SYNTHESIS, STRUCTURAL DETERMINATION AND VISCOMETRIC STUDY OF ISOXAZOLINE DERIVATIVES

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Abstract: The Synthesis of isoxazoline derivatives are done by reacting with suitable chalcone and treated with hydroxylamine hydrochloride. The spectral determination was confirmed by using spectroscopic technique i.e. IR, NMR and Mass. Further study has been done by used photophysical property, viscometric measurement, and their thermodynamics parameters Entropy, Enthalpy and Gibbs free energy. The study shows positive value of ΔS, negative value of ΔG and positive value of ΔH which confirms that the reaction is endothermic and spontaneous. The maximum absorption of synthesized derivative 3-(4' methyl phenyl)-5-(furan) isoxazoline was found at 311 nm. The data obtained have been also observed that viscosity of solution increases with increase in the concentration of solution and positive value of B-coefficient may attribute to strong solute-solvent interaction. On the other hand value of A-coefficient is almost negative which indicates weak solute-solute interaction.

Index Terms- Photophysical, viscometric, thermodynamics, isoxazoline derivative.

I. INTRODUCTION

Most commonly known hetero atoms are nitrogen, oxygen and sulphur [1]. In the ring system a part from ring's carbon atoms at least one other atom is present, and then it's designated as a heterocyclic compound [2]. Compounds incorporating heterocyclic ring systems continue to attract considerable interest due to the wide range of biological activities they possess. Amongst them five member heterocyclic compounds occupy a unique place in the realm of natural and synthetic organic chemistry. In recent years, attention has increasingly been given to the synthesis of isoxazoline derivatives as a source of antibacterial agents. The synthesis of novel isoxazoline derivatives remain a main focus in medicinal research [3].

Isoxazoles have illustrious history; their chemistry is associated with Ludwig Claisen, who first recognized the cyclic structure of 3-methyl-5-phenylisoxazole in 1888 and was shown to possess typical properties of an aromatic compound. Dunstan and Dymond were the first to synthesize the isoxazole ring; they isolated a liquid base by heating nitro ethane with aqueous alkalies to obtain 3,4,5-trimethylisoxazole.

Isoxazole derivatives have been widely employed in the commercial world and several applications in the pharmaceutical and agricultural fields can be found [4]. The isoxazole is a five membered heterocyclic ring system containing both oxygen and nitrogen atoms at the adjacent positions (1,2-positions). They are isomers where in the hetero atom occupy (1,3 position). Isoxazole is a five membered heterocyclic compound containing oxygen and nitrogen atoms in the 1,2 positions, its partially saturated analogs are called isoxazolines and completely saturated analog is isoxazolidine [5].

Isoxazoline derivatives have been widely employed in the commercial world and several applications in the pharmaceutical and agricultural fields can be found. Furthermore, isoxazoline derivatives have important application in material science, such as fluorescence sensors, plastics and organ gels. There are modest numbers of reports presenting U-V visible spectral properties of isoxazoline derivatives [6]. In present study we are dealing with U-V visible spectral properties of synthesized isoxazoline derivatives in terms of their photophysical parameter. Isoxazole derivatives are used in the market as COX-2 inhibitor and anti-inflammatory drugs.

Chalcones represent an essential group of natural as well as synthetic products and some of them possess wide range of pharmacological activity such as antimicrobial, antitumor, anticancer, intertubercular, anti-inflammatory, antioxidant, antimalarial, ant leishmanial. The presence of reactive α, β- unsaturated keto group in chalcones is found to be responsible for their biological activity [7]. The viscosity and its derived parameters help study the structural change and intermolecular forces of the electrolyte solution at different

concentration and temperatures. Viscometric studies of electrolyte solution provide important information regarding solute-solute, solute-solvent interactions and help in characterizing the structural properties of the solution. Various types of interactions help for better understanding about the nature of solute and solvent, whether the solute modifies or distorts the structure of the solvent [8]. The second law of thermodynamics requires all fluids to have positive viscosity, such fluids are technically said to be viscous or viscid [9].

A fluid with a relatively high viscosity, such as pitch, may appear to be a solid. Viscometer, which consists of a U-shaped glass tube held vertically in a controlled temperature bath. Two marks (one above and one below the upper bulb) indicate a known volume [10]. This also allows the viscometer to have more than one set of marks to allow for an immediate timing of the time it takes to reach the third marks [11] therefore yielding two timings and allowing subsequent calculation of determinability to ensure accurate results.

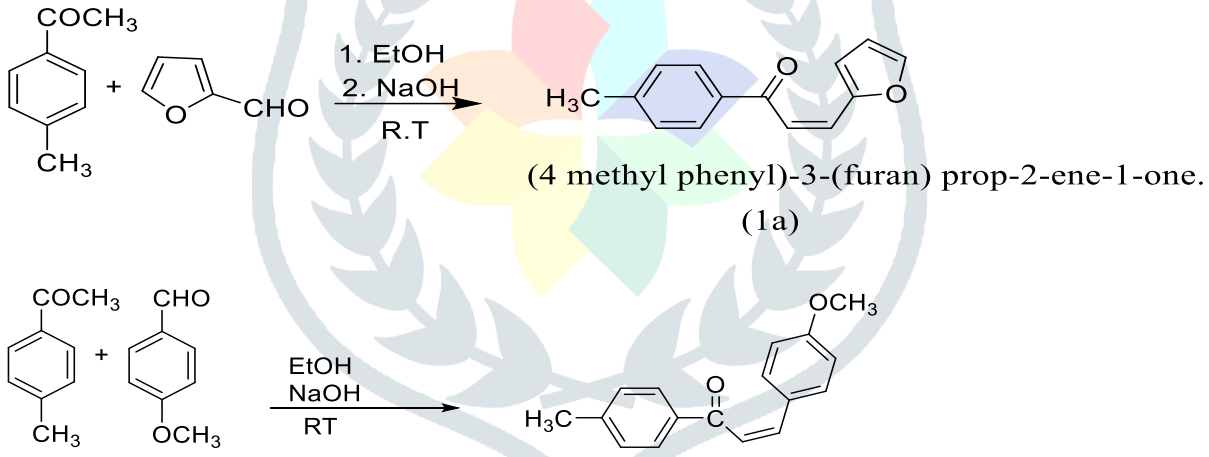
The present work deals with the viscosity study of isoxazoline derivative in different solvent at different concentrations and at different temperature. Data obtained used to calculate relative viscosity, viscosity-coefficient and thermodynamic parameters

II. EXPERIMENTAL

2.1 Synthesis of Isoxazoline Derivatives

Step-1 Preparation of Chalcones -

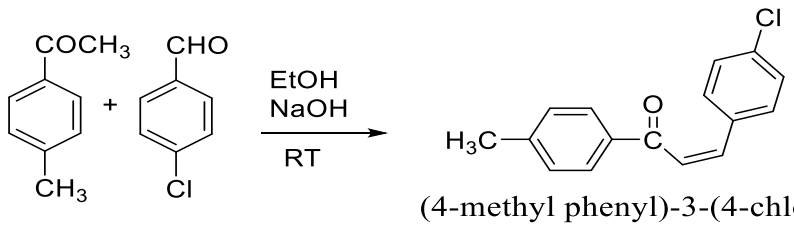
The chalcone was prepared by dissolving (0.04 M) 4 methyl acetophenone, (0.04 M)appropriate aldehyde (anisaldehyde, 4-chlorobenzaldehyde and furfuraldehyde) and 5ml ethyl alcohol in 200ml beaker. The mixture is allowed for continuous stirring for proper mixing of the reaction mixture. Now add 40% NaOH drop by drop upto 10 ml to obtain the crude solid. The solid obtained was then kept overnight at room temperature and then transferred to crushed ice followed by neutralization with ice cold HCl. The solid product was filtered, dried and recrystallized with ethanol.



(4 methyl phenyl)-3-(furan) prop-2-ene-1-one.

(1a)

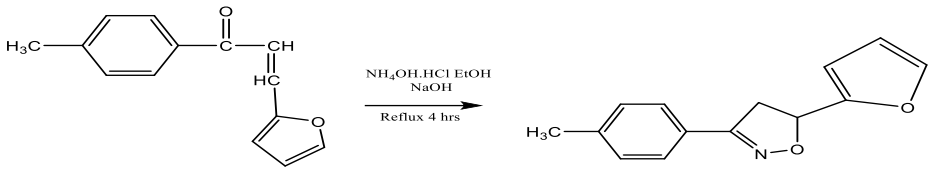
(4-methyl phenyl)-3-(4-methoxy phenyl) prop-2-ene-1-one



(4-methyl phenyl)-3-(4-chloro phenyl) prop-2-ene-1-one

Step-2. Synthesis of isoxazoline derivatives -

In a 250 ml round bottom flask mixture ofchalcone (2g) and hydroxylamine hydrochloride (1 g in 10 mL water) in ethanol (110 mL), a solution of NaOH (10g in 20 mL of water) was added in ethanol (50 mL). The reaction mixture was refluxed for 4 hours. It was cooled at room temperature and kept overnight. The reaction mixture was acidified with aqueous HCl (10%). The resulting precipitate was washed with distilled water, dried and recrystallized from ethanol to afford crystals.

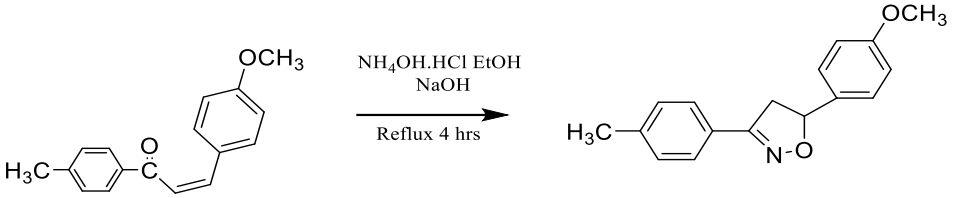


(4-methyl phenyl)-3-(furan) prop-2-ene-1-one

(1a)

3(4' methyl phenyl)-5-(furan) isoxazoline

(2a)

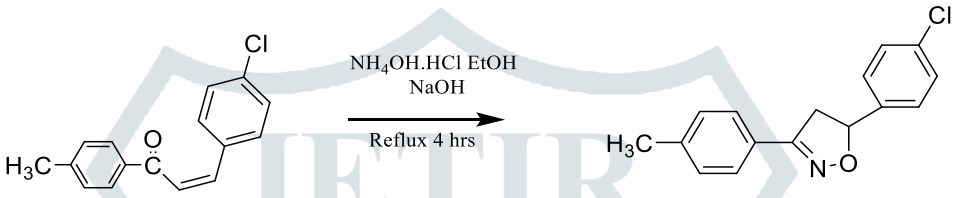


(4-methyl phenyl)-3-(4-methoxy phenyl) prop-2-ene-1-one

(1b)

3(4' methyl phenyl)-5-(methoxy phenyl) isoxazoline

(2b)



(4-methyl phenyl)-3-(4-chloro phenyl) prop-2-ene-1-one

(1c)

3(4' methyl phenyl)-5-(chloro phenyl) isoxazoline

(2c)

The compounds were characterized by ^{1}HNMR, Mass and IR spectroscopy.

3(4' methyl phenyl)- 5- (furan) isoxazoline (2a).

IR [KBr, cm^{-1}]:3491.31 (Ar-CH_3 stretch), 1361.80 (C-O-N stretch), 1022.32 (C-O stretch); ^{1}H- NMR (δ ppm, $CDCl_3$): 5.6-5.7(dd H isoxazoline ring), 7.2 (m ArH); MS: m/z 228 (M+1), 229 (M+2)

3-(4'methyl phenyl)-5-(4-methoxyphenyl) isoxazoline (2b).

IR [KBr, cm^{-1}]: 3016.80 (Ar-Hstretch), 2928.07 (Ar-CH_3 stretch), 1658.85 (C=N stretch), 1033.89(C-O stretch)

3-(4'methyl phenyl)-5-(4-chloro phenyl)isoxazoline (2c).

IR [KBr, cm^{-1}]:3036.09 (Ar-H stretch), 2924.21 (Ar-CH_3 stretch), 1651.14 (C=N stretch), 1346.37 (N-O stretch), 1014.60 (C-O stretch), 678.97 (C-Cl stretch);

2.2 Photophysical Property

In present study we are dealing with U-V visible spectral properties of synthesized isoxazoline derivatives in terms of their photophysical parameter. Ultra-violet (UV) spectra were recorded using UV 1800 Shimadzu, UV spectrophotometer and 10mm path length quartz cell, with respect to pure solvent reference. The stock solution of compound was prepared in DMSO (1:1 v/v) to ensure solubility. The stock solution is then diluted to desired concentrations i.e. 0.1%, 0.05%, 0.025%.

2.3 Viscosity Measurements

The present study deals with the viscosity measurements of isoxazoline derivatives at different compositions at 310K, 320K and 330K respectively and values of A and B coefficient was calculated.

III. RESULT AND DISCUSSION

3.1 Photophysical Property-

The absorption spectra of 3(4' methyl phenyl)-5-(furan) isoxazoline for different concentration in dilute DMSO solution are shown in the Figure-1. The concentration varies from 0.1%, 0.05%, 0.025%. It

was observed that the absorption peak centered at 311 nm, 277 nm & 272 nm for 0.1%, 0.05% & 0.025% respectively. Again for higher concentration i.e. 0.1% there are three optical absorption peak at 285nm, 305nm & 311nm. For lower concentration 0.05% & 0.025% the absorption peaks shows nearly same value.

The UV- visible absorption spectra of the hydrolysis product, isoxazoline amine was observed at 289nm [10].

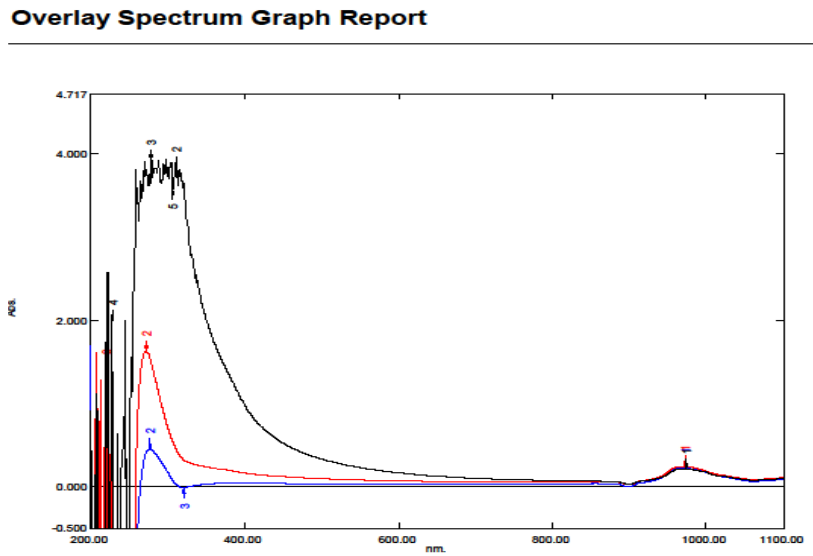


Fig.1 - Normalized Absorption Spectra of Compound(2a) in DMSO Solution with Increasing Molar Concentration

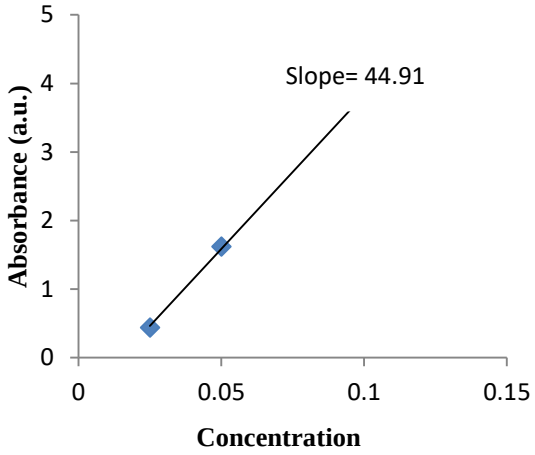


Fig. 2 – Graph Plotted between Absorbance and Concentration

The molar extinction coefficient (ϵ) were evaluated from slope of the curves from inset, using Beer-lambert's law, where the absorbance is proportional to molar concentration (c), light path length (l), and molar extinction coefficient(ϵ). The ϵ value for compound at 311 nm is 44.91 L/mol.cm. Thus the absorption in ultraviolet region makes it suitable material for UV light filter for organic solar cells.

3.2 Viscosity Measurement

Viscosity is one of the crucial physical property of liquid which throws light for better understanding of the molecular interaction as well as structural changes occur in the solutions. From the Table 2 it is observed that the values of relative viscosity (η) decreases with decrease in concentration. This increasing value of η shows the existence of molecular interaction in the solutions.

Viscosity data were analyzed in the light of Jones-Dole equation.

$$(\eta r - 1) / \sqrt{C} = A + B\sqrt{C}$$

Where, A and B are the Falken-Hagen and the Jones-Dole coefficients respectively.

From the graph of $(\eta_r - 1) / \sqrt{C}$ verses $\sqrt{C}$, 'A' which is the measure of solute – solute interactions and 'B' which is the measure of solute – solvent interactions has been calculated.

Table 2 Viscometric study with variation in concentration

System	Medium	Conc. (M)	√C ×10⁻²	Time flow (sec.)	Relative Viscosity	Specific Viscosity	A coefficient	B coefficient
					η_r	$\eta r - 1/\sqrt{C}$		
3-(4'methyl phenyl)- 5-(furan) isoxazoline	70% DMSO-water system	0.1 0.05 0.025	0.316 0.223 0.158	45 43 41	0.878 0.842 0.806	-0.386 -0.706 -1.227	-1.97	5.19
3-(4'methyl phenyl)-5-(4-methoxy phenyl) isoxazoline	70% 1,4 Dioxande-water system	0.1 0.05 0.025	0.316 0.223 0.158	48 42 38	0.961 0.868 0.793	-0.121 -0.591 -1.307	-2.39	7.38
3-(4'methyl phenyl)-5-(4-chloro phenyl isoxazoline	70% DMSO-water system	0.1 0.05 0.025	0.316 0.223 0.158	50 47 38	0.973 0.860 0.747	-0.085 -0.624 -9.60	-2.93	9.32

From the given table, the values of the 'A' coefficient are almost negative. This represents the contribution from weak inter-ionic electrostatic forces or indicates the weak solute-solute interactions. The coefficient B is the measure of effective solvodynamic volume of solvated ions which accounts for the solute-solvent interaction which measures the order or disorder introduce by the solute in the solvent [7]. The slope of straight line gave value of B –coefficient. From the table 2 values of the 'B' coefficient for isoxazoline derivatives in their specific solvent systems are positive it shows the strong solute-solvent interactions

Table 3: Thermodynamic temperature with variation in temperature:

System	Medium	Conc. (M)	Temp (K)	1 / T $(K^{-1}) \times 10^{-3}$	Time flow (sec.)	Density (ρ) g.cm^{-3}	Relative Viscosity η_r	Log (η_r)
3-(4'methyl phenyl)- 5-(furan) isoxazoline	70% DMSO-water system	0.1	310	$3.22x10^{3}$	45	0.893	0.878	-0.056
			320	$3.12x10^{-3}$	35	0.889	0.680	-0.167
			330	$3.03 x10^{-3}$	33	0.870	0.628	-0.202
		0.05	310	$3.22x10^{-3}$	43	0.896	0.842	-0.074
			320	$3.12x10^{-3}$	32	0.884	0.619	-0.208
			330	$3.03 x10^{-3}$	29	0.870	0.552	-0.258
		0.025	310	$3.22x10^{-3}$	41	0.899	0.806	-0.093
			320	$3.12x10^{-3}$	30	0.876	0.575	-0.240
			330	$3.03 x10^{-3}$	27	0.864	0.510	-0.292
3-(4'methyl phenyl)-5-(3-methoxy phenyl) isoxazoline	70% 1,4 Dioxan-water system	0.1	310 320 330	$3.22x10^{-3}$ $3.12x10^{-3}$ $3.03 x10^{-3}$	48 37 33	0.915 0.904 0.893	0.961 0.732 0.644	-0.017 -0.135 -0.190
		0.05	310	$3.22x10^{-3}$	42	0.944	0.868	-0.061
			320	$3.12x10^{-3}$	31	0.920	0.624	-0.204
			330	$3.03 x10^{-3}$	26	0.919	0.522	-0.281
		0.025	310	$3.22x10^{-3}$	38	0.954	0.793	-0.100
			320	$3.12x10^{-3}$	25	0.925	0.506	-0.295
			330	$3.03 x10^{-3}$	20	0.903	0.395	-0.040
3-(4'methyl phenyl)-5-(4 chloro phenyl isoxazoline	70% DMSO-water system	0.1	310	$3.22x10^{-3}$	50	0.890	0.973	-0.011
			320	$3.12x10^{-3}$	38	0.750	0.623	-0.205
			330	$3.03 x10^{-3}$	35	0.732	0.560	-0.251
		0.05	310	$3.22x10^{-3}$	47	0.895	0.860	-0.065
			320	$3.12x10^{-3}$	30	0.723	0.474	-0.323
			330	$3.03 x10^{-3}$	24	0.710	0.372	-0.428
		0.025	310	$3.22x10^{-3}$	38	0.899	0.747	-0.126
			320	$3.12x10^{-3}$	24	0.750	0.736	-0.404
			330	$3.03 x10^{-3}$	20	0.735	0.321	-0.493

The viscosity of a liquid generally decreases with rise in temperature. This decreasing value of η with temperature may be due to more thermal agitation and reduction of attractive forces between the solute molecule or ions which might be attributed to the decrease in solvation of ions by water. This has been explained in terms of 'Hole theory of liquids'. A liquid molecule therefore, needs some energy to move into hole. As the energy becomes increasingly available at increasing temperature, a liquid can flow more easily at higher temperature. The coefficient of viscosity thus, flow appreciably with rise in temperature as presented in Table 3. The plotted graphs between log η_r and 1/T. The graph for each system gives linear straight line shows the validity of equation. The viscosities determined at different temperatures were used to compute thermodynamic parameters and were evaluate by using equations

$\Delta G = -2.303\ R \times$ slope,

$\log \eta_{r1} - \log \eta_{r2} = [\Delta H / 2.303]\ [1/T1 - 1/T2]$ and

$\Delta S = (\Delta H - \Delta G) / T$

Table 4: Values of Thermodynamic parameters in Different Systems

System	Concentration (%)	ΔG (J mole^{-3}K^{-1}) x 10^{-34}	ΔH (J mole^{-3}K^{-1})	ΔS (J mole^{-3}K^{-1})
3-(4'methyl phenyl)- 5-(furan) isoxazoline.	0.1	-14.815	2556.33	8.24
	0.05	-18.668	3086.02	9.95
	0.025	-20.200	3385.41	10.92
3-(4'methyl phenyl)-5-(4-methoxy phenyl) isoxazoline	0.1	-17.519	2717.54	8.76
	0.05	-22.248	3293.29	10.62
	0.025	-30.348	4490.85	14.48
3-(4'methyl phenyl)-5-(4 chlorophenyl isoxazoline	0.1	-24.412	4467.82	14.41
	0.05	-36.800	5941.74	19.16
	0.025	-37.279	6402.32	20.65

IV. CONCLUSION

The different substituted isoxazolines was synthesized to explore the photophysical property. The absorption spectra of 3**(**4' methyl phenyl)-5-(furan) isoxazoline exhibits optical absorption in the Ultra-Violet region (from 285 to 311nm). The results from viscosity measurement show that positive values of viscosity 'B' coefficient for isoxazoline derivative which indicate the strong solute-solvent interactions. The viscosity determined at different temperatures were used to evaluate thermodynamic parameters enthalpy change (ΔH), entropy change (ΔS), & free energy change (ΔG). The positive value of ΔH for all synthesized compound indicates the given reaction is spontaneous & endothermic in nature. Isoxazoline derivatives in their specific solvent shows that the change in free energy (ΔG) and the change in entropy (ΔS) decreases with decrease in concentration.

V. REFERENCES

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