Sodium Acetate as a Catalyst form the Reaction between 4-Nitrobenzaldehyde 2, Malononitrile 3 and Dimedone1

4-nitrobenzaldehyde	malononitrile	Dimedone	Product 4	Time 15 min	Yield [a] 98%	M.P observed(°C) 178-179	M.P reported(°C) 177-178 [9]

[a] Yield refers to the pure isolated product

2. EXPERIMENTAL

In order to optimize the reaction conditions, the reaction of 4-nitrobenzaldehyde **2** (1 mmol), malononitrile **3** (1 mmol), and dimedone**1** (1 mmol) was carried out using different quantities of sodium acetate under different conditions. It was found that the best results were obtained with 5 mol % sodium acetate under a mixture of water and ethanol (4:1, 5mL) at 50 °C (Table **1**). The reaction was completed within 15 min.

2.1. General Procedure for the Synthesis of Tetrahydrobenzo[b]pyrans

A mixture of a 4-nitrobenzaldehyde **2** (1 mmol), malononitrile **3** (1 mmol), dimedone **1**(1 mmol) and sodium acetate (5mol %) in a mixture of water and ethanol (4:1, 5mL) was heated for an appropriate length of time. During the procedure, the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the precipitated solid re-crystallized from ethanol to give compounding a high yield (**98%**).Spectroscopic data of product is given below.

2-Amino -7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-benzo[b]pyran:

Yield: 98 % = 0.333g; IR (KBr) υ: 3385(NH_2), 3250 (NH_2), 2955 (C-H), 2180 (C≡N), 1679 (C=O), 1211 (C-O). cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.04 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.15 (1H, d, J =16.0 HZ, H-6'), 2.28 (1H, d, J =16.0 HZ, H-6'), 2.57 (2H, s, CH_2), 4.30 (1H, s, H-4), 6.28 (2H, brs, NH_2), 7.25-8.30 (4H, m, Ar-H) ppm

3. RESULTS AND DISCUSSION

3.1. KINETICS STUDIES

For further insight into the reaction mechanism between 4-nitrobenzaldehyde **2**, malononitrile **3** and dimedone **1** in the presence of sodium acetate as a catalyst, using the UV/Vis spectrophotometry technique, full kinetics study of the reaction was done. Firstly, it was necessary to find the suitable wavelength for the kinetic study of the reaction. For this reason in the first experiment, 10^{-2} M solution of compounds **1**, **2**, **3** and 10^{-2} M solution of sodium acetate were prepared in methanol as solvent. The relevant spectrum of each compound was recorded over the wavelength range 190-600 nm. (Figs. **1-4**) exhibit the ultraviolet spectra of compounds **1**, **2**, **3** and sodium acetate, respectively. In the second experiment, the reaction mixture was added into a 10 mm black quartz spectrophotometer cell along with a 10^{-2} M solution of each compound (**1**, **2** and **3**) and 10^{-2} M sodium acetate according to stoichiometry of each compound in the overall reaction. The reaction was monitored by conducting scans of the entire spectrum with 10 second intervals during the whole reaction time at ambient temperature. The ultraviolet spectra shown in (Fig. **5**) are typical. Herein, the upward direction of the arrow indicates the progress of product versus time. From this, the appropriate wavelength was discovered to be 390, 405 and 410 nm. Since at these wavelengths, compounds **1**, **2**, **3** and sodium acetate have relatively no absorbance value, it gave us the chance to find the practical conditions that allowed kinetics and a mechanistic investigation of the reaction. Herein, in all the experiments, the UV/Vis spectrum of the compound product was measured over the concentration range (10^{-3}M ≤ M product ≤10^{-2}M) to confirm a linear relationship between the absorbance and concentration values.

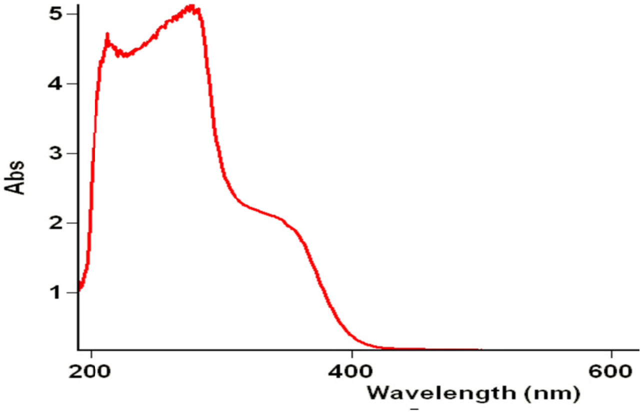


Fig. (1). The UV/Vis spectrum of 10^{-2}M, 4-nitrobenzaldehyde compound **2** in methanol.

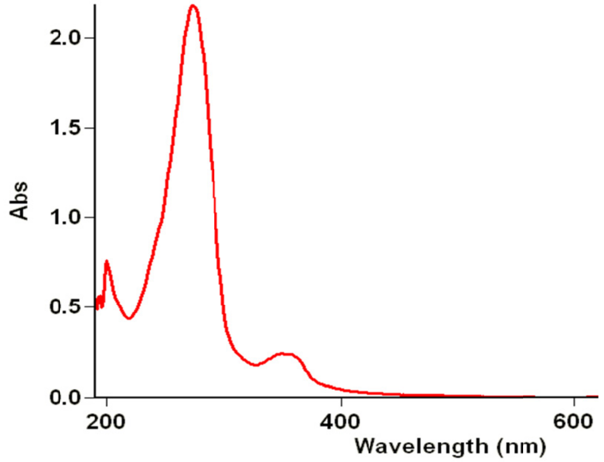


Fig. (2). The UV/Vis spectrum of 10^{-2}M, malononitrile compound **3** in methanol.

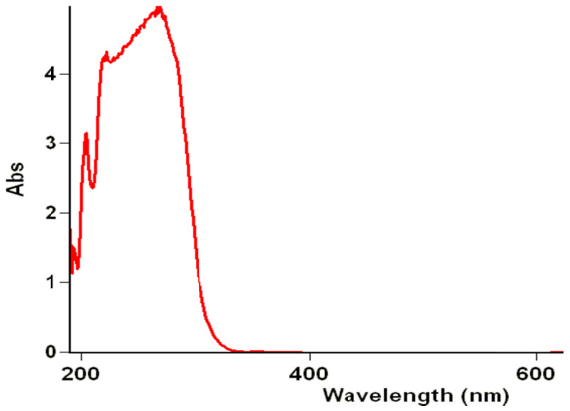


Fig. (3). The UV/Vis spectrum of 10^{-2} M, dimedone compound **1**in methanol.

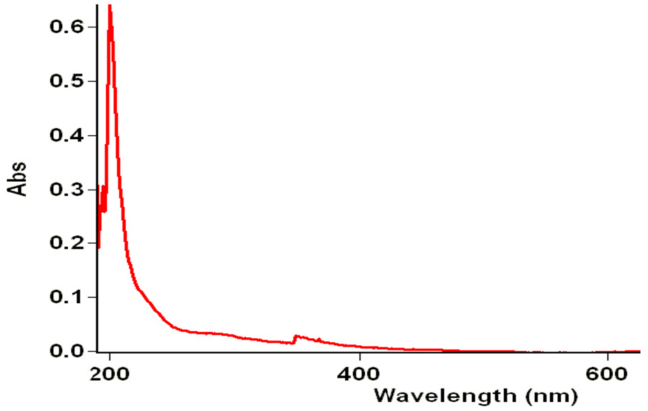


Fig. (4). The UV/Vis spectrum of 10^{-2}M, sodium acetate as a catalyst in methanol.

In the third experiment under same concentration of each compound (10^{-2}M), experimental absorbance curve was recorded versus time at 25°C temperature and wavelength 410 nm. This is shown in (Fig. **6**) (dotted line) which exactly fits to second order experimental curve (solid line). In this case, overall order of rate law (rate = $k_{ovr}[1]^{\gamma}[2]^{\beta}[3]^{\alpha}[Cat]$) (1) can be written as: $\alpha+\beta+\gamma= 2$. It is obvious that the reaction is of second order. Then the rate constant (19.6 $min^{-1}.M^{-1}$) of the reaction was automatically calculated by the software associated within the UV/Vis equipment.

3.2. Effects of Concentration

In order to obtain a partial order of reaction regarding malononitrile **3**, pseudo-order conditions were set for the reaction. So in the fourth experiment, we followed the reaction kinetics by plotting the UV/Vis absorbance versus time at wavelength 410 nm for the 10^{-2}M, 10^{-2}M and 10^{-3}M solution of each compound (**1**, **2** and **3**), respectively at 25.0°C along with 10^{-2}M solution of sodium acetate. For this case the rate law can be expressed:

$$\text{Rate} = k_{ovr}[\mathbf{3}]^{\alpha}[\mathbf{2}]^{\beta}[\mathbf{1}]^{\gamma}[\text{Cat}]$$

$$\text{Rate} = k_{\text{obs}}[\mathbf{3}]^{\alpha} \quad (2)$$

$$k_{obs} = k_{ove}\,[2]^{\beta}[1]^{\gamma}[\text{Cat}]$$

The infinity absorbance (A∞), is the absorbance at reaction completion, which is obtainable from (Fig. **7**) at t=35 min. With respect to this value, the zero, first or second curve fittings can be drawn automatically for the reaction using the software [30] associated with the UV/Vis instrument. The original experimental absorbance against time

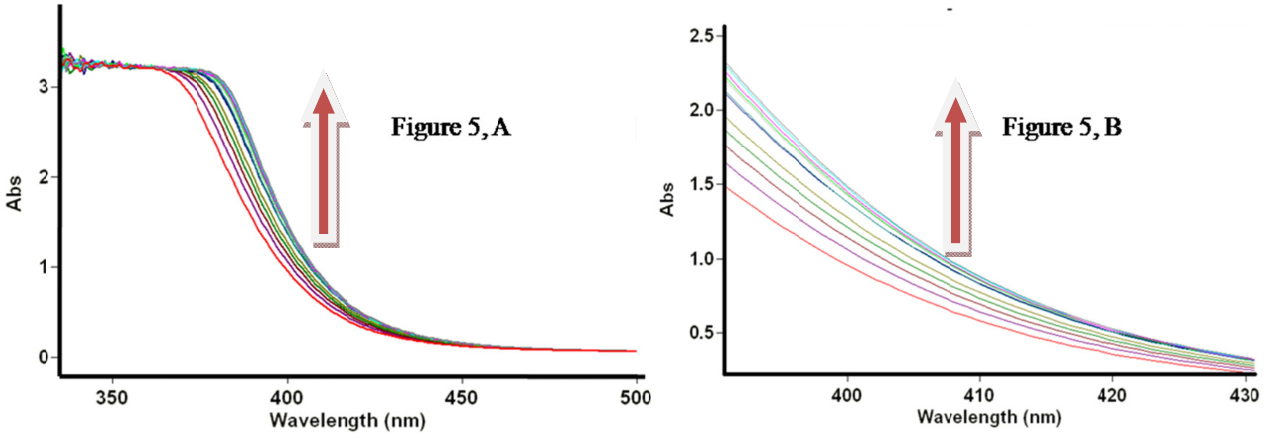


Fig. (5). A) The UV/Vis spectra of the reaction between 4-nitrobenzaldehyde **2** (10^{-2}M), malononitrile **3** (10^{-2} M**)** and dimedone **1** (10^{-2}M**)** in the presence of sodium acetate as a catalyst in methanol as a reaction proceed into a 10 mm light-path cell. **B)** Expanded section of UV/Vis spectra is over a wavelength range of 390-430 nm. Herein, the upward of direction of the arrow indicates that the progress of product versus times.

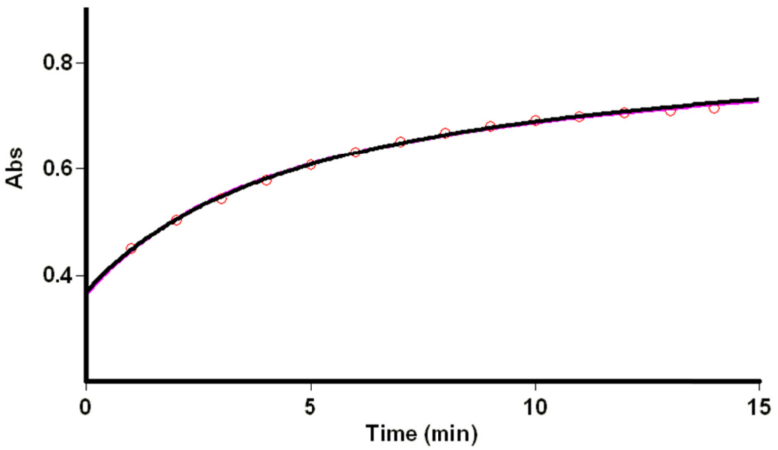


Fig. (6). The experimental absorbance change (dotted line) along with the fit curve (solid line) against time for the reaction between dimedone **1** (10^{-2}M), malononitrile **3** (10^{-2}M) and 4-nitrobenzaldehyde **2** (10^{-2} M), at 410nm, 25.0°C in methanol.

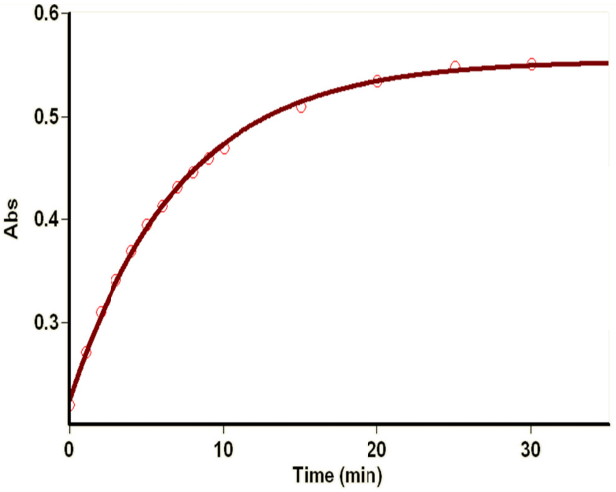


Fig. (7). First pseudo order fit curve (solid line) along with the original experimental curve (dotted line) in relation to malononitrile **3**, for the reaction between **1**, **2** and **3** which proceeded in methanol.

data made a pseudo-first-order available fit curve at 410 nm, which exactly fits the experimental curve (dotted line) displayed in (Fig. **7**). Herein, observation rate constant (k_{obs}) was automatically calculated by the equation (2) which has been defined in the software program. It is obvious that the reaction is of the first order type with respect to malononitrile **3**, α=1.

Also to gain a partial order of reaction with respect to 4-nitrobenzaldehyde **2**, (10^{-3}M), under pseudo-order condition, compounds **3** and **1**, were used in excess (10^{-2}M). Same procedure was employed as the one employed in previous experiment. The rate law can be written:

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

$$k_{\text{obs}} = k_{ovr}[\mathbf{3}]^{\alpha}[\mathbf{1}]^{\gamma}[\mathbf{Cat}] \qquad (3)$$

The original experimental absorbance against time data (Fig. **8**) creates a first order fit curve (full line) at 390nm, which fits the experimental curve precisely. Therefore, the reaction is of the first order type in relation to the 4-nitrobenzaldehyde **2**, β =1.

In the fifth experiment, the reaction was followed in the presence of an excess of compounds **3** and **2** (10^{-2}M of each) along with 10^{-3}M of compound **1**, so the rate low can be expressed:

$$\text{rate} = k_{ovr}[\mathbf{3}]^{\alpha}[\mathbf{2}]^{\beta}[\mathbf{1}]^{\gamma}[\text{Cat}] \qquad (4)$$

$$\text{rate} = k_{\text{obs}}[\mathbf{1}]^{\gamma}$$

$$k_{\text{obs}} = k_{ovr}[\mathbf{3}]^{\alpha}[\mathbf{2}]^{\beta}[\text{Cat}]$$

The experimental absorbance curve versus times was recorded at 25°C and wavelength 450 nm (Fig. **9**). Then the rate constant ($k=19.7\text{min}^{-1}.\text{M}^{-1}$) of the reaction was automatically obtained by the software program. The value of the rate constant was similar to that of the pervious experiment (Fig. **6**, for this case, concentration of each compound is same corresponding to 10^{-2}M). This curve led to similar fit curve and rate constant. In fact the experimental data indicated that the second order rate constant (k_{ovr}) of this reaction in equation 4 (page 4, equation 4 for 10^{-2}M compounds **2** and **3** and 10^{-3}M of compound **1**) for creating (Fig. **9**) is equal to the second order rate constant (k_{ovr}) (page 3, equation 1for 10^{-2}M concentration of each compound) at third experiment for obtaining (Fig. **6**). This is possible when γ is a zero in both equations 1 and 4. It means that the reaction is zero and of the second order type in relation to compound **1** and sum

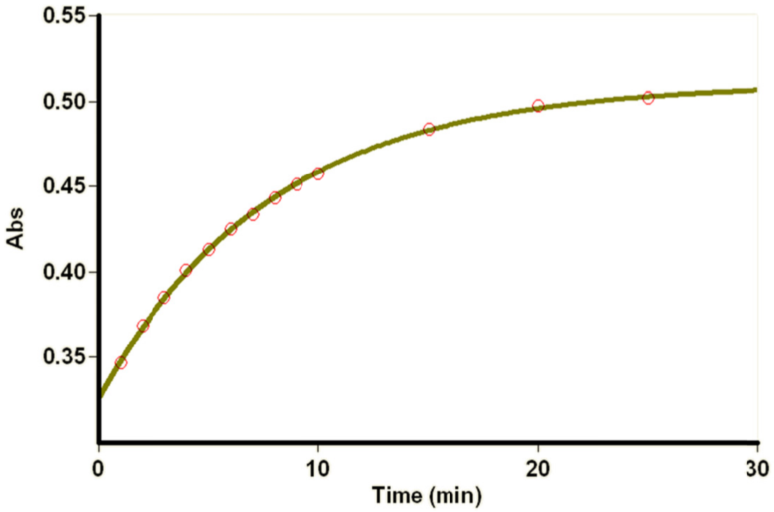


Fig. (8). First pseudo order fit curve (solid line) accompanied by the original experimental curve (dotted line) with respect to 4-nitrobenzaldehyde **2**, for the reaction between **1**, **3** and **2** which proceeded in methanol.

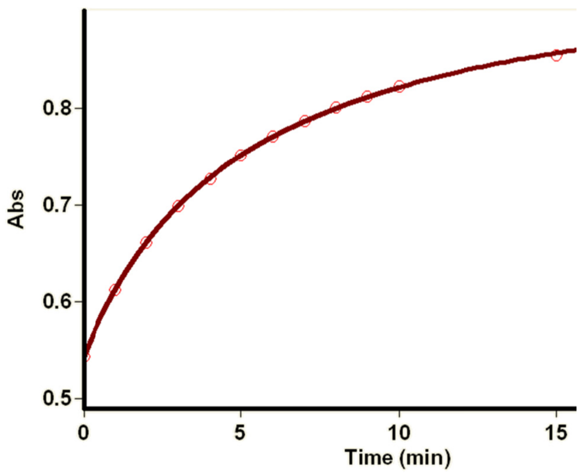


Fig. (9). Pseudo second order fit curve (solid line) along with the orginal experimental curved (dotted)for the reaction between dimedone **1** (10^{-3}M), malononitrile **3** (10^{-2}M) and 4-nitrobenzaldehyde **2** (10^{-2}M) at 450 nm and 25.0°C in methanol.

of **2** and **3** ($\alpha+\beta=2$), respectively. As a result, the overall order of reaction is two that is same with the previous experiment (third experiment).

Utilizing the above results, the simplified scheme of proposed reaction mechanism (Scheme **2**, [31-33]) as a possible explanation is shown in (Fig. **10**).

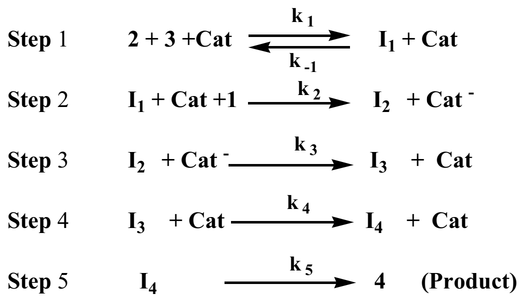


Fig. (10). The simplified Scheme for the proposed reaction mechanism [31-33].

To investigate which steps of the proposed mechanism is the rate-determining step, the rate law was written using the final step of reaction:

$$rate = k_5\,[I_4] \tag{5}$$

The steady state approximation can be applied for obtaining the concentration of $[I_4]$ which is generated from the following equations:

$$\frac{d[I_4]}{dt} = k_4[I_3][Cat] - k_5[I_4] = 0 \tag{6}$$

$$k_4[I_3][Cat] = k_5\,[I_4] \tag{7}$$

The value of equation 7 can be replaced in the equation 5 so the rate equation becomes:

$$\text{rate} = k_4[I_3][Cat] \tag{8}$$

For obtaining the concentration of intermediate $[I_3]$ the following equation is yielded by applying the steady state assumption:

$$\frac{d[I_3]}{dt} = k_3[I_2][\ Cat^-] - k_4[I_3][Cat] = 0 \text{ and } k_3[I_2][\ Cat^-] = k_4[Cat][I_3] \tag{9}$$

and with the replacement of the equation 9 in 8 the following equation is obtained:

$$\text{rate} = k_3[I_2][\ Cat^-] \tag{10}$$

and we can obtain the value of $[I_2]$ as below which can be replaced in the equation 10 for generation of equation 13

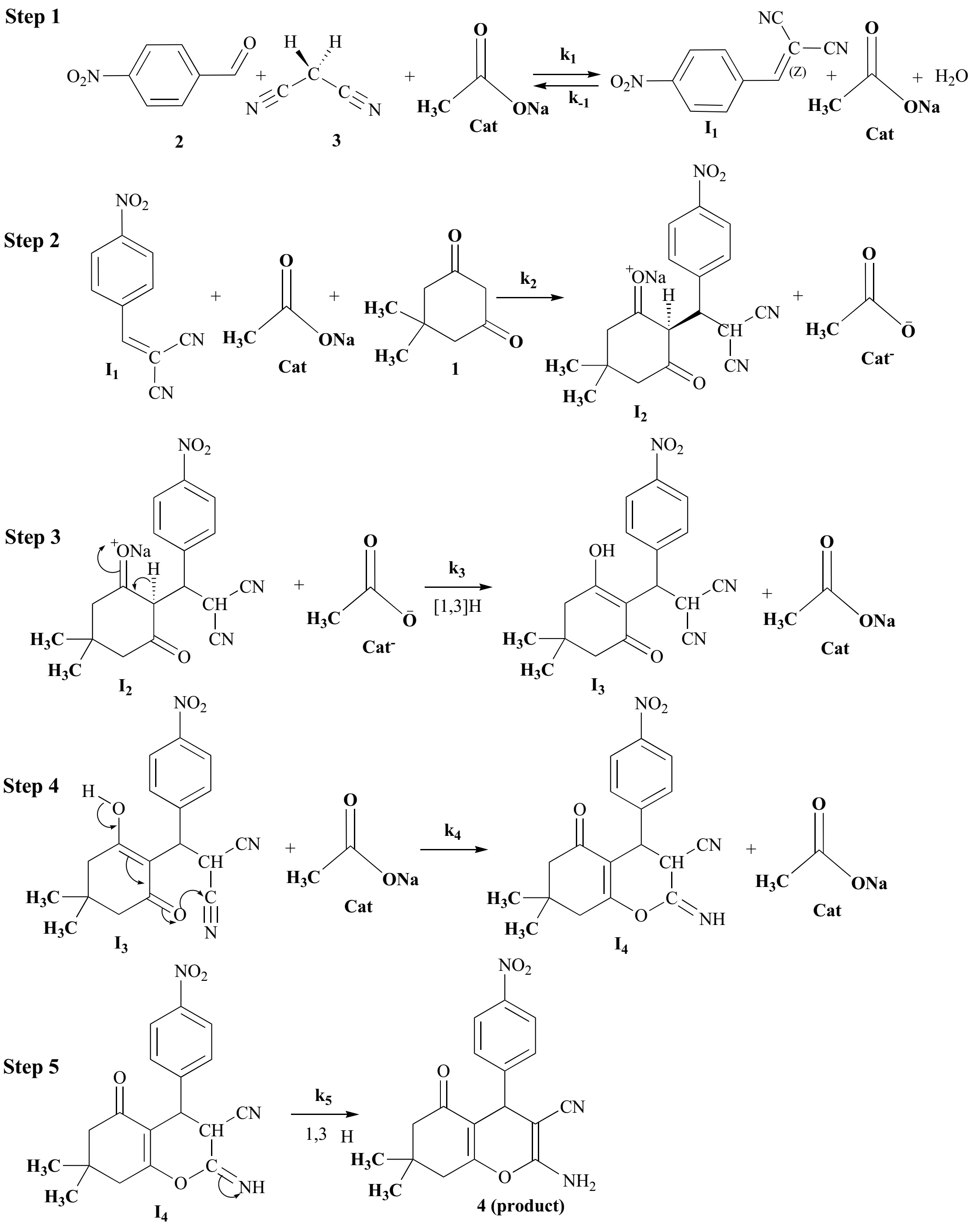
$$\frac{d[I_2]}{dt} = k_2[\ I_1][\ Cat][1] - k_3[I_2][Cat^-] = 0 \tag{11}$$

$$k_2[I_1][Cat][\mathbf{1}] = k_3[I_2][Cat] \tag{12}$$

$$\text{rate} = k_2[\ I_1][\ Cat\ ][\mathbf{1}] \tag{13}$$

The concentration of intermediate $[I_1]$ is obtained using state approximation and by substituting that in equation 13, equation 14 is yielded:

$$\frac{d[I_1]}{dt} = k_1[2][3][Cat] - k_{-1}\ [I_1][Cat] - k_2[I_1][1][Cat] = 0 \tag{14}$$



Scheme 2. A speculative proposed mechanism of the reaction between **1**, **2** and **3** for generation of 2-amino-5,6,7,8-tetrahydro-7, 7-dimthyl-4-(4-nitrophenyl) -5- oxo -4H –chromene -3-carbonitrile (**4**) [31-33].

$$[I_1] = \frac{k_1[2][3]}{k_{-1} + k_2[1]} \quad (15)$$

$$\text{rate} = \frac{k_2[1][\text{Cat}] \times k_1[2][3]}{k_{-1} + k_2[1]} \quad (16)$$

k_4, k_5 and k_3 are not found in equation 16, therefore the rate constants have no chance to be a rate determining step, nevertheless if $k_2 >> k_{-1}$ the following equations can be obtained:

$$\text{rate} = k_1[\mathbf{2}][\mathbf{3}][\text{Cat}] \text{ and , } k_{\text{ove}} = k_1[\text{Cat}] \quad (17)$$

$$\text{so: rate} = k_{\text{ovr}}[\mathbf{2}][\mathbf{3}] \quad (18)$$

The final equation 18 indicates that the overall order of the reaction is two, additionally, in accordance with this equation; the order of reaction with respect to each compound (**3**, **2** and **1**) is 1, 1 and zero, respectively which was previously confirmed by the experimental data. Because of the presence of k_1 in the rate law (18), it becomes obvious that first step (k_1) is a rate determining step. In this case, the transition state (see step 1, Scheme **2**) in reaction carries a

Table 2. The Activation Parameters Involving $\Delta G^{\#}$, $\Delta S^{\#}$and $\Delta H^{\#}$for the Reactions between 1, 2 and 3 in Methanol at *410* nm and 298.15K

Reaction	$\Delta G^{\#}$ (kJ.mol^{-1})	$\Delta H^{\#}$ (kJ.mol^{-1})	$\Delta S^{\#}$ (kJ.mol^{-1}.K^{-1})
1, 2 and 3	54.07	43.56	- 0.0352

Table 3. Rate Constants for the Reaction between 4-nitrobenzaldehyde 2 (10^{-2}M), Malononitrile 3 (10^{-2}M) and Dimedone 1, (10^{-2}M) in the Presence of Sodium Acetate (as a Catalyst) and Both Solvents Methanol and a Mixture of Ethanol and Water (1:1)

Solvent	ε	$k_1\times10^2(min^{-.1}m\text{-}^{1})$				
		T=15°C	T=20°C	T=25°C	T=30°C	T=35°C
Methanol	32.6	10.72	12.71	20.9	28.75	36.5
ethanol: water, 1:1	52.12	23.3	69.7	120.4	171.0	220.7

Table 4. Effect of Various Catalysts on a Reaction between 1, 2 and 3 Compounds in Methanol Solvent

Catalyst		$k_1\times10^2(min^{-.1}m\text{-}^{1})$				
				T=25°C		
$NaCH_3CO_2$				19.6		
of Zn $(CH_3CO_2)_2$				6.63		

dispersed charge, effect of solvent (a mixture of water and ethanol, 50%/50%) which has higher dielectric constant (ε=52.12) rather than methanol (with lower dielectric constant ε = 32.6) on this dispersed charge would be much stronger compared to that on reactants (2 and 3) that do not have any charge. The solvent thus stabilizes the species at the transition state more than it does the reactants, and therefore *E*a would be lower, and speeding up the reaction rate (see Table **3**, effect of both solvents). As is evident, the concentration of sodium acetate as a catalyst appears in the overall rate constant equation 1, since, at the end of mechanism (Scheme **2**) sodium acetate is generated once again, its concentration remains constant. With respect to equation 18, k_1 is proportional to the overall reaction rate, therefore, the activation parameters which involve $\Delta G^{\#}$, $\Delta S^{\#}$ and $\Delta H^{\#}$ can now be calculated for the first step (rate determining step, k_1), as an elementary reaction, on the basis of Eyring equation. The results are accumulated in (Table **2**).

3.3. Effect of Solvents and Temperature

In order to determine the effect of change in temperature and solvent environment change on the reaction rate, various experiments were performed with different temperatures and solvent polarity under the same conditions with the previous experiment. For this purpose, lone methanol and a mixture of ethanol and water (1:1) have been used in the experiment. The results showed that rate of reaction speeds up in solvent with high dielectric constant (a mixture of ethanol and water) with respect to lower dielectric constant (methanol) at all temperatures investigated (see Table **3**).

As is evident from this Table, the rate of reaction in each solvent increases at higher temperatures. In the studied temperature range, the second-order equation rate constant (Ln k_1) of the reaction was inversely proportional to the temperature, which is agreement with the Arrhenius equation. This behavior is show in (Fig. **11**). The activation energy, for the reaction between **1**, **2** and **3** was obtained (46.2 kJ.mol^{-1}) forming the slope of (Fig. **11**).

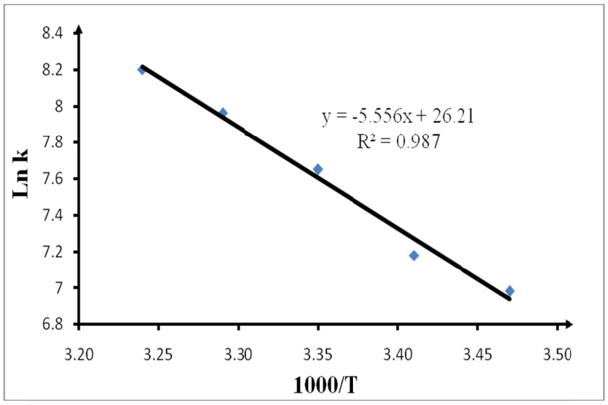


Fig. (11). The Dependence of the second order rate constant (Ln k_1) on reciprocal temperature for the reaction between compounds **1**, **2** and **3** measured at a wavelength of 410 nm in methanol according to the Arrhenius equation.

3.4. Effect of Catalyst

Rate of reaction in the presence of Zn $(CH_3CO_2)_2$ as a second catalyst in both solvents was reduced in comparison with the first catalyst ($NaCH_3CO_2$). It seems that Zn^{+2} ions have more interactions with polar solvent in relation to Na^+ ions. This reduces down the rate of reaction in the second catalyst media (see Table **4**).

4. CONCLUSION

In summary, we report a novel three-component one-pot synthesis of functionalized tetrahydrobenzo[b]pyran in the presence of NaOAc as a highly effective base catalyst under thermal conditions. There is no doubt that NaOAc is an effective catalyst and provides a new and useful method to synthesis of pyran annulated heterocyclic systems by condensation of 4-nitroaldehydes, malononitrile and dimedone compounds. The catalyst shows environmental friendly character, which is inexpensive, clean, safe, nontoxic and easily obtained. Moreover, the procedure offers several advantages including high yields, operational simplicity, clean reaction conditions and minimum pollution of the environment, which make it a useful and attractive process for the synthesis of these compounds. Kinetic investigation of recent reactions was undertaken using UV spectrophotometry. The results can be stated as follow:

1). The overall order of the reaction followed second-order kinetics and the reaction orders of each of the reactants 4-nitrobenzaldehyde **2**, malononitrile **3** and dimedone **1** compounds are one, one and zero, respectively.

2). The overall rate constants of all reactions were calculated successfully at all investigated solvents and temperatures.

3). In solvents with higher dielectric constants, the rates of all reactions increased and this can be related to the stabilization differences of the reactants and the activated complex by the solvent in the transition state.

4). Based on the experimental data, the first step of suggested mechanism was identified as a rate-determining step (k_1) and this was confirmed by the steady-state assumption.

5). The activation parameters of the reaction which involve $\Delta G^{\#}$, $\Delta S^{\#}$ and $\Delta H^{\#}$ have been calculated.

6). The rate of reaction speeds up in the presence of catalyst with more charge potential (counter ion Zn^{+2} versus Na^{+}).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Research Council of the University of Sistan and Baluchestan.

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