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PRODUCTION RATE OF HETEROCYCLIC COMPOUNDS IODINATED N-(*p*-CHLOROPHENYL)-3,5-DIMETHYL-1,1-DIOXO-1,2-THIAZINE

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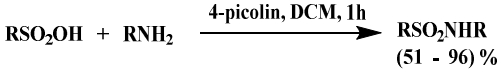
ABSTRACT. Iodinated heterocyclic molecules are crucial structural components of many natural products, including hormones, vitamins, and medicines. The pharmaceutical survey is very interested in the investigation of the kinetics of the iodination of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine. The rate of iodination is directly dependent on the concentration of both 1,2-thiazine and iodine under different molar ratios (1:10), (10:1) adopted on the isolation method, the observed rate of iodination, the pseudo-first-order and the second order using (1:1) molar ratio in the overall reaction using spectrophotometric techniques. Thermodynamic activation parameters activation energy E_a, enthalpy change $\Delta H^{\#}$, entropy change $\Delta S^{\#}$, and Gibbs free energy $\Delta G^{\#}$ of activation were calculated from the rate constant at temperatures 273, 283, 293, 303, and 318 K.

KEY WORDS: Production rate, 1,2-Thiazine, Iodine (I_2), Kinetic

INTRODUCTION

Sulfonamides have been used as antibacterial (antibiotic) agents and have been recognized as therapeutic agents for a long time [1-4]. Cyclic counterparts have attracted a lot of attention because they are also known to inhibit a number of enzymes, including cysteine protease, human immunodeficiency virus (HIV) protease carbonic anhydrase, and cyclooxygenase [5]. Due to the spacious applicability of sulfonamides, it is eligible to find general and novel methods for their synthesis.

Chantarasriwong *et al.* reported a general method used for aromatic sulfonic acids and can be applied to aliphatic and heterocyclic sulfonyl acid (Scheme 1), R - may be aromatic, aliphatic and heteroaromatic [6].



Scheme 1. Sulfonamide formation from sulfonic acids.

Due to the increased interest in benzo-fused systems and their functionalized derivatives, the synthesis of 4,6-dimethyl-1,2-oxathiine-2,2-dioxide (**1**) began with the trifunctional intermediate mesityl oxide [7], and it was then reflexed with *p*-chloroaniline to create N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine (**2**). The reaction proceeds in accordance with Scheme 2.

1,2-Thiazines under the inventions are highly stable and permit further reactions [8-10], such as a reaction with iodine with mercuric oxide as a catalyst that leads to the formation of 6-iodo and 4,6-diiodo-1,2-thiazines (**3**) and (**4**) (Scheme 3) [11].

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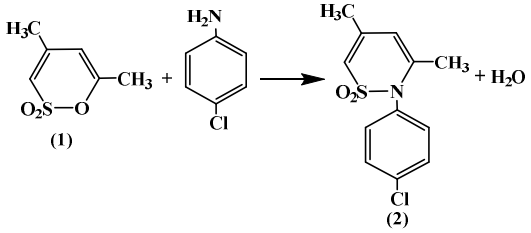
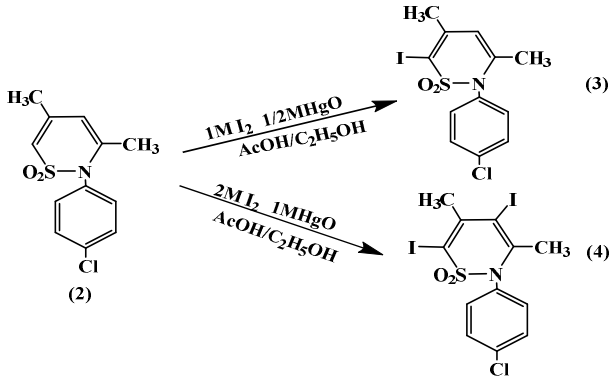


Scheme 2. 1,2-Thiazin from 1,2-oxathine.



Scheme 3. Iodination of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine.

Iodine plays a vital role in many biological organisms and is an essential trace element for humans. In the human body, iodine is mainly present in the thyroid gland in the form of thyroxine, a metabolism-regulating hormone. In natural organic compounds, iodine occurs exclusively in the monovalent state. The first polyvalent organic iodine compound, (dichloroiodo)benzene, was prepared by the German chemist C. Willgerodt in 1886 [12]. The most impressive modern accomplishment in organoiodine compounds includes discovering catalytic application organoiodine compounds. Several substituted 1,2-thiazine are valuable heterocycles for medical applications [13]. Consequently, chemical syntheses towards hetero aromatic 1,2-thiazine remain an attractive topic for intense research [14]. The kinetic and thermodynamic studies, particularly for the iodination of 1,2-thiazine and so it is our interest to perform these investigations.

The present investigation aims to demonstrate the possibility of using a modern in situ spectroscopic method (UV-Vis spectroscopy) to investigate the kinetics rate of production of the iodination reactions of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine, and to achieve the reaction rates of different concentration and other kinetic and thermodynamic parameters.

EXPERIMENTAL

Chemicals

All chemicals used were of an analytical grade reagent. Methanol and ethanol (99.9%) were purchased from TEDIA Company, Inc. (USA). N,N-Dimethylformamide (DMF) 99.8% from BioSolve, HgO > 99.4%, iodine (I_2) > 97%, acetic acid (CH_3COOH, 97%) and HCl (37%) from

Fluka, aniline 90% and mesityl oxide(4-methylpent-3-ene-2-on) ($C_6H_{10}O$, 98%) from Sigma Aldrich Co. and 4-chloroaniline from PubChem were used.

*Synthesis of 4,6-dimethyl-1,2-oxathiine-2,2-dioxide (**1**)*

In a one-liter flask with three necks and a mechanical stirrer that was placed in an ice water bath, 220 mL of acetic anhydride (2 mol) was added. Dropwise, 56 mL of sulfuric acid (99%) was added to ensure that the mixture's temperature stayed below 0 °C. Next, 115 mL of mesityl oxide was added slowly without causing the temperature to change, and after five hours, an orange-red viscous A 65 g (40%) of the pure, colorless 4,6-dimethyl-1,2-oxathiine-2,2-dioxide was obtained after the product was cleaned and recrystallized with methanol. Its melting point was (69-70) °C, and its H^1-NMR values were 2.03 (s, 3H, 4-CH_3), 2.15 (s, 3H, 6-CH_3), 5.62 (s, 1H, C5-H), and 6.20 (s, 1H, C3-H).

*Synthesis of N-(p-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine (**2**)*

A mixture of 0.1 mol (16 g) 4,6-dimethyl-1,2-oxathiine-2,2-dioxide and 0.1 mol (9.1 mL) of 4-chloroaniline was dissolved in 25 mL N,N-dimethyl formamide (DMF), the contents reflexed for 1.5 h, then cooled to room temperature and 10 mL of (0.1 N) HCl was added to remove the excess of 4-chloroaniline then the precipitate collected by filtration, washed with cold water dried and recrystallized in methanol [15]. The physical properties of the product with the molecular formula ($C_{12}H_{12}NO_2SCl$), molecular weight 268.749 g/mole with a 42% yield, and IR spectra (1310), (1170) cm^{-1} are asymmetric and symmetric vibration bands for (SO_2) and (1622) cm^{-1} for C=C bond.

Kinetic experimental techniques

Several experimental methods are employed in kinetics investigations to carry out these measurements. UV-Vis spectroscopy is the method utilized in kinetic investigations that is most useful. The reactor would be submerged in the thermostat liquid bath because the experiment should be conducted in isothermal conditions. A Spectroscan 80D instrument spectrophotometer with serial no.: 18-1884-01-0113, with UV-spectroscan software, using 1 cm matched quartz cells with a home-made cell jacket, made from a thin copper sheet, which was painted by a black dye to minimize the light reflection, connected a thermostatic digital circulating bath.

The instrument records the absorbance curve systematically for the product and automatically at a fixed cycle time (in second), between (190-1100) nm. Taking continuous readings until the absorbance remains constant for two hours, and this value represents (A_∞), for six different temperatures (273, 283, 293, 298, 303, 318) K.

Kinetic experiment of the N-(p-Chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine: I_2 molar ratio 1:10

The kinetic study was carried out under pseudo-first order condition [1,2-thiazine] $\ll$ [I_2] with a 1:10 molar ratio, and the rate studies were carried out at a constant temperature. Using a 25 mL conical flask, 0.235 g (0.001 mol) of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine and 5 mL of ethanol were added using the micro burette; the flask was placed inside the automatic liquid bath at 298 K for thermal equilibration for 30 min before the experiment. In the other flask, mercuric oxide (HgO) 2.16 g (0.016 mol) was dissolved in 10 mL acetic acid, and the two above solutions were mixed. Then the iodinating agent, (I_2) 2.53 g (0.01 mol) was dissolved in 5 mL ethanol, then added to the sample solution and quickly mixed to the cuvette and capped; the cuvette was inserted into the UV-Visible system. Then taking the baseline spectrum at full range

of wave length (190-1100) nm for all the solution mixture to auto zero all the peaks of the reactant solutions, the "start" button was pressed, and the instrument records the absorbance curve systematically for the product, taking continuous readings automatically at fixed cycle time every 300 seconds until the absorbance remains constant for two hours which represents (A_∞). All the experiments were repeated at six different temperatures (273, 283, 293, 298, 303, 318) K.

N-(p-Chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine: I_2 with molar ratio 10:1

Dissolving 2.35 g (0.01 mol) of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine in 5 mL of ethanol at 298 K and the iodinated agent, (I_2) 0.0513 ml (0.001 mol) were dissolved in 5 mL ethanol.

N-(p-Chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine: I_2 with molar ratio 1:1

Dissolving 0.235 g (0.001 mol) of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine 5 mL of ethanol at 298 K and the iodinated agent, (I_2) 0.253 ml (0.001 mol) were dissolved in 5 mL ethanol.

RESULTS AND DISCUSSION

Iodination of N-(p-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine by I_2 1:10 molar ratio

Iodination of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine were investigated under six temperatures (273, 283, 293, 298, 303, 318) K and for each temperature, the time course measurements were followed toward the completion of the reactions, as shown in two and three-dimensional spectra in Figure 1 as λ_{max} is at 455 nm.

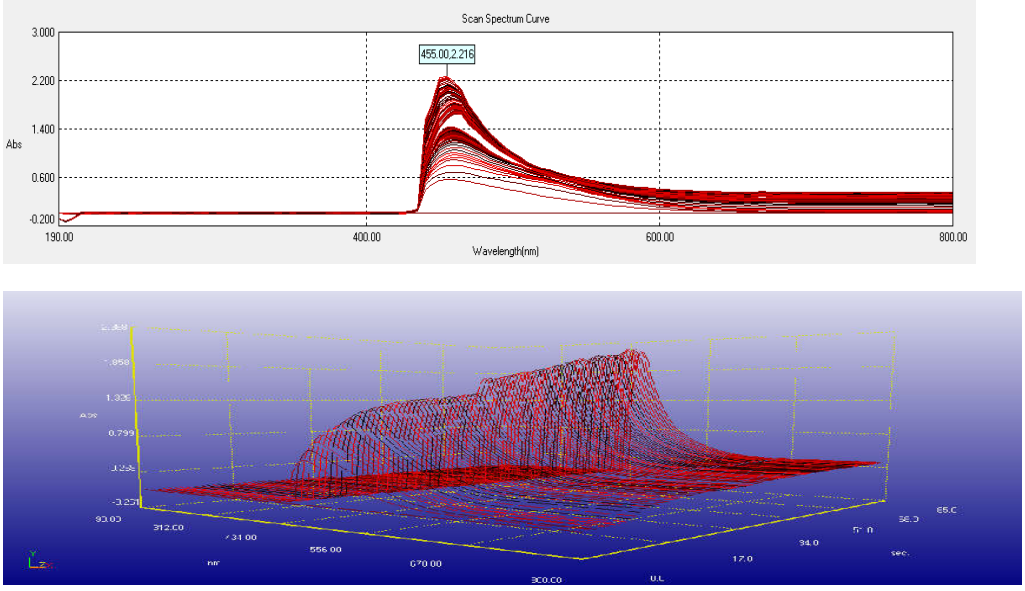


Figure 1. Spectrum for N-(*p*-chlorophenyl)-3,5-dimethyl-1,1- dioxo-1,2-thiazine: I_2 with 1:10 molar ratio at 318 K, (a) two-dimensional and (b) three-dimensional spectrum.

Following the change in product absorbance over time at six different temperatures (273, 283, 293, 298, 303, 318) K at the maximum 455 nm. The temperature rises, absorbance rises, and the reaction rate quickens.

The rate constant k for the iodination of 1,2-thiazine by I_2 with molar ratio 1:10 at different temperatures is followed by the pseudo-first-order kinetic according to the equation (1) [16, 17]:

$$Ln(A_\infty - A_t) = \ln A_\infty - k_1 t \quad (1)$$

where A_t is the absorbance of the product at each time interval t, A_∞: absorbance of the product at an infinite time t_∞, equivalent to the initial concentration of reactant (a), t: time in sec, k_1: first-order rate constant of reaction in 1/sec, $(A_\infty - A_t)$: concentration of product at any time, equivalent to the remaining concentration of reactant a-x. The value of k_1 for each temperature was evaluated from the slope of the linear plots of $\ln(A_\infty - A_t)$ against t, the data plots are shown in Figure 2 and the summary of findings of k_1, $t_{1/2}$, and R^2 are given in the Table 1, where $t_{1/2}$ is the half-life of the reaction. R^2 is the correlation coefficient.

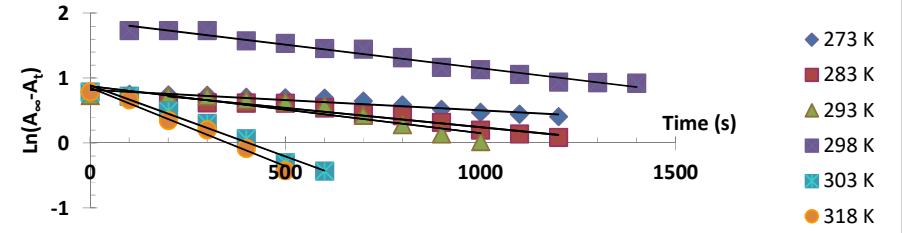


Figure 2. Pseudo first-order kinetic plot for absorbance of the product of iodination with 1,2-thiazine.

Table 1. Observed rate constants for the iodination of 1,2-thiazine by I_2 with molar ratio 1:10.

Temp. (K)	$k_1 \times 10^{-4}$ (1/sec)	$t_{1/2}$ (sec)	R^2
273	3.2	2165.6	0.93
283	5.9	1174.5	0.92
293	6.8	1019.1	0.82
298	7.0	990.0	0.97
303	21.0	330.0	0.97
318	24.0	288.7	0.98

Determination of thermodynamic activation parameters

Interpreting the Arrhenius equation's parameters is crucial to the development of the concept that when the reactants are transformed into a product:

$$lnk_1 = lnA - Ea/RT \quad (2)$$

From the obtained results of the activation energy E_a in Figure (3), the enthalpy of activation $\Delta H^{\#}$, entropy $\Delta S^{\#}$ and Gibbs free energy of activation $\Delta G^{\#}$ can be obtained using equations [18, 19]:

$$\Delta H^{\#} = Ea - RT \quad (3)$$

$$A = \frac{ek_bT}{h} e^{\frac{\Delta S^{\#}}{R}} \quad (4)$$

$$\Delta S^{\#} = R(lnA - \ln\left(\frac{ek_bT}{h}\right)) \quad (5)$$

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

where k_b = 1.3806*10^{-23} J /K, h = 6.626*10^{-34} J sec. The Arrhenius parameters, activated enthalpies and entropies obtained from the plotted graphs are tabulated in Table 2.

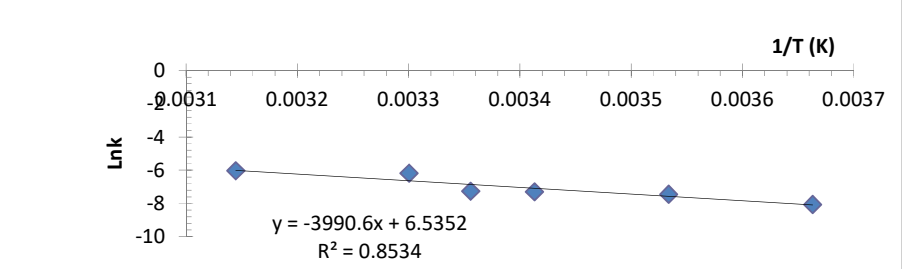


Figure 3. Arrhenius plots for iodination of 1,2-thiazine by I_2 at different temperatures using 1:10 molar ratio.

Table 2. Arrhenius and thermodynamic parameters for the iodination reaction of 1,2-thiazine.

Iodination 1,2-thiazine	Ea (kJ/mol)	Temp. (K)	$\Delta H^{\#}$ (kJ/mol)	$\Delta S^{\#}$ (J/K.mol)	$\Delta G^{\#}$ (kJ/mol)
A-factor= 0.0068×10^5 1/s	33.177	273	30.908	-189.88	82.74
		283	30.824	-190.18	84.64
		293	30.741	-190.47	86.55
		298	30.700	-190.61	87.50
		303	30.658	-190.75	88.45
		318	30.533	-191.15	91.32

Iodination of N-(p-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine by I_2 10:1 molar ratio

From the physical properties of the product, H^1- and C^{13}-NMR, IR, and UV-data are all very close to that of the reactant unsubstituted (by iodine); the reaction achieved between 1 mmol of I_2 and 10 mmol N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine but the product disappeared between the large quantities of 1,2-thiazine reactant, in addition to that the product is more soluble in solvents than reactant itself during recrystallization and this is one of the reasons that the product is undetectable even by IR, H^1-NMR and C^{13}-NMR and so it was not possible to do kinetic work for this reaction.

Iodination of N-(p-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine by I_2 1:1 molar ratio

Iodination using the same molar ratio of each reactant, the two and three-dimensional absorption spectra, Figure 4 shows the variation of absorbance of the peaks at λ_{max} 410 nm with time shows the absorbance of the product increase with time indicating that the reactions are clean forward processes since no equilibrium was observed during kinetic runs.

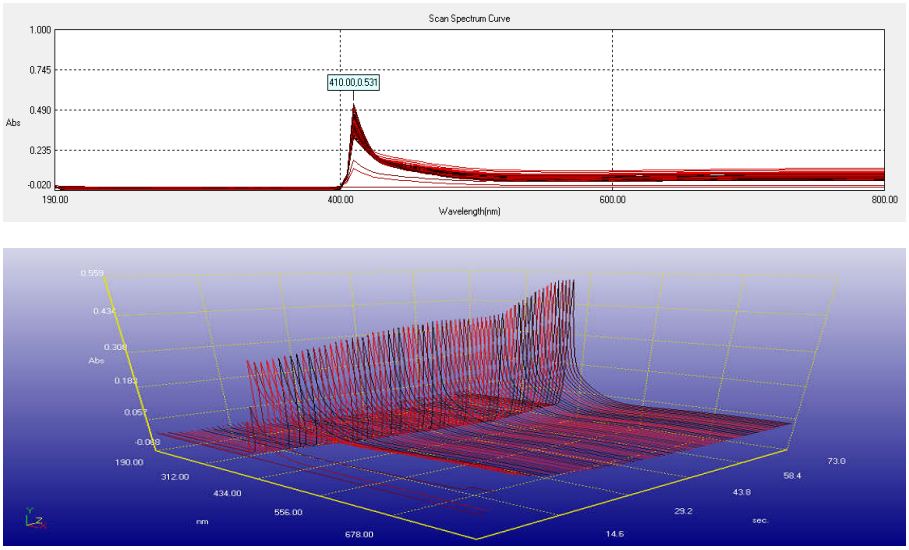


Figure 4. Spectrum for N-(*p*-chlorophenyl)-3,5-dimethyl-1,1- dioxo-1,2-thiazine: I_2 with 1:1 molar ratio at 303 K, (a) two-dimensional and (b) three-dimensional spectrum.

The rate law can be expressed by the equation:

$$\frac{d[product]}{dt} = k_2[I_2][1,2-thiazine] \tag{8}$$

These reactions were determined as second order equation; first-order with respect to each reactant and can be described by equation (9) [17, 18]:

$$\frac{A_t}{A_\infty(A_\infty - A_t)} = k_2 t \tag{9}$$

The plot of $A_t/A_\infty(A_\infty\text{-}A_t)$ with the time t has a slope k_2 which is the second order rate constant, the plots show excellent fit to the second order equation as shown in Figure 5 and the data are tabulated in the Table 3.

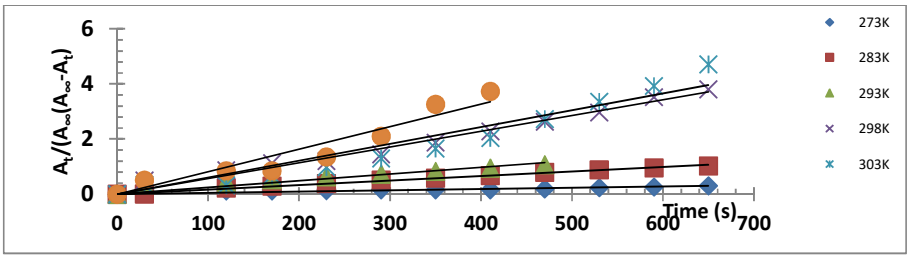


Figure 5. Second order plot for the absorbance of the product for iodination of 1,2-thiazine at different temperatures using 1:1 molar ratio.

Table 3. Observed rate constants, for the iodination of 1,2-thiazine with ICl with 1:1 molar ratio.

Temp. (K)	$k_2 \times 10^{-4}$ (dm^3/s. mol)	$t_{1/2}$ (1/sec)	R^2
273	5	4651.16	0.96
283	16	1453.48	0.99
293	24	968.99	0.97
298	57	407.99	0.99
303	61	381.24	0.97
318	82	283.60	0.96

Direct iodination of N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine with iodine undergo electrophilic attack depending on the molar ratio as $[I_2] \gg$ [1,2-thiazine] as shown in Scheme 3 obtaining 4,6-diiodo N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine (**4**) obtaining pseudo first order condition and plotting $\ln(A_\infty - A_t)$ against time t as shown in the figure 2 the small k_1 values table 1 indicates a slow reaction which depends on the nucleophilicity of the amine (N) group and the substituted chlorine (*p*-Cl) of the aromatic ring is electron withdrawing that is reduces electron density at the reaction center.

The large activation energy values E_a = 33.177 kJ/mol shown in Table 2, which increase the rate of the reaction as the temperature increase, explain that the slowness of the reaction and the reactants need high energy for the transition state to reach the product. The enthalpy of activation ($\Delta H^{\#}$) is also large and positive, which is the energy to affect the stretching or breaking of bonds that consumes more energy as the temperature decrease. The entropy of activation ($\Delta S^{\#}$), which measures the change in the degree of organization or order of both the reacting molecules themselves and the distribution energy as shown in Table 2, are negative values indicating the rigid configure with less degree of freedom for the activated complex than the reactant molecule.

Pseudo-second order plots showed good linearity as in Figure 5; the rate constants obtained from the reaction mixture prepared with different temperatures are observed in the Table 3 which R^2 value indicates a very good fitness. Results of Table 3 indicate slower reaction rate of iodine monochloride with N-(*p*-chlorophenyl)-3,5-dimethyl-1,1-dioxo-1,2-thiazine, due to electronic withdrawing group on the phenyl ring that effects on the electrophilic substitution reaction.

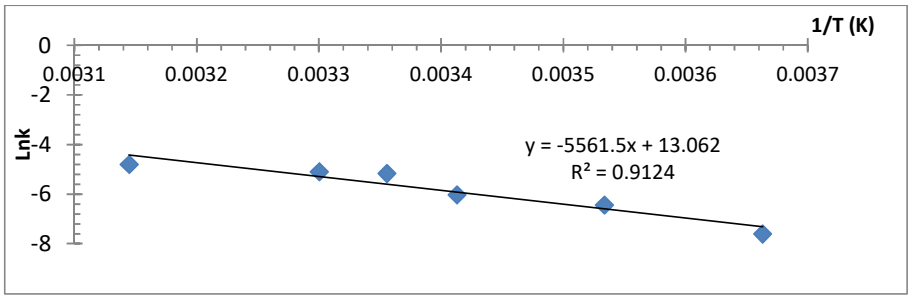


Figure 6. Arrhenius plots for iodination of 1,2-thiazine at different temperatures using 1:1 molar ratio.

From Arrhenius plots for iodination of 1,2-thiazine at six different ranged 273-318 K as presented in Figure 6, from the Table 4 E_a value 46.23 kJ/mol and A-values 4.6×10^5 mol/s. dm^3 are obtained, E_a value for 1,2-thiazine is high because of *p*-substituted chlorine is electron withdrawing group which decrease the electrophilicity of 1,2-thiazine to attack the iodine for electrophilic aromatic substitution which makes the reaction complex easier and faster for the reaction. The analogous interpretation of the A-factor is that it is a measure of the rate at which

collisions occurred, irrespective of their energy. Hence the product of A-factor gives the rate of successful collisions [20]. The entropy of activation gives a measure of the inherent probability of the transition state, apart from energetic considerations, if $\Delta S^{\#}$ is large and negative, the formation of the transition state requires the reacting molecules to adopt precise conformations and approach one another at a precise angle. As molecules vary widely in their conformational stability, in their rigidity, and in their complexity, one might expect the values of $\Delta S^{\#}$ to vary widely between different reactions [20].

Table 4. Arrhenius and thermodynamic parameters for the iodination reaction of 1,2-thiazine using 1:1 molar ratio.

1,2-Thiazine	E_a (kJ/mol)	Temp. (K)	$\Delta H^{\#}$ (kJ/mol)	$\Delta S^{\#}$ (J/K.mol)	$\Delta G^{\#}$ (kJ/mol)
A-factor = 4.6×10^5 mol/s. dm^3	46.23	273	43.96	-135.59	80.98
		283	43.88	-135.89	82.34
		293	43.80	-136.18	83.70
		298	43.76	-136.32	84.38
		303	43.71	-136.46	85.06
		318	43.59	-136.86	87.11

Iodination of electron-rich heteroaromatic 1,2-thiazine compounds is relatively easy. It can be carried out under mild reaction conditions, and a variety of halogenation reagents have been developed by chemists all over the world.

CONCLUSION

This research has mainly focused to demonstrate the rate of production of highly valuable heterocyclic compounds of iodine electrophilic substitution of (1,2-thiazine) and to demonstrates the ability to utilize a modern in situ spectroscopic method (UV-Vis spectroscopy), making the study quite simple and free from strict experimental conditions and is characterized by wide linear dynamic ranges and high sensitivity to investigate these reaction kinetics under different temperature range and determining thermodynamic activation parameters. The rate of iodinated 1,2-thiazine production is second order directly proportional to the concentrations of both I_2 and 1,2-thiazine according to kinetics, and according to the change of the thermodynamic parameters $\Delta H^{\#}$, $\Delta S^{\#}$, and $\Delta G^{\#}$, the reaction requires more energy to break bonds due to the rigid configuration and nonspontaneous transition state complex.

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