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Kinetics investigation of the synthesis reaction of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of acetic acid as a catalyst

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ABSTRACT

Acetic acid has been applied as an efficient catalyst and a green solvent for the two–component condensation reaction consisting of benzaldehyde, 2-amino-benzamide. The advantages of this protocol was excellent yield, short reaction time, mild reaction conditions, higher availability, low costs, more environmentally friendly, lack of need for column chromatography and simple work-up procedure. In addition, based on the spectral data, the partial order with respect to each reactant was one. Furthermore, useful information regarding the mechanism of the reaction was obtained from studies of the effect of solvent, concentration and catalyst on the rate of the reaction. The results showed that the first step of the mechanism was a rate-determining step. In the studied temperature range, the second order rate constant ($\ln k_1$, $\ln k_1/T$) depended on reciprocal temperature was in good agreement with the Arrhenius and Eyring equations. These data provided the suitable plots for calculating the activation energy (E_a = 52.80 kJmol^{-1}) and the related kinetic parameters ($\Delta G^{\ddagger}$ = 63.74 kJmol^{-1}, $\Delta S^{\ddagger}$ = -54.22 Jmol^{-1} and $\Delta H^{\ddagger}$ = 50.28 kJ mol^{-1}) of the reaction.

Keywords: *Catalyst, Kinetics, Mechanism, Green Solvent.*

1. Introduction

Quinazolin-4(3H)-ones are an important class of fused heterocycles with an array of biological activities such as inhibition of humane erythrocyte purine nucleoside phosphorylase [1] and poly (ADP-ribose) polymerase [2], treatment of diabetes and obesity [3], antagonist [4], anti-tumor [5], anti-inflammatory [6], insecticidal and antimicrobial activity [7]. In addition, these compounds can easily be oxidized to their quinazolin-4(3H)-one analogues [8], which also include important pharmacologically active compounds [9]. Several methods for the synthesis of these compounds have been reported. Among them, the general method includes condensation of aldehydes or ketones with 2-aminobenzamide in the presence of acid catalysts, such as $Sc(OTf)_3$ [10], NH_4Cl [11], *p*-TsOH [12], $CuCl_2$ [13] and $[Bmim]PF_6$ [14]. However, most of reported methods suffer from some limitations such as long reaction times, harsh reaction conditions, low yields, tedious workup and multistep reaction; some of them had to be performed in harmful organic solvent. Thus, development of a facile, atom-efficient, and eco-friendly method is highly desirable.

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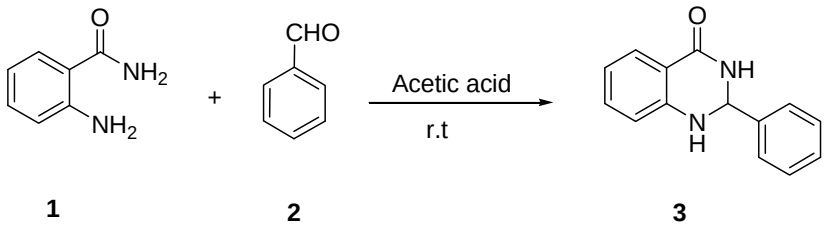
In continues of our systematic studies directed toward the development of practical, safe, and environmentally friendly procedures for several important organic transformations [15-17], we present a novel, mild, green approach, efficient and economically method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by the reaction of 2-aminobenzamide with benzaldehyde in the presence of acetic acid as a catalyst and a green solvent at room temperature (Scheme 1.). Recently, we have published kinetics investigations of some organic reactions as ylides [18-20]. These reactions occurred by at least three steps. The first step of the plausible mechanism was recognized as a rate-determining step and this was confirmed based upon the steady-state approximation. Moreover, the overall reaction order followed second-order kinetics, and also the rate of reaction was increased in solvents with upper dielectric constant value that could be related to the differences in stabilization of the reactants and the zwitterionic intermediate by the solvents.

In the current work for the first time, we describe kinetic results together with detailed mechanistic studies for the mentioned reaction based on a global kinetic analysis methodology using the UV-Vis spectrophotometry apparatus [18-20].



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Scheme 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

2. Experimental

2.1. Chemicals and apparatus

The benzaldehyde **1** and 2-amino-benzamide **2** were obtained from Merck (Darmstadt, Germany), and used without further purification. The pure solvents acetic acid and mixture of acetic acid/formic acid (1:1) were also obtained from Merck (Darmstadt, Germany). A Cary UV-vis spectrophotometer model Bio-300 with a 10 mm light-path quartz spectrophotometer cell was employed throughout the current work.

2.2. General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones

The mixture of 2-aminobenzamide (1 mmol), benzaldehyde (1 mmol), and acetic acid (3 cm^3) were stirred at room temperature. The progress of the reaction was monitored by TLC (ethyl acetate: petroleum ether 3:1). The reaction mixture was poured into 10 cm^3 ice water. On solidification, it was filtered, washed with ice water, and recrystallized from ethanol to give the pure 2,3-dihydroquinazolin-4(1*H*)-ones.

3. Results and Discussion

Acetic acid is a readily available and inexpensive reagent and can conveniently be handled and removed from the reaction mixture. Thus, the remarkable catalyst activities together with its operational simplicity make it the most suitable catalyst for the synthesis of 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one.

In the current work, initially benzaldehyde was used to react with 2-aminobenzamide in the presence of acetic acid (3 mL) as solvent and catalyst at room temperature to produce 2,3-dihydro-2-phenyl quinazolin-4(1*H*)-one in excellent yield (90%).

3.1. Kinetics

To gain further insight into the mentioned reaction mechanism, a kinetic study was performed by the UV spectrophotometry technique. First, it was necessary to find the appropriate wavelength to follow the kinetic of the reaction. For this reason, in the first experiment, 1.5×10^{-3} M solution of compounds **1**, **2** were prepared in acetic acid as solvent. The relevant spectra were recorded at the wavelength range between 200 to 800 nm.

In the second experiment, a reaction mixture was started into a 10 mm quartz spectrophotometer cell with 1.5×10^{-3} M of each reactants **1** and **2** in acetic acid as solvent with proportion to stoichiometry of each compound in overall reaction (Scheme 1). The reaction was monitored by noted scans of the consummate spectrum every 3 minutes during the whole reaction time at limited temperature (Fig. 1.). The adaption wavelengths were found to be 385 and 390 nm. Since at these wavelengths, reactants **1**, **2** and acetic acid have relatively no absorbance value, it provided the deliberation to quite investigate the kinetics of the reaction and also to find the practical conditions that permits a kinetics study of the reaction.

In the third experiment under same concentration of each reactant (1.5×10^{-3} M), experimental absorbance curve was recorded versus time at 25 ˚C temperature and wavelength 385 nm. Fig. 2 shows that the experimental curve (dotted line) exactly fits to the theoretical second order curve (solid line) [21]. In this case, overall order of rate low can be written as: $\alpha+\beta= 2$.

$$\text{Rate} = k_{ove}[1]^{\alpha}[2]^{\beta} \quad (1)$$

The experiments were repeated at 20, 25, 30, 35˚C. The results (k_{ove}) are accumulated in Table 1 at all temperature investigated and different solvent.

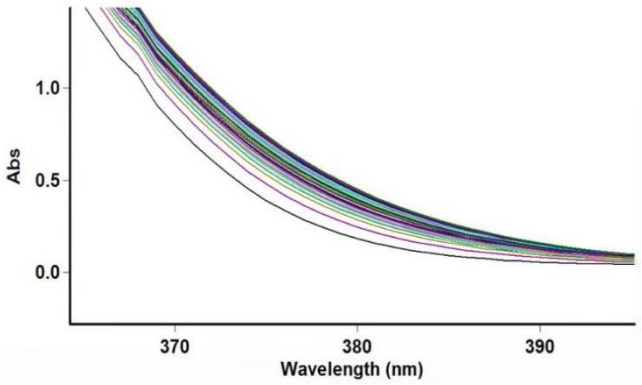


Fig. 1. The expanded UV spectra of the reaction between benzaldehyde **1** (1.5×10^{-3} M), 2-aminobenzaldehyde **2** (1.5×10^{-3} M) in the presence of acetic acid as a catalyst and solvent at the wavelength range 365-395 nm in 25 ˚C.

Table 1. Values of the overall rate constant (k_{ove}) for the reaction between **1**, **2** in the presence of acetic acid and mixture of acetic acid/formic acid (1:1) in different temperatures at 385 and 390 nm.

Wavelength(nm)	ε(D)	k_{ove} (M^{-1} min^{-1})×5×10^5			
		20 ˚C	25 ˚C	30 ˚C	35 ˚C
		Solvent: acetic acid			
385	6.2	14.695 (0.0004)[a]	20.574 (0.0004)	33.516 (0.0005)	40.014 (0.0006)
390	6.2	14.571 (0.0012)	18.197 (0.0011)	34.771 (0.0011)	40.062 (0.0009)
		Solvent: acetic acid/formic acid (1:1)			
385	32.1	53.748 (0.0011)	74.684 (0.0006)	126.48 (0.0008)	200.25 (0.0011)
390	32.1	52.928 (0.0009)	74.306 (0.0002)	126.53 (0.0002)	195.76 (0.0002)

[a]Standard Deviation.

3.2. Mechanism studies

3.2.1. Effects of concentration

In order to find the partial order of reactants under pseudo-order condition, in a separate experiment (fourth experiment), a same procedure was employed with this concentrations [(10^{-2} M, reactant **1**) and (10^{-3} M, reactant **2**)]. For obtaining equations (2), the rate law can be expressed:

$$\text{Rate} = k_{ovr}[1]^{\alpha}[2]^{\beta}[\text{Cat}]$$
$$\text{Rate} = k_{obs}[1]^{\alpha} \quad (2)$$
$$k_{obs} = k_{ove}\,[2]^{\beta}[\text{Cat}]$$

Fig. 3 shows a pseudo first order fit curve (solid line) at 385 nm that exactly fits the experimental curve (dotted line). As a result, it is reasonable to accept that the reaction is first order with respect to reactant **1** (α=1). As a result, because the overall order of reaction is 2 (α+β= 2), it is reasonable to accept the reaction is first order with respect to reactant **2** (β=1).

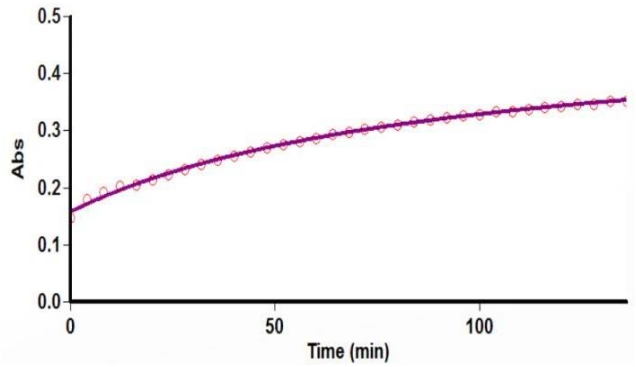


Fig. 2. Second order fit curve (solid line) accompanied by the original experimental curve (dotted line) for the reaction between **1** (1.5×10^{-3} M) and **2** (1.5×10^{-3} M) in the presence of acetic acid at 385 nm in 25 ˚C.

Utilizing the above results, the simplified scheme of the proposed reaction mechanism as a possible explanation is shown in Scheme 2.

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:

$$\text{rate} = k_3[\text{I}_2] \quad (3)$$

The steady state assumption can be employed for obtaining the concentration of [I_2] which is generated from the following equations:

$$\frac{d[\text{I}_2]}{dt} = k_2[\text{I}_1] - k_3[\text{I}_2] = 0 \quad (4)$$

$$k_3[\text{I}_2] = k_2[\text{I}_1] \quad (5)$$

The value of equation 5 can be replaced in the equation 3 so the rate equation becomes:

$$\text{rate} = k_2[\text{I}_1] \quad (6)$$

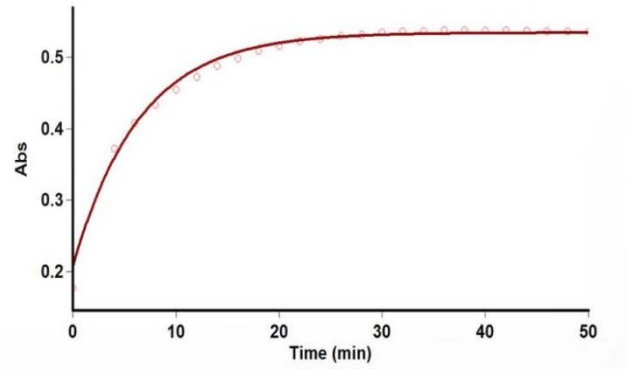
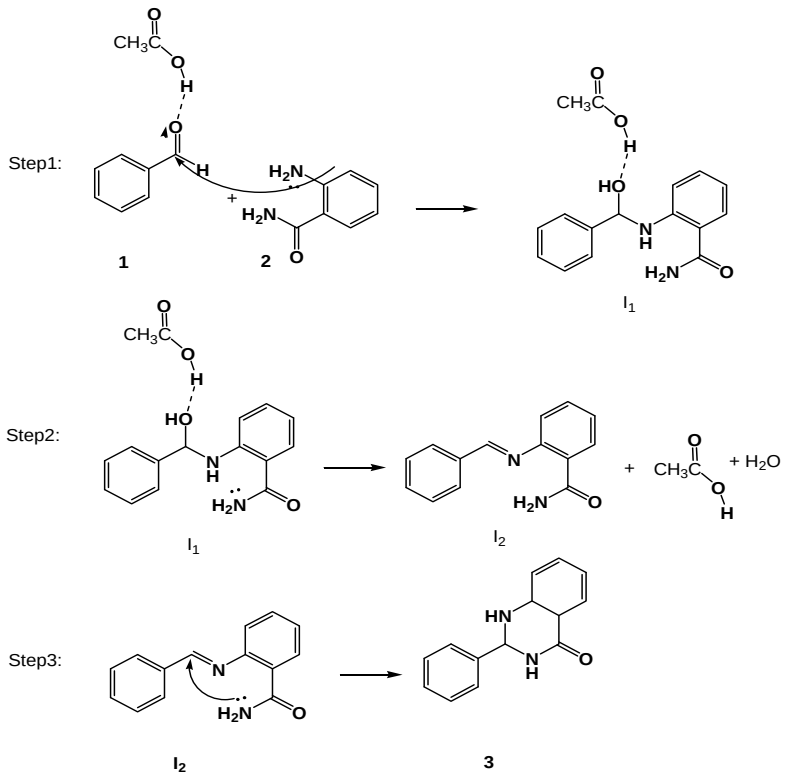


Fig. 3. First pseudo order fit curve (solid line) accompanied by the original experimental curve (dotted line) related to benzaldehyde **1** (10^{-2} M), for reaction of **1** (10^{-2} M) and **2** (10^{-3} M) in the presence of acetic acid at 385 nm in 25 ˚C.



Scheme 2. Plausible mechanism for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of acetic acid as catalyst and solvent.

For obtaining the concentration of intermediate $[I_1]$ the following equations obtained by applying the steady state assumption:

$$\frac{d[I_1]}{dt} = k_1[1][2][cat] - k_2[I_1] = 0 \quad (7)$$

$$k_1[1][2][cat] = k_2[I_1] \quad (8)$$

And with their placement of the equation 8 in 6 the following equation is obtained:

$$rate = k_1[1]\,[2][cat] \quad (9)$$

The following equations can be obtained:

$$k_{ove} = k_1[Cat] \quad (10)$$

$$Rate = k_{ove}[1][2] \quad (11)$$

The final equation (11) indicates that the overall order of the reaction is two which was formerly confirmed by the experimental data (see section 3.1.). Because of the presence of k_1 in the rate low (equation (11)), it obvious that first step (k_1) is a rate determining step.

Hence, the activation parameters which involve $\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ can be now calculate for the first step (rate determining step, k_1) as an elementary reaction on the basis of the Eyring equation (13) shown in Fig. 4a and also a different linearized form of the Eyring equation (14) as can be seen in Fig. 4b. 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) [22]:

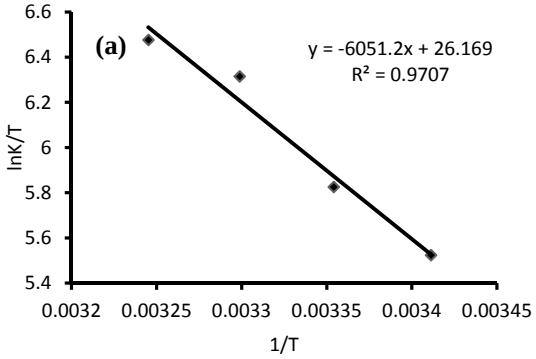
$$\sigma(\Delta S^{\ddagger}) = 1/T_{av}\sigma(\Delta H^{\ddagger}) \quad (12)$$

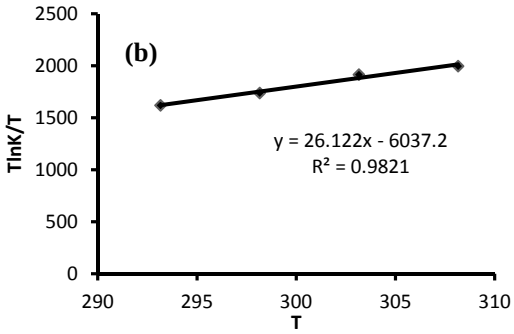
It follows that in most solution phase studies $\sigma(\Delta S^{\ddagger}) \approx \sigma(\Delta H^{\ddagger}) \times 0.0034$ K^{-1}.This correlation has been mentioned elsewhere [22-23]. The standard errors for activation parameters have been calculated according to the above instructions [22-24] and they have been reported along with this parameters in Fig. 4.

3.2.2. Effect of solvent and temperature

In order to determine the solvent and temperature environment effects on the rate of reaction, various experiments were performed at different solvent polarity and temperature under the same condition with the third experiment. For this reason, acetic acid with a dielectric constant (6.2 D) was chosen as a suitable solvent since it not only dissolved all compounds but also did not react with them.

The results of solvent and temperature effects on the rate constant are given in Table 1. The results show that the rate of reaction was increased at higher temperature in each solvent and also the rate of reaction was increased in an upper dielectric constant environment at all temperature investigated. In the temperature range studied, the dependence of the second order rate constant ($\ln k_{ove} = \ln k_1$) of the reaction





$$ln\left(\frac{k_1}{T}\right) = \left(ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}\right) - \frac{\Delta H^{\ddagger}}{RT} \qquad (13)$$

$$T \times \left(\frac{k_1}{T}\right) = T \times \left(ln\frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R}\right) - \frac{\Delta H^{\ddagger}}{R} \qquad (14)$$

$$\Delta S^{\ddagger} = -44.188 \pm 0.0015\ {}^{J}/_{mol}$$

$$\Delta S^{\ddagger} = -44.296 \pm 0.0015\ {}^{J}/_{mol}$$

$$\Delta H^{\ddagger} = 50.505 \pm 0.462\ {}^{kJ}/_{mol}$$

$$\Delta H^{\ddagger} = 50.536 \pm 0.462\ {}^{kJ}/_{mol}$$

Fig. 4. Eyring plots according to equations (13 and 14), for the reaction between **1**, **2** in acetic acid. According to the values of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ on the basis of Eyring equation (14), the free Gibss energy for the reactions between **1** and **2** is $\Delta G^{\ddagger}$=63.74 kJ.mol^{-1} in acetic acid at 385 nm and 298.2 K.

on reciprocal temperature was consistent with the Arrhenius equation. The activation energy (E_a= 52.808 kJ.mol^{-1}) for this reaction was obtained from the slope of Fig. 5.

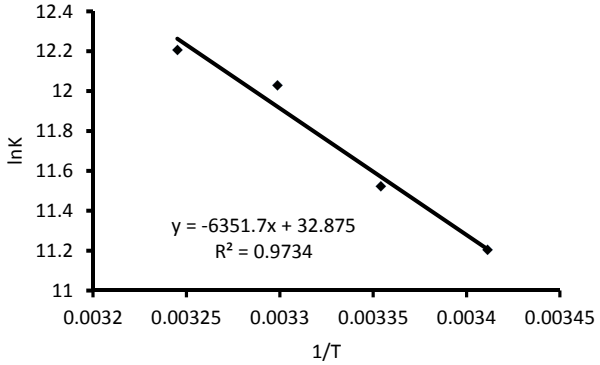
3.2.3. Effect of catalyst

The rate of reaction was increased in the presence of trichloroacetic acid as a second catalyst in comparison with acetic acid as catalyst. As can be seen in Table 2, trichloroacetic acid speeds up the rate of reaction. The only difference between these two acids is the degree of chloro group substitution. Chlorine atoms are electronegative (three pairs of non-bonded electrons in their valence shell) and thus have an-Induction effect. Thus they help stabilize the negative charge of the conjugate base formed upon the ionization of an acid by electron withdrawal through carbon-carbon bonds. Note the substantially higher acidity (nearly 100-fold) of chloroacetic acid relative to acetic acid as indicated by pK_a values.

4. Conclusions

The overall order of reaction for the formation of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of acetic acid follows second-order kinetics and the partial orders with respect to each of reactants are one. The first step of proposed mechanism was recognized as a rate-determining step (k_1) and this was confirmed based upon the steady-state approximation.

In addition, synthesis in the presence of acetic acid offered several advantages such as 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 with excellent yield.



$$E_a = 52.808 \pm 0.004\ {}^{kJ}/_{mol}$$

Fig. 5. Dependence of second order rate constant (ln k_1) on reciprocal temperature for the reaction between compounds **1** and **2** measured in acetic acid at 385 nm.

Table 2. Effect of various catalysts on a reaction between **1** and **2** compounds in the presence of acetic acid at 25 ˚C.

Catalyst	$k_1 \times 5 \times 10^5$ ($min^{-1} M^{-1}$)	SD[a]
Acetic acid (pK_a=4.76)	20.574	0.0005
Trichloroacetic acid (pK_a=0.64)	27.009	0.0012

[a]Standard Deviation.

Acknowledgment

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References

[1] R.O. Dempcy, E.B. Skibo, Biochemistry 30 (1991) 8480-8487.
[2] K. Hattori, Y. Kido, H. Yamamoto, J. Ishida, A. Iwashita, K. Mihara, Bioorg. Med. Chem. Lett. 17 (2007) 5577-5581.
[3] J. Rudolph, W.P. Esler, S. O'Connor, P.D.G. Coish, P.L. Wickens, M. Brands, D.E. Bierer, B.T. Bloomquist, G. Bondar, L. Chen, C. Chuang, T.H. Claus, Z. Fathi, W. Fu, U.R. Khire, J.A. Kristie, X. Liu, D.B. Lowe, A.C. McClure, M. Michels, A.A. Ortiz, P.D. Ramsden, R.W. Schoenleber, T.E. Shelekhin, A. Vakalopoulos, W. Tang, W. Lei, L. Yi, S.J. Gardell, J.N. Livingston, L.J. Sweet, W.H.J. Bullock, J. Med. Chem. 50 (2007) 5202-5216.
[4] J.K. Padia, M. Field, J. Hinton, K. Meecham, J. Pablo, R. Pinnock, B.D. Roth, L. Singh, N. Suman-Chauhan, B.K. Trivedi, L.Webdale, J. Med. Chem. 41 (1998) 1042-1049 .
[5] Y. Xia, Z. Yang, M. Hour, S. Kuo, P. Xia, K.F. Bastow, Y. Nakanishi, P. Nampoothiri, T. Hackl, E. Hamel, K. Lee, Med. Chem. Lett. 11 (2001) 1193-1196.
[6] M.R. Yadav, S.T. Shirude, A. Parmar, R. Balaraman, R. Giridhar, Khim. Geterotsikl. Soedin. 470 (2006) 1198-1205.
[7] T. Singh, S. Sharma, V. K. Srivastava, A. Kumar, Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem. 45 (2006) 25-58.
[8] R.J. Abdel-Jalil, W. Volter, M. Saeed, Tetrahedron Lett. 45 (2004) 3475-3476.
[9] J.F. Liu, J. Lee, A.M. Dalton, G. Bi, L. Yu, C.M. Baldino, E. McElory, M. Brown, Tetrahedron Lett. 46 (2005) 1241-1244.
[10] J.X. Chen, H.Y. Wu, W.K. Su, Chin. Chem. Lett. 18 (2007) 536-538.
[11] A. Shaabani, A. Maleki, H. Mofakham, Synth. Commun. 38 (2008) 3751-3759.
[12] J.A. Moore, G.J. Sutherland, R. Sowerby, E.J. Kelly, S. Palermo, W.J. Webster, J. Org. Chem. 34 (1969) 887-892.
[13] R.J. Abdel-Jalil, W. Voelter, M. Saeed, Tetrahedron Lett. 45 (2004) 3475-3476.
[14] J .Chen, W. Su, H. Wu, M. Liu, C. Jin, Green Chem. 9 (2007) 972-975.
[15] M. Lashkari, M.T. Maghsoodlou, N. Hazeri, S.M. Habibi-Khorassani, S.S. Sajadikhah, R. Doostmohamadi, Synth. Commun. 43 (2013) 635-644.
[16] N. Hazeri, M.T. Maghsoodlou, S.M. Habibi-Khorassani, J. Aboonajmi, M. Lashkari, S.S. Sajadikhah, Res. Chem. Intermed. 40 (2014) 1781-1788.
[17] M. Rostamizadeh, M.T. Maghsoodlou, N. Hazeri, S.M. Habibi-Khorassani, L. Leishams, Phosphorus Sulfur Silicon Relat. Elem. 186 (2011) 334-337.
[18] S.M. Habibi-Khorassani, A. Ebrahimi, M.T. Maghsoodlou, O. Asheri, M. Shahraki, N. Akbarzadeh, Y. Ghalandarzehi, Int. J. Chem. Kinet. 45 (2013) 596-612.
[19] M. Shahraki, S.M. Habibi-Khorassani, A. Ebrahimi, M.T. Maghsoodlou, A. Paknahad, Prog. React. Kinet. Mech. 37 (2012) 321-343.
[20] S.M. Habibi-Khorassani, A. Ebrahimi, M.T. Maghsoodlou, M. Zakarianezhad, H. Ghasempour, Z. Ghahghayi, Curr. Org. Chem. 15 (2011) 942-952.
[21] L.M. Schwartz, R.I. Gelb, Anal. Chem. 50 (1978) 1592.
[22] G. Lente, I. Fabian, A.J. Poe, New J. Chem. 29 (2005) 759-760.
[23] J.H. Espenson, Chemical kinetics and mechanisms, 2nd ed., McGraw-Hill, New York, 1995.
[24] A.J. Poe, Mechanisms of inorganic and organometallic reaction, Plenum Press, New York, 1994, p. 220.