

## Kinetic Investigation of the Synthesis Reaction of 2-phenyl-1H-benzo[d]imidazole Catalyzed by Xylose

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For the first time, xylose has been used as green and biodegradable catalyst for the synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives using 1, 2-phenylenediamine and arylaldehydes in H<sub>2</sub>O under thermal condition. This procedure has many advantages such as easy work-up, inexpensive materials, use of non-toxic catalyst and eco-friendly conditions. To specify the kinetic parameters of the reaction, it was monitored by the UV spectrophotometry method. Based on the experiment data, the order of reaction with respect to each reactant (1 and 2) is 1, 1 and overall order of the reaction is two. The reaction was followed at different temperatures and the correlate of overall rate constant ( $\ln k_{\text{ovc}}$ ) and ( $\ln k_{\text{ovc}}/T$ ) on reciprocal temperature was in a good agreement with Arrhenius and Eyring equations, respectively. This provided (data) the suitable plots for calculate the activation energy ( $E_a$ ) and parameters ( $\Delta S^\ddagger$ ,  $\Delta H^\ddagger$ ,  $\Delta G^\ddagger$ ). In addition, useful information was obtained regarding mechanism of reaction from studying the effect of solvent, concentration and catalyst. The proposed mechanism was confirmed according to the obtained results and the steady state approximation and the first and second steps ( $k_1$ ,  $k_2$ ) of the reactions were recognized as the rate determining steps.

**Key words:** Kinetics, Mechanism, Catalyst, Xylose

Imidazoles are the main structures of many biological systems<sup>1</sup>, The correctness of imidazole in natural products and pharmacologically active compounds has resulted in a number of synthetic approaches to these compounds. They act as inhibitors of p38 MAP kinase<sup>2</sup>, B-Raf kinase<sup>3</sup>, transforming growth factor b1 (TGF-b1) type 1 active in receptor-like kinase (ALK5),<sup>4</sup> cyclooxygenase- 2 (COX-2)<sup>5</sup> and biosynthesis of interleukin-1 (IL-1)<sup>6</sup>. Appropriately substituted imidazoles are extensively used as glucagon receptors<sup>7</sup> and CB1 cannabinoid receptor antagonists<sup>8</sup>, modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR)<sup>9</sup>,

antibacterial<sup>10</sup> and antitumor<sup>11</sup> agents and also as pesticides<sup>12</sup>. While many strategies are available for benzimidazole synthesis<sup>13-22</sup>, there are two general methods for the synthesis of 2-substituted benzimidazoles. One is the coupling of phenylenediamines and carboxylic acids<sup>23</sup> or their derivatives (nitriles, imidates, or orthoesters),<sup>24</sup> which often requires strong acidic conditions, and sometimes combines with very high temperatures or microwave irradiation<sup>25-28</sup>. The other way involves a two-step procedure that includes the oxidative cyclo-dehydrogenation of Schiff bases, which are often generated from the condensation of phenylenediamines and aldehydes. Because of the availability of a vast number of aldehydes, the condensation of phenylenediamines and aldehydes has been extensively used. While many published

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methods are effective, some of these methods suffer from one or more disadvantages such as high reaction temperature, prolonged reaction time, and toxic solvents etc. Therefore, the discovery of mild and practicable routes for synthesis of 2-substituted benzimidazoles continues to attract the attention of researchers. In continue of our research on application of different carbohydrates as green and biodegradable catalyst<sup>29-31</sup>, herein we report green synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives using 1,2-phenylenediamine and arylaldehydes in H<sub>2</sub>O under thermal condition in the presence of xylose (Scheme 1), (Scheme 2), along with full kinetics and a mechanistic investigation of the reaction by UV spectrophotometry technique.

#### Chemicals and Apparatus used

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a Bruker Avance DRX 400 MHz instrument. The spectra were measured in DMSO-d<sub>6</sub> relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points were determined in open capillaries with a electro thermal 9100 melting point apparatus. TLC was performed on Silica-gel polygram SILG/UV 254 plates. A Cary UV/Vis spectrophotometer model Bio-300 with a 10 mm light-path quartz spectrophotometer cell was employed throughout the kinetic investigation.

#### General procedure for the synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives

Xylose (20 mol%) were solved in H<sub>2</sub>O (3mL), then aldehyde (1 mmol) and *o*-phenylenediamine (1 mmol) were mixed in mentioned solution and the solution heated and stirred at 45 °C for appropriate time (monitored by TLC). When the reaction was finished, the solution

was cooled to r.t. The precipitated product was filtered off and recrystallized from ethanol to afford the pure product.

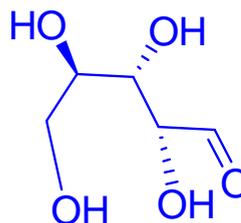
All of the compounds are known compounds. They were identified from their <sup>1</sup>H NMR spectroscopic data and by comparing their mps with those reported in the literatures.

2 - ( 3 - m e t h o x y p h e n y l ) - 1 H - benzo[d]imidazole (Table 2, Entry 2) <sup>1</sup>H NMR (400 MHz, (DMSO-d<sub>6</sub>): δ (ppm)= 3.83 (3H, CH<sub>3</sub>, s), 7.013-7.85 (8H, Ar, m), 0.99 (1H, NH, s).

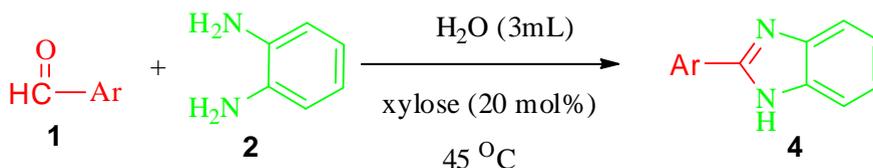
## RESULTS AND DISCUSSION

### Synthesis

In preliminary experiments, the model reaction of benzaldehydes and 1, 2-phenylenediamine in H<sub>2</sub>O was studied to establish the optimal conditions. The results are summarized in Table 1. In the absence of catalyst and temperature, only trace amount of the desired product was obtained, even after long reaction time (Table 1, entry 1). To determine the appropriate amount of catalyst, the model reaction was investigated with different quantities of xylose, such as 5, 10, 15, 20 and 30 mol% at different temperature. The results indicate that 20 mol% of xylose at 45 °C is the best to carry out the reaction efficiently (Table 1, entry4). The reaction was also examined in solvents such as H<sub>2</sub>O/ EtOH, and EtOH in which the reaction was sluggish and the product was obtained in a low yield.



Scheme 1. Structure of xylose



Scheme 2. Xylose catalyzed synthesis of 2-phenyl-1H-benzo[d]imidazole derivatives

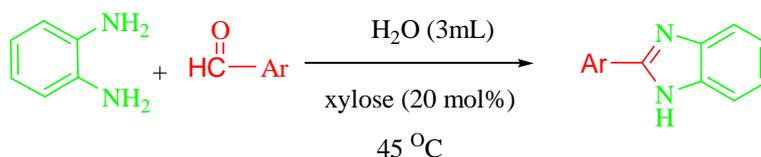
Using these optimized reaction, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted 2-phenyl-1H-benzo[d]imidazole derivatives using 1,2-phenylenediamine and arylaldehydes (Scheme 3). The results are summarized in Table 2.

### Kinetics

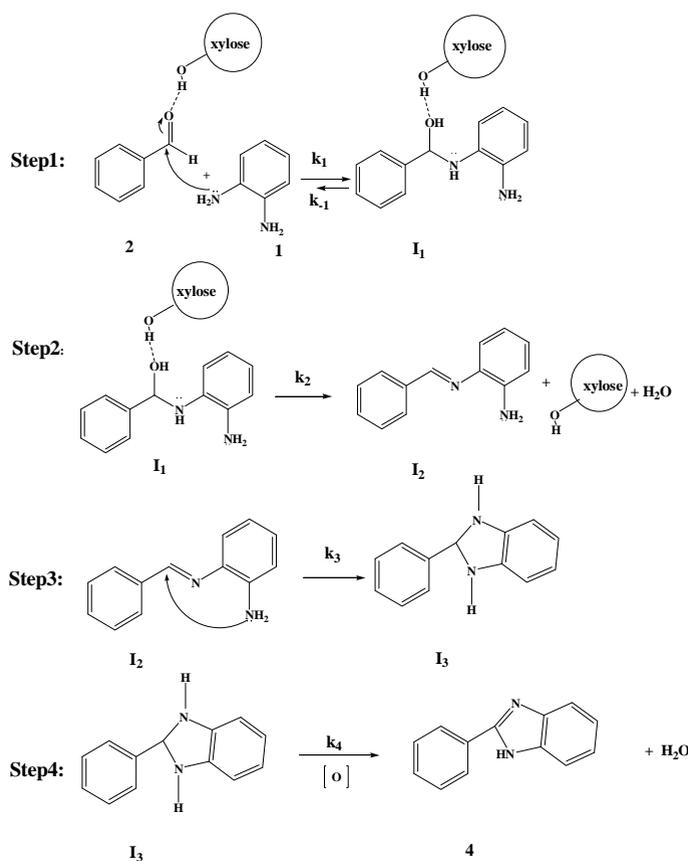
To get further insight into the reaction mechanism among 1, 2-phenylenediamine **2**, benzaldehyde **1** in the attendance of xylose as a catalyst, a kinetic etude of the reaction was undertaken by UV spectrophotometric method.

First it was require to find the suitable wavelength to follow the kinetic study of the reaction. For this cause in the first experiment,  $10^{-3}$  M solution of each compound **1**, **2** and  $2 \times 10^{-4}$  M solution of xylose were prepared in water as solvent. The relevant spectrum of each compound was recorded over the wavelength range 200-800 nm. Figs 1, 2 and 3 show the ultra violet spectra of compounds **1**, **2** and xylose (as a catalyst), respectively.

Also Fig. 4. show the ultra violet spectra of product (2-phenyl-1H-benzo[d]imidazole).



**Scheme 3.** Synthesis of substituted 2-phenyl-1H-benzo[d]imidazole derivatives in the presence of xylose in H<sub>2</sub>O at 45 °C

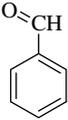
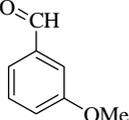
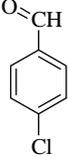
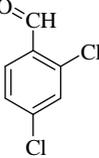
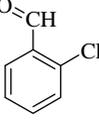
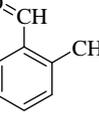


**Scheme 4.**

**Table 1.** Optimization of solvents and amount of catalyst in the synthesis of 2-phenyl-1H-benzo[d]imidazole

Entry	Solvent (mL)	Temperature (°C)	Catalyst (mol %)	Time	Isolated yields
1	H <sub>2</sub> O (3 mL)	Room temperature	-	24 hr	-
2	H <sub>2</sub> O	45	Xylose /5	50 min	45
3	H <sub>2</sub> O	45	Xylose/10	60 min	67
4	H <sub>2</sub> O	45	Xylose/20	60 min	80
5	H <sub>2</sub> O/EtOH(3:1)	70	Xylose /30	70 min	65
6	H <sub>2</sub> O	65	Xylose/ 20	2 hr	52
7	EtOH	65	Xylose/20	5 hr	20

**Table 2.** Synthesis of benzo[d]imidazole derivatives using xylose

Entry	Aldehyde	Time (min)	Isolated yields	Found M.P.(°C)	Lit.M.P (°C)] <sup>13-19</sup>
1		60	80	292-294	290-292
2		120	72	203-206	205-206
3		50	75	287-290	288-290
4		45	80	220-222	224-227
5		58	76	230-232	233-235
6		90	71	200-202	200-202
7		80	61	>300	>300

In the second experiment, first 1mL of aliquot  $6 \times 10^{-4}M$  of solution catalyst and 1mL of aliquot  $3 \times 10^{-3}M$  of solution compound 2 were first pipetted into a quartz spectrophotometer cell later 1mL of aliquot  $3 \times 10^{-3}M$  solution of reactant 1 (benzaldehyde) was added to the mixture according to stoichiometry of each compound in the overall reaction. The reaction was monitored by recording scans of the entire spectrum every 3 minutes during the whole reaction time at ambient temperature. The ultra-violet spectra shown in Fig.5. Here in, the upward direction of the arrow indicates the progress of product versus time. From this, the

**Table 1.** Values of the observed rate constants for the reaction between **1**, **2** and xylose in the presence of water solvent at temperature 10.0 °C investigated and 326 nm

$(\lambda)$ (nm)	Solvent	$k_{obs}$ (M.min <sup>-1</sup> )	
		10.0 °C*	SD
326 <sup>a</sup>	water	114.64	0.0019
326 <sup>b</sup>	water	117.50	0.0164

a: with these concentrations [( $10^{-3}$  M, compound **1**), ( $10^{-3}$  M, compound **2**) and ( $2 \times 10^{-4}$  M, xylose)]

b: with these concentrations [( $2 \times 10^{-3}$  M, compound **1**), ( $2 \times 10^{-3}$  M, compound **2**) and ( $2 \times 10^{-4}$  M, xylose)]

appropriate wavelengths were found to be 326, 330 and 340 nm (corresponding mainly to product 3). Since at this wavelengths, compounds 1, 2 and xylose have relatively no absorbance value, it provided the chance for full investigation of the kinetics of the reaction between 1, 2-phenylenediamine 2, benzaldehyde 1.

In the third experiment under same concentration of each compound ( $10^{-3}M$ ), experimental absorbance curve was recorded versus time at 25°C temperature and wavelength 340 nm.

Fig.6 shows the absorbance change (dotted line) versus time for the 1:1 addition reaction between 1, 2 at 25°C. The infinity absorbance ( $A_{\infty}$ ) that is the absorbance at reaction completion, can be obtained from Fig.6-A at  $t=9$  min. With respect to this value, zero, first, or second curve fitting could be drawn automatically for the reaction by the software associated<sup>32-33</sup> with the UV instrument. Using the original experimental absorbance versus time data provided a second-order fit curve (solid line) that fits exactly with the experimental curve (dotted line) as shown in Fig.6- Thus, the reaction between 1, 2-phenylenediamine 2, benzaldehyde 1 in presence xylose as a catalyst follows second-order kinetics. In this case, overall order of rate law can be written as:  $\alpha+\beta= 2$ .

**Table 2.** Values of the overall rate constants for the reaction between **1**, **2** and xylose in the presence of different solvents at all temperatures investigated and 340 nm

Wavelength(nm)	$\epsilon$ [(D)	$K_{obs}$ (M.min <sup>-1</sup> )			
		10.0 °C	15°C	20°C	25°C
Solvent: water					
340	80	117.67	163.88	254.66	357.06
Solvent: mix water/methanol(4:1)					
340	70.6	%	%	%	172.58
Solvent: mix water/ethanol(4:1)					
340	68.86	%	%	%	61.909

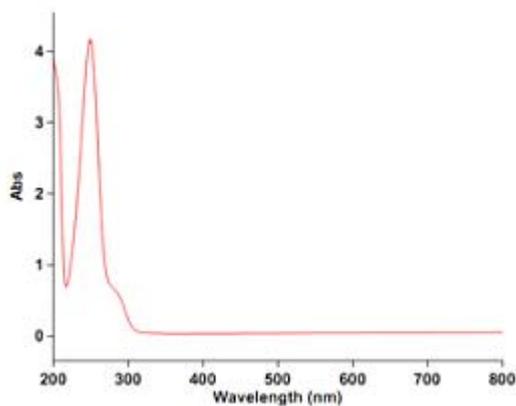
**Table 3.** Effect of various catalysts on a reaction between **1** and **2** compounds in the presence of in water solvent

catalyst	$K_{obs}$ (min. <sup>-1</sup> M) T=25°C	SD
xylose	358	0.0016
glucose	504	0.0029

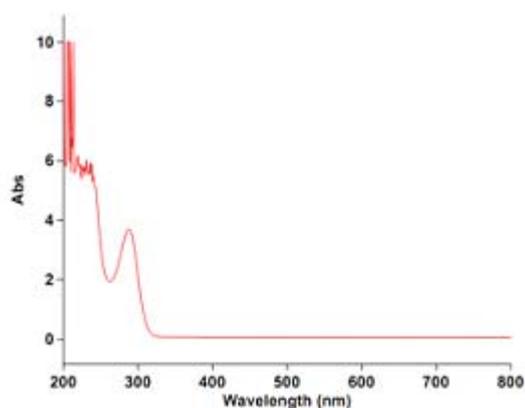
$$\text{Rate} = k_{ove} [1] [2] [cat]$$

$$k_{obs} = k_{ove} [cat] \quad \dots(1)$$

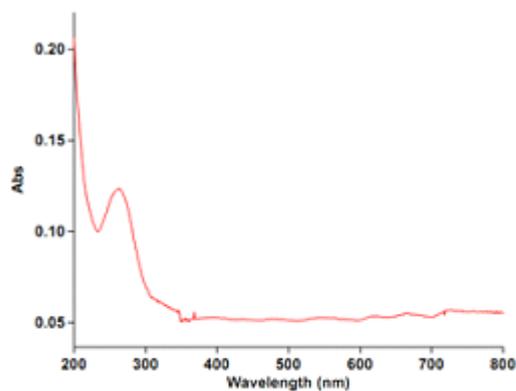
The repeat experiments were achieved at 10, 15, 20, 25 °C. The results ( $k_{obs}$ ) are accumulated in Table 2 at all temperature investigated, different solvent at 340 nm.



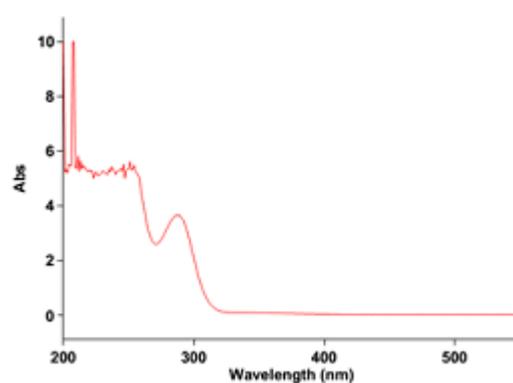
**Fig. 1.** The UV spectrum of  $10^{-3}$  M solution of benzaldehyde **1** in water



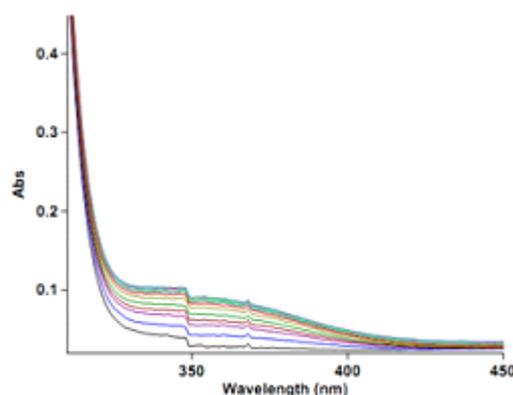
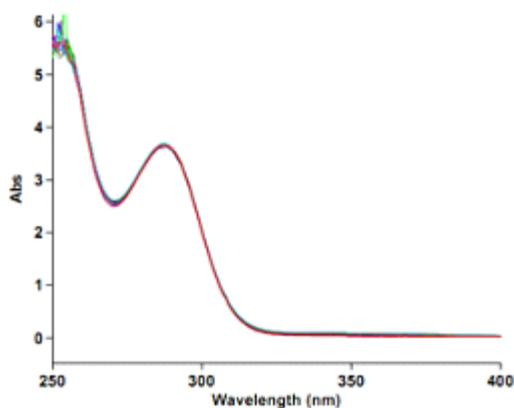
**Fig. 2.** The UV spectrum of  $10^{-3}$  M solution of 1,2-phenylenediamine **2** in water



**Fig. 3.** The UV spectrum of  $2 \times 10^{-4}$  M solution of xylose as a catalyst in water

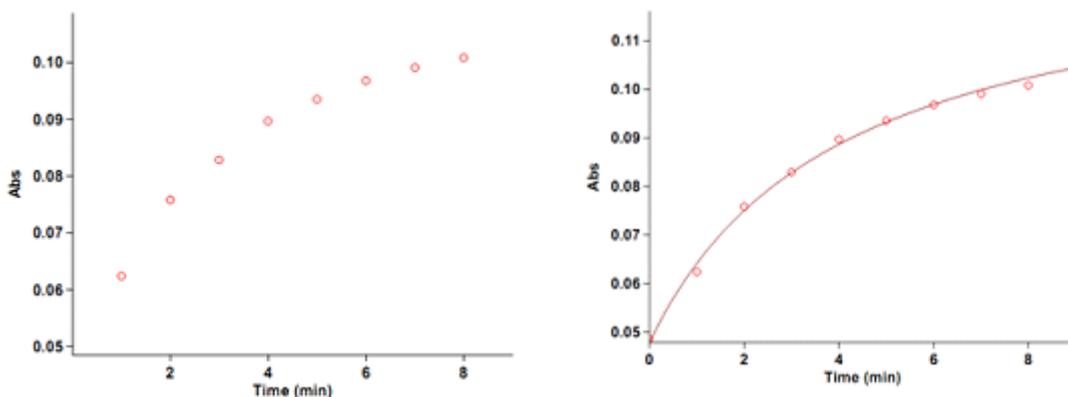


**Fig. 4.** The UV spectrum of 2-phenyl-1H-benzo[d]imidazole (product)

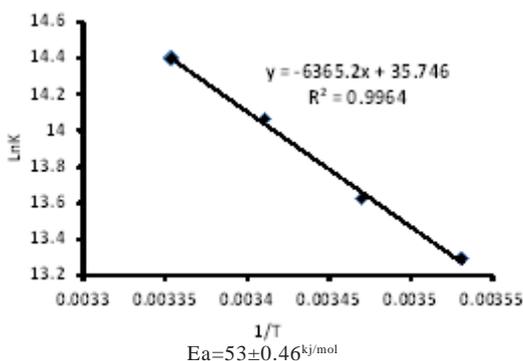


**Fig. 5. (A)** The UV spectra of the reaction between benzaldehyde **1** ( $10^{-3}$ ), 1,2-phenylenediamine **2** ( $10^{-3}$ ) in the presence of xylose as a catalyst in water as reaction proceeds with a 10 mm light-path cell.

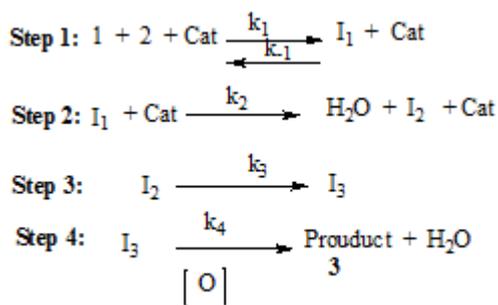
**(B)** Expanded section of UV spectra over the wavelength range 300-450 nm. Herein, the upward of direction of the arrow indicate that the progress of product versus times



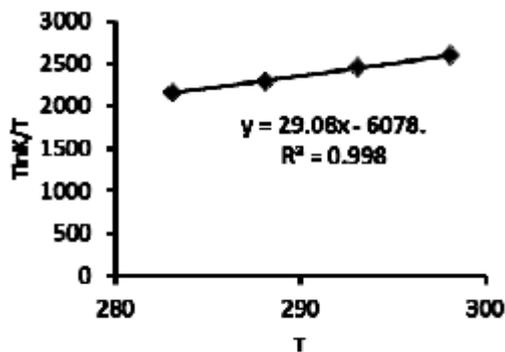
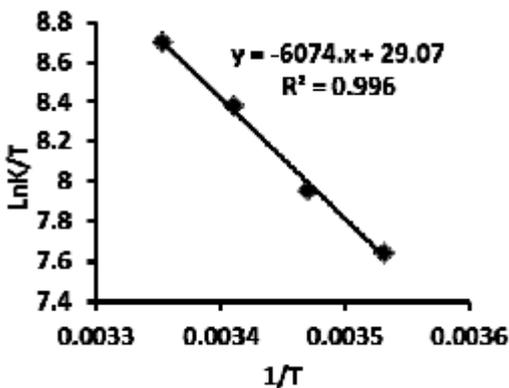
**Fig 6.** **A)** The original experimental absorbance curve versus time (dotted line). **B)** Second order fit curve (solid line) accompanied by the original experimental curve (dotted line), for the reaction between **1**( $10^{-3}$ ), **2** ( $10^{-3}$ ) and **3** ( $2 \times 10^{-4}$ ) which proceeded in water



**Fig. 7.** Dependence of second order constant ( $\text{Ln}k_{\text{obs}}$ ) on reciprocal temperature for the reaction between compounds **1** and **2** in the presence of xylose catalyst measured at wavelength 340 nm in accordance with Arrhenius equation



**Fig. 8.** The simplified Scheme for the proposed reaction between benzaldehyde **1**, 1, 2-phenylenediamine **2** in the presence of xylose in  $\text{H}_2\text{O}$



**Fig. 9.(A-B).** Eyring plats according to equation (15-16), for the reaction between **1**, **2** and xylose in the presence of water

### Effect of concentration

In order to determine the overall order of reaction ( $k_{obs}$ ), in the two separate experiments same procedure were employed with these concentrations [ $10^{-3}$  M, compound 1] and [ $10^{-3}$  M, compound 2] and also [ $2 \times 10^{-3}$  M, compound 1] and [ $2 \times 10^{-3}$  M, compound 2]. The same rate constants ( $k_{obs}$ ) were obtained from the relevant fit curves. The results ( $k_{obs}$ ) are accumulated in Table 1 at temperature 10.0 °C. As a result, in both experiments the second order of rate constants ( $k_{obs}$ ) is nearly same and independent of concentration.

### Effect of solvent and temperature

To determine the effect of change in solvent and temperature environment on the rate of reaction, it was needed to pay various experiments at different solvent polarity and temperature but otherwise under the same condition as for the previous experiment. For this cause, water with a dielectric constant (80 D) was chosen as a suitable solvent since it not only dissolved all compounds but also did not react with them.

The effects of solvent and temperature on the rate constant are given in Table 2. The results show that the rate of reaction in each solvent was increased at higher temperature also the rate of reaction between 1 and 2 was decreased in a lower dielectric constant environment (water & ethanol) in comparison with a higher dielectric constant environment (water & methanol) at all temperature investigated.

In the temperature range studied, the dependence of the second order rate constant ( $\ln k_{obs}$ ) of the reaction on reciprocal temperature consistent the Arrhenius equation, given activation energy ( $52.92 \text{ KJ.mol}^{-1}$ ). The activation energy, for this reaction was obtained from the slope of Fig. 7.

Utilizing the above results, the simplified scheme of the proposed reaction mechanism (scheme 3) as a possible explanation is shown in Fig. 8.

To investigate which steps of the proposed mechanism could be rate determining step (RDS), the rate law is written using the final step for the product:

...(2)

The steady state assumption can be employed for obtaining the concentration of  $[I_3]$

which is generated from the following equations

$$\frac{d[I_2]}{dt} = k_3[I_2] - k_4[I_3] = 0 \quad \dots(3)$$

$$k_3[I_2] = k_4[I_3], [I_3] = k_3 \frac{[I_2]}{k_4} \quad \dots(4)$$

The value of equation 4 can be replaced in the equation 2 so the rate equation becomes:

$$rate = k_3[I_2] \quad \dots(5)$$

For obtaining the concentration of intermediate  $[I_2]$  the following equations yielded by applying the steady state assumption:

$$\frac{d[I_2]}{dt} = k_2[I_1] - k_3[I_2] = 0 \quad \dots(6)$$

$$k_2[I_1] = k_3[I_2], [I_2] = \frac{k_2[I_1]}{k_3} \quad \dots(7)$$

And with there placement of the equation 7 in 5 the following equation is obtained:

$$rate = k_2[I_1] \quad \dots(8)$$

$$ra \frac{d[I_1]}{dt} = k_1[1][2][cat] - k_{-1}[I_1] - k_2[I_1] = 0 \quad \dots(9)$$

$$k_1[1][2][cat] - [I_1](k_{-1} + k_2), [I_1] = \frac{k_1[1][2][cat]}{(k_{-1} + k_2)} \quad \dots(10)$$

$$rate = \frac{k_1 k_2 [1][2][cat]}{(k_{-1} + k_2)} \quad \dots(11)$$

$$If : k_1 \rightarrow RDS \quad k_{-1} \ll k_2 \quad rate = k_1[1][2][cat] \quad \dots(12)$$

$$If : k_2 \rightarrow RDS \quad k_2 \ll k_{-1} \quad rate = \frac{k_1 k_2 [1][2][cat]}{(k_{-1})} \quad \dots(13)$$

The final equation (11) indicates that the overall order of the reaction is two which was formerly confirmed by the experimental data. Because of the presence of  $k_2$  in the rate law (11), it obvious that first step ( $k_2$ ) is a rate determining step and both  $k_1$  and  $k_{-1}$  should be the fast steps.

Hence, the activation parameters which involve  $\Delta G^\ddagger$ ,  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  can be now calculated for the reaction, on the basis of Eyring equation (15), Fig. 9.-A,  $\ln(k_{ove})/T$  versus  $1/T$  and also a different linearized form of Eyring equation (16), Fig. 10.-B,  $T \times \ln(k_{ove})/T$  against  $(T)^{3/4}$ . The results are

collected in Figure 9 (A, B). Statistical analysis of the Eyring equation clearly confirms that the standard errors of  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  correlate ( $T_{av}$  is the center of the temperature range used):

$$\sigma(\Delta S^\ddagger) = 1/T_{av} \sigma(\Delta H^\ddagger) \quad \dots(14)$$

$$\ln\left(\frac{k_1}{T}\right) = \left(\ln\frac{k_B}{h} + \frac{\Delta S^\ddagger}{R}\right) - \frac{\Delta H^\ddagger}{RT} \quad \dots(15)$$

$$\Delta H^\ddagger = 50.5 \pm 0.46 \text{ kJ/mol}$$

$$T \times \left(\frac{k_1}{T}\right) = T \times \left(\ln\frac{k_B}{h} + \frac{\Delta S^\ddagger}{R}\right) - \frac{\Delta H^\ddagger}{R} \quad \dots(16)$$

$$\Delta H^\ddagger = 50.5 \pm 0.46 \text{ kJ/mol}$$

It follows that in most solution phase studies  $\sigma(\Delta S^\ddagger) \approx \sigma(\Delta H^\ddagger) \times 0.003 \text{ K}^{-1}$ . This correlation has been mentioned elsewhere<sup>34-35</sup>. The standard errors for activation parameters have been calculated according to above instructions<sup>34-36</sup> and they have been reported along with this parameters in Fig.9. (A- B).

With respect to the vales of  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  (see Figure 9 (A- B)), ( $\Delta G^\ddagger = 37.3 \text{ kJ mol}^{-1}$ ) is reported for the reactions between **1** and **2** in the water solvent at 340 nm and 298.15 K.

#### Effect of catalyst

Rate of reaction was increased in the presence of glucose as a second catalyst in the water in comparison with the first catalyst xylose (see Table 3).

#### CONCLUSION

In summary, an efficient and simple method has been developed for the formation of highly functionalized 2-phenyl-1H-benzo[d]imidazole via two-component reaction under mild conditions using xylose as catalyst in water. This reaction can be employed as an efficient approach for the preparation of synthetically and pharmaceutically important benzimidazole systems. This methodology offered several advantages such as mild reaction conditions, easy work-up procedure, simple and readily available precursors; high atom efficiency, clean reaction profiles, non-toxic and inexpensive catalyst, and no need to column chromatography, environmentally friendly

catalyst and good to high yields. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-cancer and etc.

In addition, full kinetic and a mechanistic investigation of recent reaction was undertaken using UV spectrophotometry technique. The results can be summarized as follow:

- 1) The overall reaction order followed second-order kinetics.
- 2) The rates of all reactions increased in solvents with higher dielectric constant and this can be related to differences in stabilization of the reactants and the activated complex by the solvent in the transition state.
- 3) With respect to the experimental data, the first and second steps ( $k_1$ ,  $k_2$ ) of proposed mechanism was recognized as a rate-determining steps ( $k_1$ ,  $k_2$ ) and this was confirmed based upon the steady-state approximation.
- 4) Activation energy (53  $\text{kJ mol}^{-1}$ ) and parameters ( $\Delta G^\ddagger = 37.3 \text{ kJ mol}^{-1}$ ,  $\Delta S^\ddagger = 44.2$  and  $\Delta H^\ddagger = 50.5$ ) were calculated for the reaction.
- 5) Rate of reaction speed up of higher temperature.
- 6) The rate of reaction was accelerated in lower concentration at catalyst.

#### ACKNOWLEDGEMENTS

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