International Journal of Advanced Chemistry, 2 (1) (2014) 20-23

International Journal of Advanced Chemistry

Journal home page: www.sciencepubco.com/index.php/IJAC
doi: 10.14419/ijac.v2i1.1628
Research Paper

Synthesis, complexation, spectral and antimicrobial study of some novel 5-bromo-2-fluorobenzaldehydeoxime and semicarbazone under ultrasonic irradiation

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Abstract

In this newly approached method a novel series of Transition metal complexes were synthesized by ultrasonic irradation. The reaction of 5-bromo-2-fluorobenzaldehydeoxime (L1OX) and 5-bromo-2-fluorobenzaldehydesenicarbazone (L2SC) by reaction with Cu(II) and pd(II)chloride salts. The complexes were characterized by elemental analysis, Ultraviolet, Infrared and NMR spectral studies. The anti-microbial activities of the ligand and its metal complexes were estimated.

Keywords: *Substituted Benz aldehyde, metals, complexes, antibacterial and antifungal activity*.

1. Introduction

Semicarbazone are the Schiff bases, usually obtained by the condensation of semicarbazone with suitable aldehydes and ketones (Fig1).

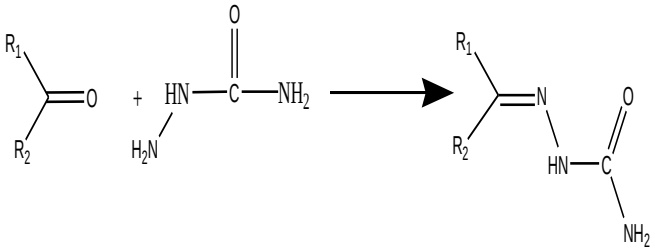
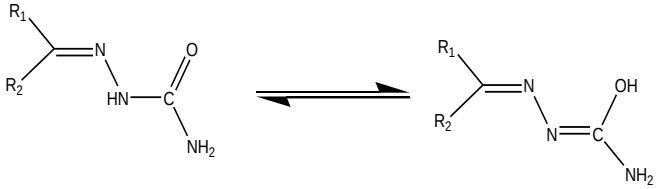


Fig. 1: Method of synthesis of the semicarbazone

An interesting attribute of the semicarbazones is that in the solid state, they predominantly exist in the keto form, whereas in solution state, they exhibit a keto-enol tautomerism (Figure 1). Keto form acts as a neutral bidentate ligand and the enol form can deprotonate and serve as monoanionic bidentate ligand in metal complexes. Thus semicarbazones are versatile ligands in both neutral and anionic forms.



keto (A) enol (B)

Fig. 2: Scheme1.2.Keto-enol tautomerism of semicarbazone.

Both tautomeric forms have an efficient electron delocalization along the semicarbazone moiety. Aromatic substituents on the semicarbazone skeleton can further enhance the delocalization of electron charge density. These classes of compounds usually react with metallic cations giving complexes in which thesemicarbazones behave as chelating ligands. Upon coordination to a metalcenter, the delocalization is further increased through the metal chelate rings. The coordination possibilities are further increased if the substituent has additional donor atoms.

In recent years, the chemistry of coordination compounds has shown rapid development in diverse disciplines as a result of possible use of these new compounds in biological applications. Transition metal complexes with potential biological activity are the main focus of extensive investigation. The biological importance of oximes and their complexes is very well known. Metal complexes with ligands containing nitrogen and oxygen donor atoms have act as the fungicidal agents. Synthesis of oximes and semicarbazone and their complexes with different transition metals are reported in the literature[1-7]and found to be active as antibacterial , ant tubercular [8-9] ,antilepral [10], antiviral [11], antimalarial[12] tumours [13-14] pesticide [15] herbicide [16]anticonvulsant activity[17]and hypnotic[19] properties or the ability of some of their Cu(II) complexes to mimic superoxide dismutase activity [20]Semicarbazonecomplexesof some metal ions have been reported[21-24] .In this paper, a novel series of transition metal complexes with oxime and semicarbazone were synthesized and they were screened for antimicrobial activities. Most of the complexes were shown moderate to good antibacterial and antifungal activity.

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2. Experimental methods

The chemicals such as 5-bromo-2-fluorobenzaldahyde, Palladium (II) chloride were procured from Sigma-Aldrich Chem, Bangalore. Melting points were observed in open capillaries and were uncorrected. IR spectra of all compounds were recorded in Perkin-Elmer 883 spectrometer using KBr pellets. The antibacterial and antifungal activities of all compounds were observed using cup-plate method [11].

3. Results and discussion

In the present work, 5-bromo-2-fluorobenzaldehyde oxime and5-bromo-2-fluorobenzaldehyde semicarbazone was prepared by reaction of 5-bromo-2-fluorobenzaldehyde (dissolved in ethanol) was added to aqueous solution of semicarbazide hydrochloride and hydroxylamine hydrochloride under ultrasonic irradiationin the water bath of an ultrasonic cleaner at room temperature in accordance with the method described in the literature [25] . Ultrasound irradiation has been increasingly used inorganic synthesis in last three decades. Large number of organic reactions can be carried out in higher yield, shorter reaction time and milder conditions under ultrasonic irradiation. It was observed that the reaction time decreased considerably and the yields of the products promoted in the presence of ultrasonic irradiation.

3.1. Synthesis of 5-bromo-2-fluorobenzaldehyde oxime (L1OX)

A mixture of 5-bromo-2-fluorobenzaldehyde (0.02 mol) in 15mL ethanol was added to aqueous solution of hydroxylamine hydrochloride (0.08 mol) and sodium acetate (0.1 mol). The mixture was irradiated by an ultrasonic generator in a water-bath at 30-35 °C for 3 min. Evaporation of this solution gave a colorless solid.The solid productsformed were isolated and recrystallized with hot alcohol mixture the purity was checked by TLC paper.(yield: 84.3%).

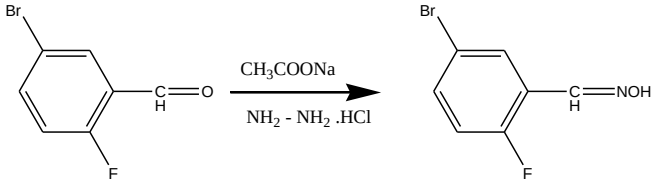
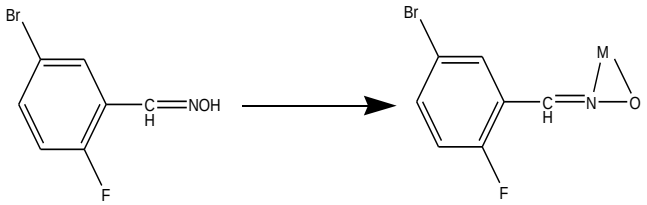


Fig. 3: Synthesis of oxime

3.2. Synthesis of Complexes of 5-bromo-2-fluorobenzaldehydeoxime with Cu (II) and Pd (II).

5-bromo-2-fluorobenzaldehydeoxime (0.002 mol) was dissolved in 15 mL Acetonitrile and was added to dissolve copper chloride and palladium (II) chloride (0.001 mol) in 15 mL acetonitrile. The mixture was irradiated by an ultrasonic generator in a water-bath at 30-35 °C for 8 min and then left to cool. Evaporation of this solution gave color solids.The solid products formed were isolated and recrystallized withhot alcohol the purity was checked by TLC paper.63.1% and 68.6%)

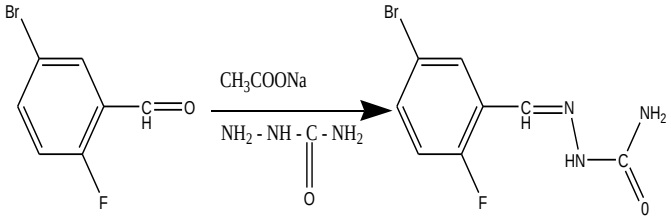


O and N Coordinate bond

Fig. 4: Synthesis of Complexes (M = Cu (II) &Pd (II)

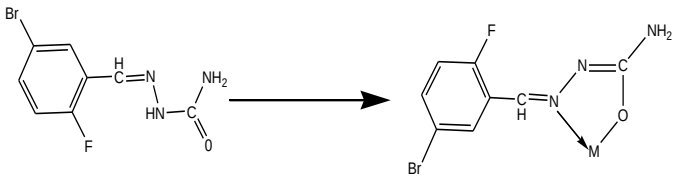
3.3. Synthesis of 5-bromo-2-fluorobenzaldehyde semicarbazone (L1SC).

A mixture of 5-bromo-2-fluorobenzaldehyde (0.02 mol) in 15mL ethanol was added to aqueous solution of semicarbazide hydrochloride (0.08 mol) and sodium acetate (0.1 mol). The mixture was irradiated by an ultrasonic generator in a water-bath at 30-35 °C for 12 min. Evaporation of this solution gave yellow solid.The solid products formed were isolated and recrystallized with hot alcohol mixture the purity was checked by TLC paper. (Yield: 76.1%).



3.4. Synthesis of Complexes of 5-bromo-2-fluorobenzaldehyde semicarbazone with Pd (II).

5-bromo-2-fluorobenzaldehydesemicarbazone (0.002 mol) was dissolved in 15 mL Acetonitrile and was added to dissolvedpalladium (II) chloride (0.001 mol) in 15 mL acetonitrile. The mixture was irradiated by an ultrasonic generator in a water-bath at 30-35 °C for 30 minand then left to cool. Evaporation of this solution gave a color solids,The solid products formed were isolated and recrystallized with hot alcohol mixture the purity was checked by TLC paper. (Yields 73.1% and 68.5%).



M = Pd (II)

4. Results and discussion

Table 1: CHN elemental analysis data (in %) of the ligands and complexes.

Compound	Color	M.P °C	Empirical formulae	Elemental analysis found (calculated %) C	H	N	M
L^1OX	White	82 – 86	C_7H_5NOBrF	38.49 % (38.54)	2.11 % (2.31)	6.15% (6.08)	-
L^2SC	Yellow	184 -186	$C_8H_7N_3ObrF$	36.84 % (36.93)	2.62 % (2.71)	16.16 % (16.45)	-
$Cu[L^1OX]$	Green	158 – 162	$C_7H_5NOBrFCu$	41.24 % (41.39)	2.96 % (3.04)	5.98% (6.04)	-
$Pd[L^2OX]$	Brown	>250	$C_7H_5NOBrFPd$	41.29 % (41.37)	2.96 % (3.06)	5.95% (6.05)	-
$Pd[L^2SC]$	Brown	>250	$C_8H_7N_3OBrFPd$	36.85 % (36.93)	2.63 % (2.74)	16.16 % (16.47)	-

Table 2: UV – VISIBLE DATA

S.No	Name of the Compound	ʎ (max)
1	L^1OX	310, 297 and 250 nm
2	L^2SC	375, 305 and 280
3	Cu[L^1OX]	517 , 307, 297,and 250
4	Pd[L^2OX]	588 , 326, 307 and 297 nm
6	Pd[L^2SC]	454, 342 and 235

Table 3 (a): IR spectra (Oxime complexes)

Compound	υ(O-H)	υ (C=N)	υ(N-O)	υ (M-N)	υ(M–O)
L^1OX	3294	1633	972	-	-
Cu [L^1OX]	-	1593	975	526	621
Pd [L^1OX]	-	1591	974	619	677

Table 3 (b): IR spectra (SemicarbazoneComplexes)

Com-pound	υ(NH)	υ(C=N)	υ(C=O)	υ(NH_2)	υ(C-O)	υ(N–M)	υ(M–O)
L^1SC	3475	1604	1705	1463	-	-	-
Pd [L^1SC]	3307	1593	-	1487	1251	509	748

From the spectra of free ligand, $\pi \rightarrow \pi^*$ transitions were obtained. Then $n \rightarrow \pi^*$ transitions are also associated with nitrogen of the azomethine and oxime group in the free ligand. In the complexes, the $n \rightarrow \pi^*$[27] transition was shifted to higher energy level. These results were indicated that the nitrogen and /or oxygen atom of the oxime groups were coordinated to the metal ions. These bands were assigned to both a charge transfer transition from the metal to anti-bonding orbital of the ligand and to spin allowed transition of the ligand. The observed absorptions of ligand such as 310, 297 and 250 nm were assigned to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions [15].

The infrared spectra of free ligand shown broad band at 3294 cm-1which correspond to –OH group of oxime. The IR frequency of all the complexes was shifted to lower frequencies for –OH of oxime. This may be due to formation of coordinate covalent bond through oxygen atom of hydroxyl group to metal. The IR frequency at 1633 cm-1 had indicated the existence of –C=N group. The IR spectra of the –entire C=N group of azomethine had also shifted to lower frequencies and it was shown the existence of coordinate bond formation with metals through nitrogen atom of azomethine group.

IR spectra of ligands show bands at 3320, 3325 and 3315 cm-1 which can be assigned to (N-H) of imino group17. The spectra of all the complexes show down shift (N-H) of imino group to the 3312-3155 cm-1 The next IR band of structurals significance in the spectra of the ligands appears at 1580, 1610 and 1605 cm-1. These bands can be assigned to the (C=N) groups. These bands have also down shift to the 1600-1580 cm-1 and clearly indicates the coordination of nitrogen to the metal ion.

IR spectra of ligands show broad bands at 3430, 3450 and 3420 cm-1 which can be

Assigned to (N-H) groups. These bands have also down shift to the 3323-3145 cm-1 and clearly

Indicates the coordination of nitrogen to the metal ion. The next IR band of structural significancein the spectra of the ligands appear at 1600, 1610 and 1600 cm-1. These bands can be assigned tothe(C=N) group. These bands have also down shift to the 1590-1575 cm-1 and clearly indicatethe coordination of nitrogen to the metal ion. On the basis of the above discussions.It's clear thatthe complexation of the free ligands and the transition metals have been formed.Moreover the shift in the C-O (carbonyl) vibration band on complexationsupported the coordination of carbonyl and oxime groups to the metal ion[27 -28].The presence of these bands supported the coordination of the ligands under investigation with the metal ion[29-30].

5. H-NMR spectra

5.1. 5-bromo-2-fluorobenzaldehydeOxime:

1H NMR (300MHz, CDCl3): 8.30 s, 2H (CH=NOH), 7.89 -7.48 d, 3H (Ar-H) 13C-NMR (DMSO, ppm): 161.01 (C=N-OH), 133.30-129.70 (Ar-C).

5.2. [5-bromo-2-fluorobenzaldehydeOxime) Cu]:

1H-NMR (DMSO, ppm): 11.82 s, 1H (O...H), 8.17 s, 1H (CH=NOH), 7.84 – 7.60 s, 3H (Ar-H). 13C-NMR (DMSO, ppm): 160.04 (C=N-OH), 140.83-129.01 (Ar-C).

5.3. [5-bromo-2-fluorobenzaldehydeOxime) Pd]:

1H-NMR (DMSO, ppm): 11.818 s, 1H (O...H), 8.17 s, 1H (CH=NOH), 7.84 – 7.62s, 3H (Ar-H). 13C-NMR (DMSO, ppm): 140.84 (C=N-OH), 133.67-129.01 (Ar-C).

5.4. [5-bromo-2-fluorobenzaldehyde semicarbazone]:

1H NMR (300MHz, CDCl3): 8.8 s, 2H (NH2), 8,26 -7.54 d,3H (Ar-H) 8,27 s , 1H(NH) , 13C-NMR (DMSO, ppm): 154.80 (C=O), 135.81-130.30 (Ar-C).

5.5. [5-bromo-2-fluorobenzaldehyde semicarbazone) Pd]:

1H-NMR (DMSO, ppm): 11.787 s, 1H (NH), 7.32 s, 2H (NH2), 7.54 -7.58S,3H (Ar-H). 13C-NMR (DMSO, ppm): 140.83 (C=N-OH), 133.67-129.01 (Ar-C).

1H-NMR spectra of the ligand and its Copper and Palladium complexes were recorded in DMSO-d6 solution. The 1H-NMR chemical shift at 8.30 ppm with sharp singlet had indicated the presence of aldehydic proton, which is lower field shifted to 8.13 ppm in the spectrum of the aldoxime ligand through the oximation reaction [17a-17b]. The spectrum of the 5-bromo-2-fluorobenzaldehydeoximeligand exhibited singlet at 7.45–7.60 ppm due to aromaticprotons[31].

In addition, the spectrum of the ligand 5-bromo-2-fluorobenzaldehydeoxime showed a singlet signal at 10.20 ppm due to the hydrogen of the –OH group. The 1H-NMR spectrum of the ligand exhibited a signal at 14.20 ppm, which can be attributed to the hydrogen bonded OH proton of the hydroxyl imino group.The coordination of the ligands have been further substantiated by the 1H NMR spectra of the ligands and some of their complexes with Cu(II), and Pd(II).

In the spectra of the ligands, the protons observed at (δ 8.0-8.1 ppm) shift downfield in the spectra of the complexes (δ 8.5-8.6 ppm), this deshielding is possibly due to the donation of the lone pair of electrons by the azomethine nitrogen to the metal atom resulting in formation of a coordination bond.

6. Antimicrobial assay

Synthesized compounds were tested for inhibition against the human pathogenic bacteria and fungi. Microbial assay were carried out by disc diffusion technique followed by Kelmanet al., 2001. Pathogenic bacterial strains were inoculated in sterile nutrient broth and incubated at 37 °C for 24h. Pathogens were swabbed on the surface of the Muller Hinton Agar plates and discs (Whatmann No.1 filter paper with 9 mm diameter) were impregnated with the 50 µl of synthesized compound on the surface.

In vitro antifungal activity of synthesized compound was determined against CzapexDoxAgar, inoculums of 24h old culture of Aspergillusflavuswell drained spores were distributed uniformly on the surface of the agar plates with the help of sterile cotton swab. Fungalstrain, Mucorsp. was inoculated by taking a piece of fungal colony using a sterile cotton swab and gently swabbed on the surface of the medium. Control discs were placed with antibiotic and solvents to assess the effect of antibiotic and solvents on pathogens. The plates were incubated at 37 °C for 24h and the antimicrobial activity was measured based on the inhibition zone around the disc impregnated with synthesized compounds.

The zone of inhibition in different bacterial strains against synthesized compoundss shown in Table 1. Among the various bacterial strains maximum zone of inhibition (13 mm) was recorded in Salmonella typhistrain and minimum zone of inhibition (2 mm) was observed in Vibrio cholera, Streptococcus pneumonia and Staphylococcus aureusstrains.

The antifungal activity of the synthesized compounds shows maximum activity (12 mm) in Mucorsp.

Table 4: Antimicrobial activity of synthesized compounds against human pathogens

S.No	Human pathogens	L^1OX	L^2SC	Cu(II)	Pd(II)	Pd(II)
1	Pseudomonas aeruginos	+	+	++	-	++
2	Vibrio cholera	+	+	++	+	+
3	Vibrio parahaemolyticus	+	+	-	+	+
4	Staphylococcus aureus	+	+	++	+	+
5	Escherichia coli	+	+	_	++	++
6	Streptococcus pneumonia	+	+	++	++	+
7	Salmonella typhi	+	+	++	++	++
8	Klebsiella pneumonia	+	+	+	++	+
9	Aspergillusflavus	+	+	+	++	++
10	Mucorsp	+	+	++	+	-
11	Ampicillin standard	+++	+++	+++	+++	+++

+++ (Std) ++ Moderately active + Active - Less active

7. Conclusion

In this paper, we have explored the synthesis and coordination chemistry of some mononuclear complexes derived from the di substituted benzaldehydeoxime and benzaldehydesemicarbazoneligandsunder ultrasonic irradiationin the water bath of an ultrasonic cleaner at room temperature.Its containing various transition metal complexes such us Cu (II) and Pd (II) were synthesized and evaluated, their antimicrobial activities using disk diffusion method against bacteria and fungi were determinated. According to the UV–Vis, IR and NMR data of the azomethine linked oxime ligand, the complexes coordinated to the metal ion through the oxime nitrogen and oxygen atom of the hydroxyl group in substituted benzaldehyde. Based on the obtained results, the structure of the coordination compound sunder investigation can be formulated as in Scheme II. In this work someobservations have been achied that lead to establish the followingpoints:

a) Benzaldehyde semicarbazone and oxime acts as bidentate chelating ligand, joint to Cu (II) andPd (II) ion through nitrogen and oxygen atoms.

b) (b)Mononuclear complexes have been proposedforall the resulted complexes.

c) It is observed that, in a complex, thepositive charge of the metal is partially shared with

The donor atoms present in the ligands, and there may be π-electron delocalization over the whole chelating.

Acknowledgement

The Sharmila Institute of Medicinal Products Research Academy (SIMPRA) Thanjavur, supported by providing necessity facilities for this research work. We are grateful to founder and chairman Mr. R.J.A. Ra.

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