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Synthesis, Characterization of β- amino ketone Complexes and Study of their Antibacterial Activity

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ABSTRACT

One pot mannich reaction of aromatic amine, aromatic aldehyde and aromatic ketone, in preference of catalytic amount of sulphamic acid furnish β- amino carbonyl compounds in good yields. These β- amino ketone was reacted with metal acetate of Co (II), Ni(II) and Mn (II), form square planer complexes in good yields. All the ligand and metal complexes obtained were well characterized by spectroscopic and analytical methods. The new metal complexes were tested for antibacterial activity against three pathogenic bacteria. B.subtilis, E.coli and B.cereus show good activity.

Keywords: Mannich reaction, β-amino carbonyl compounds, antibacterial activity, Transition Metal Complexes of β- amino ketone.

INTRODUCTION

Catalytic three component Mannich reaction is important reaction in organic synthesis foer carbon-carbon bond formation [1-3]. The β- amino carbonyl compounds are useful building blocks for the synthesis of drug intermidiates [4-5].

The β- amino carbonyl derivatives are the best ligands for formation of metal complexes due to present active functional group of 1, 4 position, carbonyl and NH groups gives facile hexagonal coordination compounds with transition metal salts. The asymmetric matal complexes are important, can be used in organic synthesis as catalyst.

The properties of coordination compounds depends upon the nature of donor ligands. The precursor of polar atoms such as O, N and the group OAc can increase the water solubility of these complexes. While the presence of aromatic group enhance lipid solubility. Hence these complexes can be easily penetrate in the bacteria cells and inhibit the cells division to prohibit their growth.

MATERIALS AND METHODS

NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Melting points were determined on a Gallenkamp melting point apparatus. The ^{1}H Chemical shifts were reported in ppm relative to tetramethylsilane

(TMS) and multiplicities are given as *s* (singlet), *bs* (broad singlet), *d* (doublet), *t* (triplet), *q*(quartet), or *m* (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectrum was recorded on Shimadzu MS mass spectrometer. Elemental analyses were performed on Thermo Quest Flash 1112 Series EA analyzer. Reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel 60 F254 (Merck) plates using UV light of 254 and 366 nm for detection. Compounds were purified by column chromatography using silica gel (Merck, 60-120 mesh) and column dimension is 39 x 2 cm2 and elution volume used was about 200-400 mL for each product.

2.1. General Procedure for the synthesis of β- amino carbonyl ligand

Aniline (0.42 mmol), Acetophenone (0.42 mmol), Benzaldehyde (0.42 mmol) were successively added to a solution of sulfamic acid (0.04 mmol) in alcohol (7ml). The resultant mixture was stirred at room temperature for 5-7 hrs and then etiolate with saturated aq. $NaHCO_3$ (3ml). The mixture was extracted with ethyl acetate, dried over Na_2SO_4, the solvent remove under vacuum and crystallized from ethanol. The solid obtained are dried at 100 °C for 8 hrs.

2.1.1. 1, 3-Diphenyl-3-(phenylamino) propan-1-one ***1a***

White solid: MP: 215-217. IR(KBr):1670(C=O), 1597(C=C), 3384(N-H) cm^{-1}, ^{1}H: NMR (500 MHz,$CDCl_3$) δ ppm: 3.44(d J= 6.2 Hz, 1H), 3.50 (d, J= 6.2 Hz, 1H), 5.03 (m, 1H), 6.54 (d, J= 7.8 Hz, 2H), 6.62-6.68 (m, 1H), 7.05-7.34 (m, 1H), 7.23 (d, J= 6.4 Hz, 1H), 7.29-7.34 (m, 2H), 7.42-7.55 (m, 5H), 7.89 (d, J= 7.8 Hz, 2H), MS (m/z): 301 (M^+): *Anal.* Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65; Found: C, 83.54; H, 6.47; N, 4.42.

2.1.2. 3-(4-Chlorophenylamino)-1,3-diphenylpropan-1-one ***1b***

White solid: MP: 257-260. IR(KBr):1666(C=O), 1598(C=C), 3371(N-H), 1091(Ar-Cl) cm^{-1}, ^{1}H: NMR (500 MHz,$CDCl_3$) δ ppm: 3.39(d J= 6.2 Hz, 1H), 3.45 (d, J= 6.2 Hz, 1H), 4.93 (m, 1H), 6.61 (d, J= 7.8 Hz, 2H), 6.61-6.67 (m, 1H), 7.04-7.31 (m, 2H), 7.19 (d, J= 6.4 Hz, 1H), 7.25-7.31 (m, 2H), 6.37(d,J= 8Hz,2H)7.05(d, J= 8Hz, 2H), 7.89 (d, J= 7.8 Hz, 2H), MS (m/z): 335 (M^+): *Anal*. Calcd for $C_{21}H_{17}ClNO$: C, 75.11; H, 5.40; N, 4.17; Found: C, 75.01; H, 5.53; N, 4.25.

2.2 General Procedure for the synthesis of Metal Complexes

The Solution of ligand amino ketone (0.20 mmol) in ethanol was added in the solution of [$MnCl_2$.6H2O] (0.20 mmol) in ethanol. To this mixture Triethyl amine (1 mL) was added and resultant reaction mixture was stirred at room temperature and then refluxed for 4-5 Hrs. During reflux, the precipitated metal complex was collected by filtration, washed with ethanol, dried in vacuum for 4 Hrs. Similar procedure was used for the synthesis of metal complexes with [$NiCl_2$.6H2O] and [$CoCl_2.2H_2O$].

2.2.1. [Co($C_{25}H_{24}NO_5$)] ***2***

Brown: MP: 201-204. IR: 1655(C=O), 1544(C=C), 3336(N-H), MS (m/z): 477 *Anal*. Calcd for [Co($C_{25}H_{24}NO_5$)]: C, 62.90; H, 5.07; N, 2.93, Co, 12.34; Found: C, 62.67; H, 4.93; N, 3.04, Co, 12.39.

2.2.2. [Ni($C_{25}H_{24}NO_5$)] ***3***

Green: MP: 198-202. IR: 1649(C=O), 1548(C=C), 3331(N-H), MS (m/z): 476 *Anal*. Calcd for [Ni($C_{25}H_{24}NO_5$)]: C, 62.93; H, 5.07; N, 2.94; Ni, 12.30; Found: C, 63.16; H, 5.26; N, 2.72, Ni, 12.42;

2.2.3. [Co($C_{25}H_{23}ClNO_5$)] ***4***

Brown: MP: 232-236. IR: 1645(C=O), 1590(C=C), 3639(N-H), MS (m/z): 511 *Anal.* Calcd for [Co($C_{25}H_{23}ClNO_5$)]: C, 58.66; H, 4.53; N, 2.74, Co, 11.51; Found: C, 58.59; H, 4.41; N, 2.87, Co, 11.32.

2.2.4. [Mn($C_{25}H_{23}ClNO_5$] ***5***

Light Brown: MP: 221-225. IR: 1650(C=O), 1595(C=C), 3375(N-H), MS (m/z): 507 *Anal*. Calcd for [Mn($C_{25}H_{23}ClNO_5$]: C, 62.90; H, 5.07; N, 2.93, Mn, 10.84; Found: C, 63.07; H, 5.23; N, 3.12; Mn, 10.77.

2.3 Antimicrobial

The antibacterial activity was estimated against, *B.subtilis, E.coli* and *B.cereus.*, as gram positive , and evaluated by using of agar disc diffusion method on the basis of the size of inhibition zone formed around the paper discs. For each concentration, the mean diameter [mm] of inhibition zone developed was calculated. The test complexes were dissolved in DMSO to obtain 200,100 ppm concentration. Twenty five milliliter nutrient agar media was poured in each Petri plates. After solidification, 0.1 mL of test bacteria spread over the medium using a spreader. The discs of

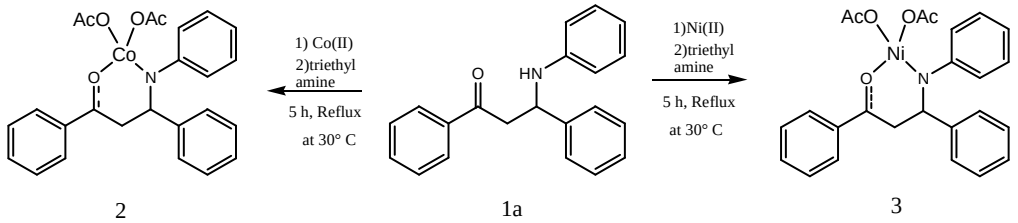
Whatmann No. 1 filter papers having the diameter 5 mm were placed at four equidistant places at a distance of 2 cm from the center in the inoculated Petri plates. Filter paper disc treated with DMSO served as control and Amoxicillin used as a standard drug. These Petri plates were kept in refrigerator for 24 h for prediffusion. Finally, Petri plates were incubated for 24 hrs at 30 °C. The zone of inhibition was calculated in millimeters carefully.

RESULT AND DISCUSSION

3.1. Characterization of ligand and metal complexes

The pure ligand showed the sharp m.p., expected elemental composition IR, NMR spectra. Melting point of ligand and elemental analysis confirms the stoichiometries of ligand [2]. The ligand-1 show broad band at 3384 cm^{-1} corresponding to frequency (N-H) of amine group. While spectra of metal complexes shows 3384 cm^{-1} band indicating replacement of a proton from the amine group. The band at 1670 $cm^{-1}{}_{str}$ (C=O) group in the ligand spectra was found to be shift to lower values in all complexes, indicating coordination through oxygen atom of (C=O) group. These coordination sites were supported by presence of band at 580 cm^{-1} and 430 cm^{-1} attributed to M-N and M-O bands respectively. (Scheme 1 and 2)

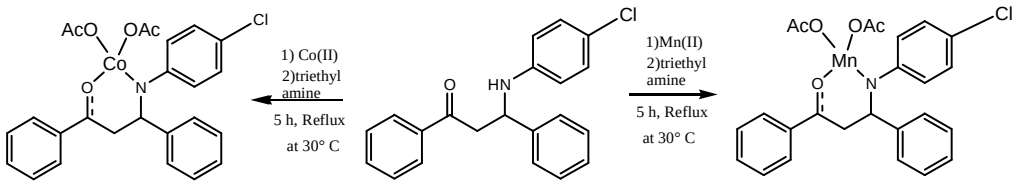
A.



2 1a 3

Scheme 1

B.



4 1b 5

Scheme 2

Table 1: Optimization of time and yield of synthesized compounds

Comp. No.	Time (h)	Yield (%)
1a	7	72
1b	6	74
2	5	69
3	5	71
4	4	68
5	6	70

3.2. Biological Activity

Zone of inhibition values of investigated compound against bacteria is summarized in table 2. Streptomycin and Amoxicillin have been used as reference compound for antibacterial activity. The observed value for complexes shows higher activity than the ligand. Such an increase activity of complexes can be explained on the basis of chelation theory [3]. On chelation polarity of metal ions are reduced due to the overlapping of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Moreover, delocalization of the -electrons over the whole chelate ring is increased and lypophilicity of complexes is enhanced. The increased lypophilicity enhance the penetration of the complexes into lipid membranes and blocks the metal binding sites in the enzymes of microorganisms. These complexes also disturbed the respiration process of the cell and thus block the synthesis of

proteins, which restrict further growth of organism. Investigation on similar type of complexes [4-6] reveals that the metals complexes exhibit higher activity than their ligand. The compounds of our interest also exhibit higher activity than respective ligands, but in no case it is effective to towards their standard drug.

Table 2: Antibacterial and antifungal activity

Entry	*B. Substils*	*E.Coli*	*B. cerus*
	[a]ZI	[a]ZI	[a]ZI
1a	12	*n.t.*	12
1b	13	14	14
2	**20**	**17**	**18**
3	**16**	**16**	**17**
4	**17**	**18**	**19**
5	**18**	**20**	**22**
Strept.	16.2	16.4	[c]***n.t.***
Amoxi.	16.8	17.1	17.2

(Bold values indicates better results; [a]Zone of inhibition in mm; [c]n.t. not tested)

CONCLUSION

β-Amino carbonyl compound has been synthesized using aromatic aldehyde, ketone and amine. Metal complexes were obtained from corresponding β-amino carbonyl compound and metals such as Co(II), Ni(II) and Mn(II) with M:L ratio 1:1. were obtained an square planner structure has been proposed for all metal(II) complexes.

By previous study, the chelate effect, i.e bidentate ligands shows higher antimicrobial efficiency toward complexes with monodentate ligands, the present work will contribute in the field of new antibacterial for human pathogenic organism.

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