

Studying the Optimum Conditions for the Synthesis the Derivatives of Salicylaldehyde with Halides Compounds

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Abstract: Three Dialdehydes were synthesized by the reaction of Salicylaldehyde and many Aliphatic and Aromatic Halides. The optimal condition (Catalysts, Temperature, Time of Reaction and Effect of Solvents) to get a high selective compounds and high yields have been studied. The reactions were followed by using Thin Layer Chromatography (TLC). The synthesized compounds were purified and characterized by means of High Performance Liquid Chromatography (HPLC) and spectroscopy methods: Infrared Spectra (IR), ¹H-NMR, ¹³C-NMR.

Keywords: Salicylaldehyde, Heterogeneous Catalysts, Dialdehyde, Aliphatic and Aromatic Halides

1. Introduction

The cyclic or open chain Schiff bases compound are an important class of compounds because it has useful physical and chemical properties and also for their biological importance [1], [2]. It attracted an important attention for their pharmacological properties, coordination behavior and their capacity for extracting selectively some anions and metals of biochemical and environmental importance.[3], [4]. The macrocyclic Schiff bases containing heteroatoms such nitrogen played similar role as metal incorporation as it happened in proteins, in which the concerning metal ion is bound in a macrocyclic cavity or cleft produced by the conformational arrangement of the protein [5], [6]. Metal ions have enormous importance in many biological processes, but the increased concentration of metal ions especially heavy metal ions exerts toxic effects on living system. Therefore, separation and determination of metal ions in environmental sources and living organisms play an important role for the sustainability of healthy life [7], [8]. In spit of the metal ions have enormous importance in many biological processes, but when their concentration increase, the metal ions especially heavy metal ions exert toxic effects on living system, Therefore, it is very important for the sustainability of healthy life to find the possibility to separate and determinate the metal ions in environmental sources and

living organisms. The need for the selective extraction of some heavy metal ions encourages for synthesizing the Schiff base compounds having effective extractability, Some of the Macrocyclic Schiff bases ligands exhibit high selectivity in the extraction and removing of different metal ions [9].

The present article deals the synthesis of some compounds which after a condensation with an appropriate amine can used as macrocyclic Schiff base. The synthesis of the dialdehyde compounds were achieved by the reaction between Salicylaldehyde (salOH) and many aliphating and aromatic halides. The conditions of these reactions were studied and the optimum condition of their synthesis using different organic solvents and different heterocatalysts such as the (K₂CO₃, KOH, NaHCO₃). In addition, the effect of the temperature and solvents on the yield of the reactions to obtain the better conditions to the synthesis of the target molecules. [10-13].

2. Experimental Section

2.1. Experimental Material

Salicylaldehyde (98%) was obtained from (QUALIKEMS), 1, 2-Dibromoethane, Bis (2-chloroethyl) ether 98% and Dichloro-m-xylene (by Sigma Aldrich),

Dimethylformamide, Dimethyl sulfoxide, Sodium Hydrogen Carbonate and Anhydrous Potassium Carbonate (by CHEMLAB), Potassium Hydroxide Anhydrous, Tetrahydrofuran, Methanol, Ethanol and Diethyl ether (by BDH), Methanol and Acetonitrile (High purity for HPLC) (by Sigma Aldrich), Thin Layer Chromatographic of aluminum coated by Silica Gel 60F₂₅₄ measuring 20 X 20 from the German Company Merck.

2.2. Instrumentation

The purification was achieved by High performance Liquid chromatography (HPLC), system (Smartline, D-14163, Germany) equipped with an isocratic pump (Smartline Pump, K-1001), UV detector (Smartline, G1314B). Equipped with an isocratic pump (Smartline Pump, K-1001), UV detector (Smartline, G1314B). HPLC data were Purity using (Eurochrom HPLC Software. Version 3.05 P5) Chromatographic tests were achieved on an ODS C18 (250 x 4.6 mm) column (Eurospher, Germany) at room temperature. The used mobile phase consisted of MeOH and Acetonitrile with a flow rate of 1.0 ml.min⁻¹. The detection wavelength was set at 320 nm. Infrared spectra of compounds were recorded in KBr Pellets from the Japanese Company Jasco spectrophotometer in the range 4000-400 cm⁻¹, ¹H, ¹³C NMR (proton and carbon) spectra were recorded on a Bruker 400 MHz.

2.3. General Procedure for the Synthesis of Dialdehyde Compounds

The dialdehydes were synthesised by reaction between the Salicylaldehyde with 1,2-dibromoethane using different heterogeneous catalysts, solvents and temperatures. (salOH)

and a heterogeneous catalysts were added to the two-neck flask. Several types of catalysts (KOH, K₂CO₃, NaHCO₃ and non-Catalyst) were added in the presence of different solvents (DMF, Methanol, Acetonitrile and non-Solvent), then the 1, 2-dibromoethane was added. After confirming the end of the reaction via (T. L. C), the product separated, purified and dried, then recrystallized by ethanol and then washed several times with diethyl ether. The bright brown crystals compound was obtained with M. P: 120°C. The quantity of used compounds presented in the *table 1*.

Table 1. The quantity of used reagents and the yield of the synthesized compounds.

No	Compound	Halide	Catalyst	Reagent	Yield %
1	[EDOD]	(0.558 gr, 0.003mol)	K ₂ CO ₃	(0.414 gr, 0.003mol)	80
2	[OEBOD]	(0.429 gr, 0.003mol)	K ₂ CO ₃	(0.414 gr, 0.003mol)	80
3	[PMOD]	(0.525 gr, 0.003mol)	K ₂ CO ₃	(0.414 gr, 0.003mol)	82

3. Results and Discussion

Three dialdehyde compounds have been synthesized by the reaction of the Salicylaldehyde with some alkyl and aryl halides as demonstrated in the *table 2* following the general equation:

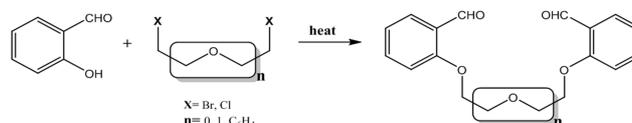


Figure 1. Reactions of synthesis of the Dialdehydes.

Table 2. Different Halides used in the synthesis of the Dialdehydes.

Entry	Aromatic and aliphatic halides	products
n = 0	1,2-dibromoethane	2,2'-(ethane-1,2-diylbis(oxy))dibenzaldehyde [EDOD]
n = 1	bis(2-chloroethyl)ether	2,2'-(oxybis(ethane-2,1-diyl)) bis(oxy) dibenzaldehyde [OEBOD]
n = C ₆ H ₄	Dichloro-m-xylene	2,2'-(1,3-phenylenebis(methylene))bis(oxy)dibenzaldehyde [PMOD]

The mechanism of these reactions can be supposed as the following general mechanism, which explain the formation of the synthesized compounds:

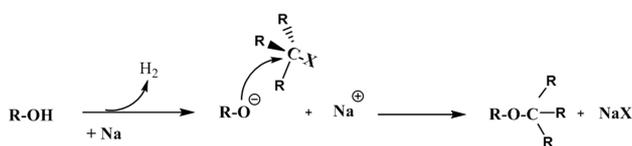


Figure 2. General Mechanism of Organic Synthesis Reactions.

3.1. Studying the Optimum Conditions

In order to adjust the optimum conditions for the preparation the dialdehyde compound (EDOD) by the reactions between Salicylaldehyde with Dibromopropane. The effect of the Solvents, Catalysts, Temperature and Time was studied.

3.1.1. Studying Effect of Solvent on Yield

Table 2. The effect of different Solvents on yield of synthesized compounds.

Solvent	Yield %
Methanol	55
CH ₃ CN	65
DMF	78
DMSO	71
non-solvent	13

In the beginning, the influence of polar solvents such methanol and some non-protonated polar solvents: (Tetrahydrofuran (THF), Dimethylformamide (DMF), Dimethyl sulfoxide (DMSO) have been studied, The non-protonated polar solvents gave better yield than others, due to the hard necessary conditions for the bimolecular nucleophilic substitution (S_N2) such as solvents [17] to deprotonating the hydroxyl group. It is clear from table 3 that

the best yield is with the DMF in comparing to the other solvents, it must say that the reaction without any solvent decreases dramatically the yield, due to the oxidization of the aldehyde, The reaction in inert atmosphere such Argon is necessary to prevent any oxidization of the aldehyde functional group.

3.1.2. Studying Effect of Catalyst on Yield

Several heterogeneous catalysts have been used during the synthesis of dialdehydes, such (K_2CO_3 , KOH, $NaHCO_3$) and also without catalyst (Table 4). The best yield was obtained with K_2CO_3 catalyst, while the reaction without catalyst was incomplete due to the acidity of hydrogen atom in the hydroxyl group, which needs a weak alkaline catalysts in order to induce the formation of carbocation (OK^+), the intermediate compound as it demonstrated in the following mechanism Figure 3.

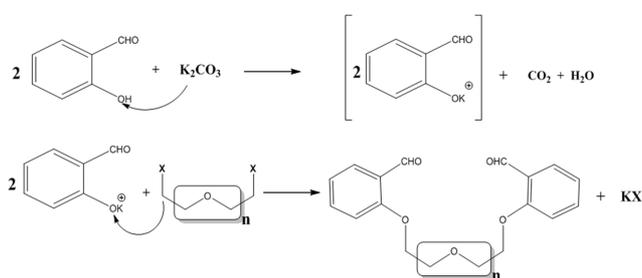


Figure 3. Mechanism of the Carbocation and the Synthesized Compounds Formation.

Table 4. The effect of catalysts on the Yield of synthesized Dialdehydes.

Catalyst	Yield %
KOH	65
K_2CO_3	80
$NaHCO_3$	50
non-catalyst	—

3.1.3. Studying Effect of Temperature on Yield

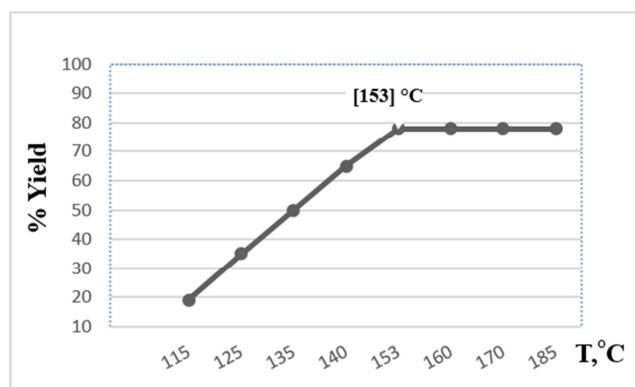


Figure 4. The effect of temperature on yield.

Temperature can play an important role in yielding in nucleophilic substitution reactions [18]. The high temperature improved the yield, until $T = 153^\circ C$ (boiling point of solvent), after this degree, the yield didn't changed because the solvent will remain boils at the same degree. The

effect of temperature on reactions is demonstrated in Figure 4. In order to orient the substitution on the hydroxyl group, the higher temperature above the boiling point of solvent is necessary, while in low temperature the yield was not good, that is due to hard conditions which it is necessary to the bimolecular nucleophilic substitution [17-19].

3.1.4. Studying Effect of Time on Yield

The effect of reaction time on the yield has been studied, it has been noticed that the best yield of the compounds at the optimum temperature ($153^\circ C$) needs to 12 h, but at the longest time, the yield begins to decrease, because the oxidization of the aldehyde group to a carboxylic acid ($COOH$), that is confirmed by observing the reaction via (T. L. C) Figure 5.

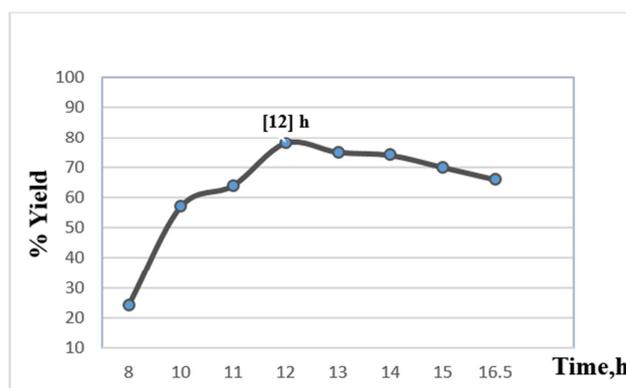


Figure 4. The effect of time of reaction on yield.

3.1.5. Studying Effect of Catalyst on Yield

The best yield obtained with the Basic Catalysts, weak and strong base such K_2CO_3 or KOH, both improved the yield in comparison to the acidic catalysts such $NaHCO_3$; The following Table 5 illustrates the comparison between Base Catalysts in terms of yield and reaction time.

Table 5. Comparison between Weak Base Catalysts and Strong Base Catalysts.

Solvent	K_2CO_3		KOH	
	Time (h)	Yield (%)	Time (h)	Yield (%)
MeOH	24	55	28	50
CH_3CN	18	58	24	55
DMF	12	78	12	68
DMSO	10	71	10	68

After this study, the optimum conditions for the preparation of EDOD, The compounds: OEBOD and PMOD by the reaction between the salOH and the Aromatic and aliphatic halides.

3.2. Spectroscopic Studies of the Resulting Compounds

3.2.1. Physical Properties of the Synthesized Compounds

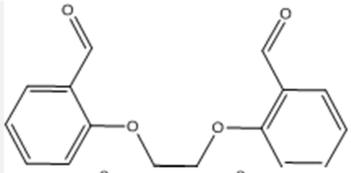
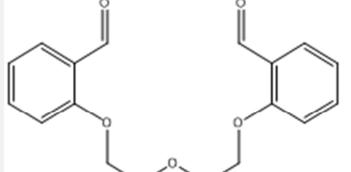
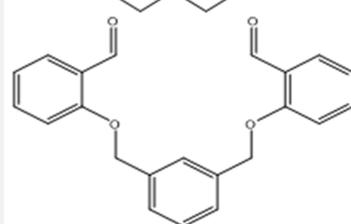
Three dialdehyde compounds have been synthesized in the selected optimum condition as demonstrated above, some Physical Properties, Yields and Element Analysis are presented in the Table 6:

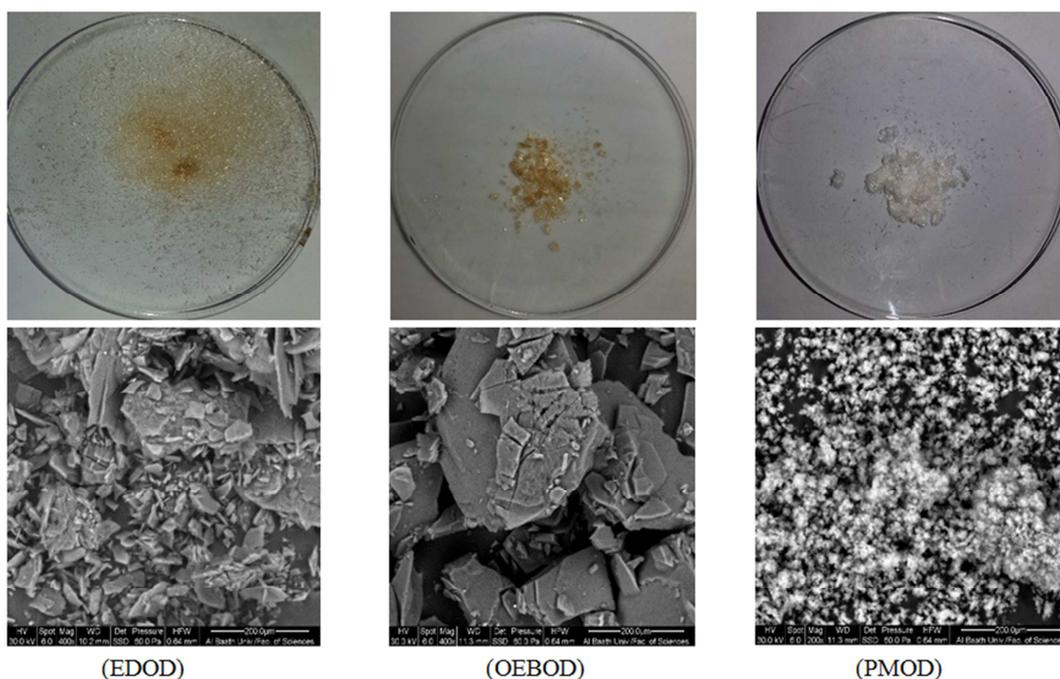
3.2.2. IR and NMR Spectra of Synthesized Compounds

The FT-IR spectra of the studied Compounds shown the characteristic EDOD absorption bands at 2923 cm^{-1} ($\text{C}_{\text{SP}^3}\text{-H}$ stretching), 1686 cm^{-1} (-C=O stretching), 1627 cm^{-1} (-C=C stretching), 1290 cm^{-1} (Ar-O bending), and 1045 cm^{-1} (C-O-C stretching), which provided evidence of the Ethers, and Aldehydes functional groups. The spectra of the OEBO and PMOD compounds, shown absorption bands at 2932 cm^{-1} ($\text{C}_{\text{SP}^3}\text{-H}$ stretching) and 1688 cm^{-1} (-C=O stretching). The successful synthesis of the three compounds confirmed by the disappearance of the large absorption of the OH stretching in the resulting compounds at 3435 cm^{-1} and Shift of the

stretching band of the carbonyl group (-C=O stretching) at $1680\text{-}1670\text{ cm}^{-1}$, and it confirmed by the it the obvious absorption band at $1180\text{-}1045\text{ cm}^{-1}$ and binding absorption of the C-O-C bond. In another hand, the confirmation of the purity of the formed compounds achieved by the HPLC chromatograms of the standard (salOH) and resulting compounds in the following selected conditions: ($\lambda_{\text{max}} = 320\text{ nm}$, MeOH and Acetonitrile as mobile phase by using reversed-phase ODS column for 10 min. The retention time of the three dialdehydes: EDOD, OEBO and PMOD as well as the standard (salOH) eluted between 4.80 and 5.20 min. (Figure 8).

Table 6. Physical Properties, elemental Analysis and yields of synthesized compounds.

Entry	Yield	color	Elemental Analysis % Found (% Calc)	
			C	O
	80	Bright brown	70.69 (71.10)	23.42 (23.68)
	80	Bright brown	66.89 (68.78)	25.13 (25.45)
	82	White needle	64.30 (65.45)	28.64 (29.06)



(EDOD)

(OEBO)

(PMOD)

Figure 6. Crystals form the three Compounds and their Dimensions under the Electronic Microscope.

Finally, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ spectra of resulting compounds EDOD, OEBOD and PMOD in CDCl_3 were recorded. The multiple observed in the region around δ 9.0-10.5 ppm in all the Synthesized Compound have been assigned to the aromatic protons. The signal in the region 0.5-4.5 ppm is due to methylene protons near to oxygen. The absence of an absorption in the region δ 14.0-15.0 ppm in the compounds indicate deprotonation of the phenolic (-OH) group of the Aromatic aldehydes and coordination to alkyl halide through the phenolic oxygen.

EDOD Yield: 80%, m. p: 120°C , $^1\text{H-NMR}$ (CDCl_3 , δ ppm): 4.29(s, 2H, $-\text{OCH}_2-$), 9.75-10.57(m, Ar-H), 13.15(s, 1H, CHO), $^{13}\text{C-NMR}$ (δ , ppm) CH_2 : 67.01, Aromatic: 112.69, 121.52, 125.21, 128.73, 135.94, 160.72, CHO: 189.37.

OEBOD Yield: 80%, m. p: 76°C , $^1\text{H-NMR}$ (CDCl_3 , δ ppm): 0.9-1.1(dd, 2H, $\text{CH}_2\text{-O-ph}$), 0.6-0.8 (ddd, 2H, O- CH_2), 3.5-4.75 (m, Ar-H), 4.0 (s, 1H, CHO), $^{13}\text{C-NMR}$ (δ , ppm) OCH_2 : 68.32, CH_2Oph : 69.91, Aromatic: 112.84, 121.12, 125.09, 128.45, 135.95, 161.09, CHO: 189.70.

PMOD Yield: 82%, m. p: 75°C , $^1\text{H-NMR}$ (CDCl_3 , δ ppm): 1.55(s, 4H, $2\text{CH}_2\text{O}$), 5.20-7.88 (m, Ar-H), 10.52 (s, 1H, CHO), $^{13}\text{C-NMR}$ (δ , ppm) CH_2 : 70.22, Aromatic: 112.97, 121.20, 125.18, 126.05, 127.20, 128.66, 129.24, 135.95, 136.74, 160.86, CHO: 189.68.

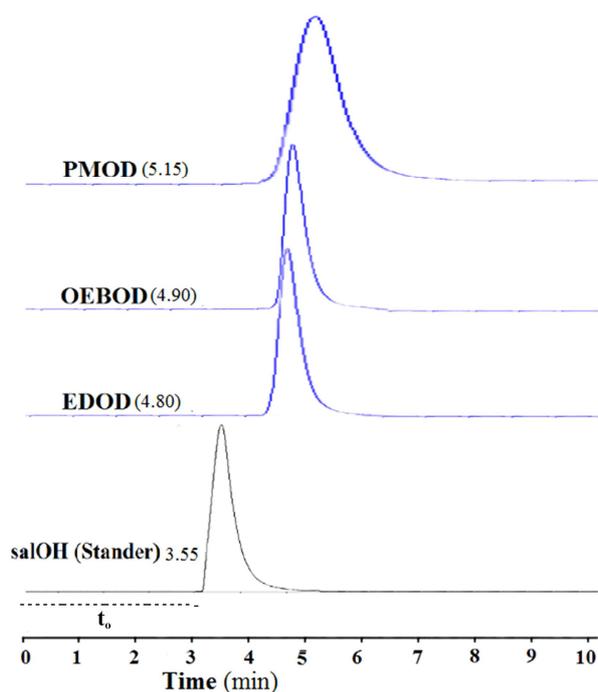


Figure 7. Chromatograms of 20 μml solutions of the standard and samples of the synthesised compounds, $\lambda_{\text{max}} = 320 \text{ nm}$; MeOH, Acetonitrile; flow rate = 1 ml/min; $t_0 = 3.10 \text{ min}$. samples: (I) EDOD; (II) OEBOD; (III) PMOD.

4. Conclusions

From the above mentioned results, The synthesis of three dialdehyde compounds was achieved by the condensation of salicylaldehyde with 1,2-dibromoethane, bis (2-chloroethyl)

ether and dichloro-*m*-xylene in percentage of 2:1 molar ratio (salOH: Halide), these compound can be used as in the synthesis of Schiff bases by condensation with a suitable amine. The effect of heterogeneous (K_2CO_3 , KOH, NaHCO_3) catalysts on the yield of the resulting compounds were studied in comparison with the yield without using the catalyst. The using of K_2CO_3 catalyst improved the yield. The influence of many polar solvents such: Methanol, Tetrahydrofuran, Dimethylformamide and Dimethyl sulfoxide and the influence the temperature and the effect of the time have been studied. The best yield obtained with the DMF in 153°C at time of 12 h. The three compounds can be used as beginning compound to synthesis of many macrocyclic Schiff bases in condensation with many open or cyclic amine.

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References

- [1] Misbah. R, Imran. M, Arif. M, 2013, Synthesis, Characterization and in Vitro Antimicrobial Studies of Schiff-Bases Derived from Acetylacetone and Amino Acids and their Oxovanadium (IV) Complexes, *Am J of Appl Chem*, V. 4, P. 59-66.
- [2] Arif. M, Qurashi. M, Shad. M, 2011, Metal-based antibacterial agents: synthesis, characterization, and in vitro biological evaluation of cefixime-derived Schiff bases and their complexes with Zn(II), Cu(II), Ni(II), and Co(II), *J of Coord Chem*, V. 64, P. 1914-1930.
- [3] Min. W, Liu-Fang. W, Yi-Zhi. L, Qin-Xi. L, Zhi-Dong. X, 2001, Antitumour activity of transition metal complexes with the thiosemicarbazone derived from 3-acetylumbelliferone, *Trans Metal Chem*, V. 26, P. 307-310.
- [4] Abdullah. M, Salman. A, 2010, Synthesis and Anti-Bacterial Activities of Some Novel Schiff Bases Derived from Aminophenazone. *Molecules*, V. 15, P. 6850-6858.
- [5] Maji. M, Ghosh. S, Chattopadhyay. S, 1999, Studies on Ru(II) complexes of 4 (4- tolyl) thiosemicarbazone of 2-acetylpyridine (LH). First synthesis and structural characterization of a Ru complex containing the imine (mpi). Crystal structure of $[\text{Ru} (\text{LH}) (\text{PPh}_3)_2 \text{Cl}] \text{Cl} \cdot \text{CH}_2\text{Cl}_2$ and $[\text{Ru} (\text{LH}) (\text{PPh}_3) (\text{mpi})] \text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2 \cdot 3\text{H}_2\text{O}$, *J. Chem. Soc. Dalton Trans*, P. 135-140.
- [6] Sengupta. P, Dinda. R, Ghosh. S, Sheldrick. W, 2003, Synthesis and characterization of some biologically active ruthenium (II) complexes of thiosemicarbazones of pyridine 2-aldehyde and thiophene 2-aldehyde involving some ring substituted 4-phenylthiosemicarbazides and 4-Cyclohexylthiosemicarbazide. Crystal Structure of Cis- $[\text{Ru} (\text{PPh}_3)_2 (\text{L}_6\text{H})_2] (\text{ClO}_4)_2 \cdot 2\text{H}_2\text{O}$ [$\text{L}_6\text{H} = 4-$ (Cyclohexyl) Thiosemicarbazone of Pyridine 2-Aldehyde]. *Polyhedron*, V. 22, P. 447-453.

- [7] Christian. G, 1996, Analytical strategies for the measurement of lithium in biological samples, *J Pharm Biomed Anal*, V. 14, P. 899-908.
- [8] Ibrahim. U, Ismet. B, Turgut. K, 2006, Synthesis, complexation and antifungal, antibacterial activity studies of a new macrocyclic schiff base. *J of Heterocyclic Chem*, V. 43, P. 1679-1684.
- [9] Ariadni. Z, George. P, Antonios. H, 2016, Synthesis, structural, thermal characterization and interaction with calf-thymus DNA and albumins of cationic Ni(II) complexes with 2,2'-dipyridylamine and salicylaldehydes, *Polyhedron*, p. 1-33.
- [10] Eila. P, Markku. L and Hannu. E, 2011, Substituted Salicylaldehydes as Potential Antimicrobial Drugs: Minimal Inhibitory and Microbicidal Concentrations, *Z. Naturforsch*, V. 66, P. 571-580.
- [11] Mounika. K, Anupama. B, Pragathi. J and Gyanakumari. C, 2010, Synthesis, Characterization and Biological Activity of a Schiff Base Derived from 3-Ethoxy Salicylaldehyde and 2-Amino Benzoic acid and its Transition Metal Complexes, *J. Sci. Res*, V. 2, P. 513-524.
- [12] Michael. S, Jerry. M, 2007, MARCH'S ADVANCED ORGANIC CHEMISTRY, John Wiley & Sons, Inc, p. 1-2357.
- [13] Hongchuan. X, Liangning. Hu, Jianqiang. Yu, 2017, A green catalytic method for selective synthesis of iodophenols via aerobic oxyiodination under organic solvent-free conditions, *Catalysis Communications*, p. 1-18.
- [14] Selmi. B, GontierE, Ergan. F and Thomas. D, 1997, Enzymatic synthesis of tricaprylin in a solvent-free system: lipase regiospecificity as controlled by glycerol adsorption on silica gel, *Biotechnology Techniques*, V. 11, pp. 543-547.
- [15] Meenakshisundaram. S, Nikolaos. D, 2012, Designing bimetallic catalysts for a green and sustainable future, *Chem. Soc. Rev*, V. 41, P. 8099-8139.
- [16] Olayinka. B and Ibitola. B, 2004, Rationalization of the conflicting effects of hydrogen bond donor solvent on nucleophilic aromatic substitution reactions in non-polar aprotic solvent: reactions of phenyl 2, 4, 6-trinitrophenyl ether with primary and secondary amines in benzene-methanol mixtures, *Tetrahedron*, V. 60, P. 4645-4654.
- [17] Mikhail. K, Oleg. B, 2014, The mechanisms of nucleophilic substitution in 1-methyl-3, 4, 5-trinitropyrazole, *Computational and Theoretical Chemistry*, V. 1033, P. 31-42.
- [18] Henry. M, Adele. R, 2012, Impact of fluorine substituents on the rates of nucleophilic aliphatic substitution and b-elimination, *Journal of Fluorine Chemistry*, V. 135, P. 167-175.
- [19] Michele. A, Germani. R, 2013, Effects of temperature on micellar-assisted bimolecular reaction of methylphtalene-2-sulphonate with bromide and chloride ions, *Journal of Colloid and Interface Science*, V. 402, P. 165-172.