Synthesis, Characteristics and Physico-chemical Study of Some Dichloro Pyrazoles

Suchita Nimbalkar

St. Vincent Pallotti College of Engineering & Technology

Nagpur (Maharashtra), India

Tel: 94-23-410-141   E-mail: suchitadn@yahoo.co.in
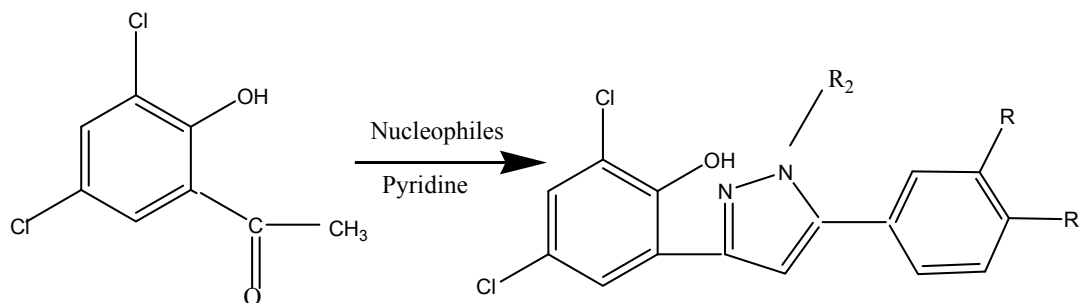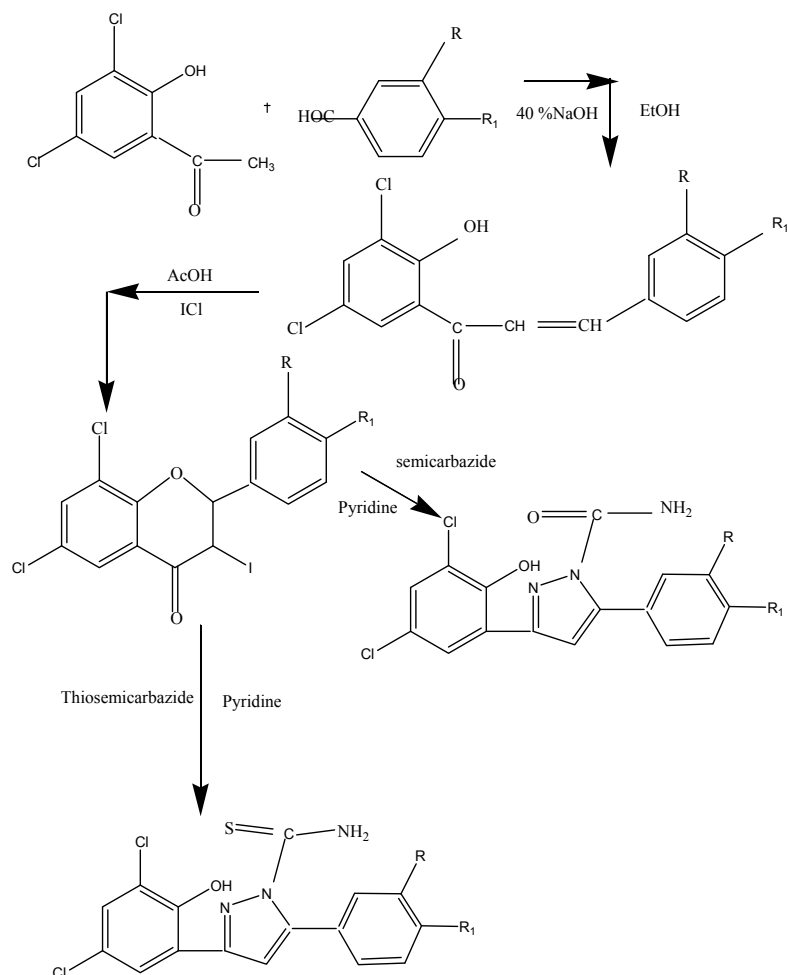
Abstract

Some new 3,5-Diaryl-1-substituted pyrazoles have been synthesized by the action of isonicotinic acid and thio-semicarbazide on 3-iodo flavanones in pyridine medium. 3-iodo flavanones obtained from 2-hydroxy-3,5-dichloro chalcones and ICl in acetic acid. Structure of these compounds has been established by chemical and spectral analysis (NMR & IR). Purity of these heterocycles was checked by TLC. The interaction of Cu(II), Co(II) with 1-carboxamido-3-(2-hydroxy-3,5-dichloro pheyl)-5-(4-methoxy phenyl) pyrazole (L_1), 1-thiocarbaxomedo-3(2-hydroxy-3,5-dichloro pheyl)-5-(4-methoxyphenyl) pyrazole (L_2) have been carried out by employing Bjerrum -Calvin pH metric titration technique, at 27 $°C$ in 70 % dioxane-water medium. The data obtained can be used for the determination of proton ligand formation numbers (η). From the formation curve, the proton-ligand stability constant pK values have been evaluated using half integral method. The metal ligand formation numbers (η) are estimated by using Irving Rossotti's expression.

Metal-Ligand stability constants for 1:1 complex & 1:2 complex have been calculated which are designated by letters log K_1 & log K_2 respectively.

Keywords: 1-(2-hydroxy-3,5-dichlorophenyl)-3-aryl-prop-2-ene-1-ones, 3-iodo flavanones, 3,5-Diaryl-1-substituted pyrazoles, Proton-Ligand formation numbers, Metal-Ligand stability constants

1. Introduction

The literature survey reveals the importance of chalcones and flavanones as a valuable starting materials for synthesis of hetero cycles like pyrazolines, pyrazoles & isoxaxolines etc. Formation of pyrazoles has been reported by many scientists. Pyrazoles are found widely useful in drugs & dyes. These compounds also show physiological activities (E. Herman & J. Gablis, 1961; I. I. Grandbery et al., 1962; M. V. Kadu & V. S. Jamode, 1998). Trifluoromethyl-1-aryl derivatives of pyrazoles are used as analgesic, antipyretic and anti inflammatory agents (R. G. Micetich & R. B. Rastigl, 1983), 1-phenyl derivatives are effective antidiabetics (P. L. Anderson & N. A. Paolella, 1982). Acyl amine and chloro pyrazoles have been found to be effective herbicide (El Saied A. Aly et al., 2004) Phenyl pyrazoles act as insecticides (Thakre V. G., 1989), antimicrobial agents (Moged A. Berghot & Evelin B. Moawad, 2003), hypolipidermic agents (Seki, K. et al., 1984) etc. Substituted pyrazoles are found to be excellent anti fungal agent (Sakamepo Hidekazu et al., 1988), Number of pyrazole derivatives have been synthesized and found to posses biological activity (Rajeev Jain & Seema Gupta, 1996).

It has been suggested that biological evaluation of new bio active molecules containing pyrazol nucleus is important for the creation of promising new analgesic agents (J. Milano et al., 2008; Z. Tabarelli et al., 2004; M. C. Godoy et al., 2004).

Some new heterometalic Ge(IV) and Co(II), Ni(II) and Cu(II) complexes based on ethylene diamine tetra acetic acid (EDTA) were synthesized (E. E. Martsinko et al., 2005).

Some physicochemical constants of some compounds were analyzed by spectral characteristics (Ya. A. Shuster et al., 1974).

Some substituted benzyl groups resulted in marked improvements in potency, ligand efficiency and Ligand-lipophilicity efficiency (Charles E. Mowbray et al., 2009).

The route for the synthesis of some pyrazole derivatives from substituted 3-iodo flavanones are obtained according to the literature procedure (M. G. Joshi, 1983). The literature survey clearly indicate these newly

1-substituted-3,5-diaryl pyrazoles are not get synthesized.

In view of analytical application of pyrazoles dissociable hydroxy (-OH) group is necessary to know the physico-chemical properties such as proton-ligand & metal-ligand stability constant. Sawalakhe P. D., Narwade M. L. (1994), have investigated the metal-ligand stability constant of Fe(II), Cr(III), Al(III) metal ion complexes with some substituted pyrazoles & pyrazolienes. Narwade et al. (1994) studied formation and stability constants of Th(IV) complexes with some substituted pyrazolines. The complexes of some bivalent metal ions such as Co(II), Ni(II), Zn(II), Cd(II) and Hg(II) with 4-amino-3-thio-6-methyl-2,3,4,5-tetrahydro-1,2,4-triazine have been investigated by Singh et al. (1988). Similarly the derivative of triazines formed complexes with Ni(II), Pd(II), and Pt(II) metal ion have been reported (Vogel A. I., 1977).

But Cu(II), Ni(II) with newly synthesized substituted pyrazoles in the laboratory have not been studied for complex formation. It was therefore thought of interest to confirm the dissociation of -OH group and study the stability constant of these substituted pyrazoles with Cu(II) and Ni(II) metal ions under the suitable condition pH-metrically at 0.1 M ionic strength.

2. Experimental

Melting points are uncorrected. IR spectra in KOH were recorded on PE-577/ PE-781 IR spectrophotometry. NMR in DMSO were in Brucker spectrophotometer (EM 390).

2.1 Preparation of 2-hydroxy-3-5-dichloro Chalcones (1a)

To the boiling solution of 2 hydroxy-3,5-dichloro acetophenone (0.01 Mole) in ethanol (20 ml), aromatic aldehyde (0.01 mole) was added. Then 40 % solution of NaOH (3 mole) added slowly. The mixture was stirred mechanically at room temp for one hour till it was solidified. It was decomposed after 6 to 8 hours with ice cold 1:1 HCl. Yellow colored solid obtained was filtered. Wash with sufficient water. The product obtained was crystallized from ethanol acetic acid mixture to get yellow crystals of chalcone physical data of 2-hydroxy-3-5-dichloro chalcones (1a) were recorded in table 1.

2.2 Preparation of 3-iodo Flavanones (2a)

Chalcone was suspended in ethanol and then treated with ICl in glacial acetic acid. The reaction mixture was brought to boiling. The solid that separated on cooling that filtered after two hours and crystallized from acetic acid and ethanol mixture. Physical data of 3-iodo flavanones (2a) is recorded in table 2.

2.3 Preparation of 3-5 diaryl Pyrazoles (3a-3b)

A Mixture of 3-iodoflavanone (0.01 mole), nucleophile (0.02 mole) such as Isonicotinic acid hydrazide, semicarbazide and thiosemicarbazide in pyridine (40 ml) was refluxed for 5 hours. The reaction mixture was diluted by 1:1 HCl. The product obtained was crystallized from ethanol-acetic acid mixture to get pale yellow product. Physical data of series (3a-3b) recorded in table 3.

3. Experimental for Physico-chemical Studies

pH metric titration are carried out by using following chemicals

1)   Distilled water: Carbon dioxide free distilled water is used. This water was redistilled by passing over alkaline $KMnO_4$ and having pH 6.94.

2)   Sodium hydroxide solution: Solution of NaOH free from carbonate was prepared (Vogel A. I., 1977). Solution was standardized having 0.10 M concentration.

3)   Potassium nitrate: Desire amount of KNO_3 was dissolved in double distilled water to prepared 1.0 M concentration solution.

4)   Nitric acid: HNO_3 was diluted with double distilled water to prepared 0.01 M solution and it then standardized with NaOH Solution.

5)   Metal Solutions: A.R. Grade Copper Nitrate and Nickel nitrate salts are used for preparing metal ion solution and their concentration were estimated by slandered procedure (Vogel A. I., 1977).

6)   Ligand Solution: 0.01 M ligands synthesized in our laboratory were prepared by dissolving appropriate quantity in dioxane (AR). The purity of compounds was checked by melting points, I.R. and N.M.R. Spectral data.

3.1 Systronics Model

pH meter (accessory + 0.05 unit) along with standard calomel electrode and glass electrode calibrated with buffer solution of pH 4.0, 7.0 and 9.2 at 27 ℃ was used for the pH measurements. The titrations were carried out in 100 ml Pyrex glass beaker and temperature is maintained at 27 ℃. Nitrogen gas was slowly bubbled to remove oxygen

and carbon dioxide. The pH- meter readings were taken only after the gas bubbling system were considered.

Set I-Free acid titration.

A solution containing nitric acid and potassium nitrate (1.0×10^{-2} M) in 70 % dioxane - water mixture.

Set II -Free acid ligand titration.

A solution containing nitric acid, potassium nitrate and ligand (20×10^{-4} M) in 70 % dioxane - water mixture.

Set III - Free acid Metal - ligand titration.

A solution containing nitric acid, potassium nitrate, ligand and metal ion (4×10^{-4} M) in 70 % dioxane - water mixture.

From free acid titration and acid-ligand titration proton-ligand formation numbers (ηA) can be calculated by using formula.

$$\eta A = r - \frac{(E_0 + N) \times (V_2 - V_1)}{(V_0 + V_1) TL_0}$$

where,

r - Number of dissociable protons from ligand

E_0 - Concentration of HNO_3

N - Normality of NaOH

V_1 & V_2 - Volume of alkali consumed by acid and ligand on same pH

V_0 - Initial Volume

TL_0 - Ligand concentration

From free acid titration and Metal ligand titration, Metal-Ligand formation numbers (η) can be calculated by using formula-

$$\eta = \frac{(E_0 + N) \times (V_3 - V_2)}{(V_0 + V_2) \times T^0M \times \eta A}$$

Where, T^0M - Metal concentration.

The graphs were constructed between pH Vs ηA and pH Vs η. From these graphs another graphs were constructed between volumes of NaOH Vs pH of solution.

4. Result and Discussion

4.1 Proton - ligand Dissociation Constant (pK)

The algebraic method has been used to determine the dissociation constants of ligands at 0.1 M ionic strength pH-metrically.

The deviation of (acid + ligand) curve from acid curve started at pH 2.8. It remains constant up to pH- 9.0 and it increased continuously up to pH 12. This indicated dissociation of -OH group from ligand with respect to change in pH of solution

4.2 Proton - ligand Formation Number

Proton-ligand formation numbers ηA were calculated from acid titration curve (A) and (A + L) by Irving and Rassotti's expression. It was found that values of ηA decreased with increasing pH of solution due to replacement of H^+ ion from -OH group.

Formation curves were constructed between the value of ηA and pH. The proton-ligand stability constants (pKL) were calculated from half integral methods i.e. pH at $\eta A = 05$ The pK Value of ligands are presented in table 4.

4.3 Metal - ligand Formation Number (η)

The deviation of ($\eta + L + M$) curves from (A + L) curves started at about pH-2.5 it indicated the complex formation. The metal-ligand formation numbers (η) were calculated by standard equation, which shows n value goes on increasing with increase in pH value.

The formation curves were constructed between the value of pH and η. The metal-ligand stability constant were

calculated by half integral method at pH = 0.5 and 1.5 showing 1:1 and 1:2 complex formation respectively.

For 1:1 complex log K_1 is calculated from following formula

$$\log K_1 = \log \frac{\left[H^+\right]}{KLX\left(TL_0 - TM_0 X_n\right)} \quad \eta = 0.5$$

And for 1:2 complex log K_2 is calculated from following formula

$$\log K_1 = \log \frac{\left[H^+\right]}{KLX\left(TL_0 - TM_0 X_n\right)} \quad \eta = 1.5$$

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Table1. Physical characterization data of 2-hydroxy-3-5-dichloro chalcones (1a)

Compounds	R_1	R_2	yield %	m.p. ℃	Molecular formula
1a	H	OCH_3	85	168-170	$C_{16}H_{12}O_3Cl_2$

Spectral Interpretation of 1a

IR (max cm^{-1}): 3068.2 (Ar-H); 1599 (C=C); 702, 737,780, (C-H); 824 (C-Cl); 1045 (C-O-C); 1637.3 (C=0)

HNMR: OH (CDCL$_3$, ppm); 3.87(S, 3H), 6.9-7(m 64), 3.53 (S$_2$lH)

Table 2. Physical characterization data of 3-iodo flavanones (2a)

Compounds	R_1	R_2	yield %	m.p. ^{0}c	Molecular formula
2a	H	OCH_3	70	180	$C_{16}H_{12}O_3Cl_2$

Spectral Interpretation of 2a

IR (max): 3075 cm^{-1} (Ar-H); 1588.4 cm^{-1} (c=c); 736, 821.9 cm^{-1}, (C-H); 635.5 cm^{-1} (C-Cl); 1068.9 cm^{-1} (C-I); 1685.6, 1173.6 cm^{-1} (C=0)

1HNMR: OH (CDCl$_3$, ppm); 3.8 (5, 3H), 4.64 (d$_1$ H$_a$) 4.84 (d$_1$ H$_b$) 6.9-7.66 (m 6h)

Table 3. Physical characterization data 1-substituted-3,5-diaryl pyrazoles (3a-3b)

Compounds	R_1	R_2	R_3	yield %	M.P	Rf value	Molecular formula
3a	H	OCH_3	$CONC_5H_4$	55	212	0.71	$C_{22}H_{15}O_3Cl_2N_3$
3b	H	OCH_3	$CSNH_2$	50	220	0.52	$C_{16}H_{11}O_2Cl_2N_3S$

Spectral Interpretation of (3a, 3b)

IR (max cm^{-1}): 3075.1 (Ar-H); 1588, 1514 (c=c); 876.6, (C-H); 635, 736 cm^{-1} (C-Cl); 3349 (O-H); 1068, 1024 (C-O);1773 (C=O); 2365.8: 3349 (C-N)

1HNMR: OH (CDCl$_3$, ppm); 3.92(Si, 3H); 6.3-7.99 (m$_1$ 64)

Table 4. Proton - ligand stability constants (pK) of the ligands

System	Ligand - L_1	Ligand - L_2
pK - values	7.80	10.80

pK ligand 2 > pK value 1

It is observed form table 4, that the proton - ligand stability constant (pK) of ligand - L_1 is found to be less. The reduced value of the ligand may be due the presence of dichloro and methoxy (-OCH$_3$) electron withdrawing group.

Table 5. Metal ligand stability constants of the complexes

System	Stability constants	Difference in stability constants
	Log K_1	Log K_2
Cu (II) - L_1 complex	8.8250	3.1669
Ni (II) - L_1 complex	8.9250	7.7670
Cu (II) - L_2 complex	7.9447	5.3538
Ni (II) - L_2 complex	6.6447	3.2538

It could be seen from table 5, Ni (II) - L_1 Complex occurs simultaneously because there is no as an appreciable difference between log K_1 and log K_2 values. Rest of complexes occurs step wisely due to sufficient difference between log K_1 and log K_2 values. It is also observed that ligands L_1 and L_2 both are good chelating agents due to higher stability constant values.

These pyrazoles are identified as good complexing agents and antimicrobial agents.

Plot between n̄ Vs pH
Ligand No. 1
System – Cu(II) – Complex

Plot between n̄ Vs pH
Ligand No. 1
System – Ni(II) – Complex

Plot between n̄ Vs pH
Ligand No. 2
System – Cu(II) – Complex

Plot between n̄ Vs pH
Ligand No. 2
System – Ni(II) – Complex