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Efficient Ultrasound synthesis of β-diketone and its metal complexes

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ABSTRACT

1-(5-chloro,2-hydroxyphenyl)-3-(4-ethoxyphenyl)propane-1,3-dione and its transition metal complexes have been synthesized by ultrasound irradiation method. The diketone is offered by employing Baker-Venkatraman rearrangement on 5-chloro, 2-acetylphenyl,4-ethoxy benzoate. The synthesized compounds were confirmed by the spectroscopic analysis such as IR, ^{1}H-NMR, ^{13}C-NMR ,Mass, Elemental analysis, magnetic susceptibility and evaluated for antimicrobial screening.

Keywords :β-diketone, Baker-Venkatraman rearrangement, metal complexes, magnetic susceptibility, antimicrobial screening, ultrasound irradiation

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INTRODUCTION

β-diketone and its metal complexes have been widely used in diverse areas because of their unique structural features, chemical functionalities, and toughness for light and heat as electroluminescence materials[1]. β-diketones have gained a lot of interest due to their importance as good ligands[2] ,for the chelation with metals, as intermediate in the synthesis of core heterocycles such as flavones[3], pyrazole[4]. β-diketones have shown pharmacological activities like prophylactic antitumor [5], antibacterial[6] and antioxidant[7]. They have also been used as an anti-sunscreen agent[8]. β-diketones are well known to have keto-enol tautomerism and recently it is reported that they have the important pharmacophores for the HIV-integrase(1N) inhibitors[9].

Owing to β-diketones having such varying pharmacological activities, we were interested to synthesize a novel β-diketone and its transition metal complexes. However, in most cases, synthesis of β-diketone and its transition metal complexes by ultrasound irradiation method has received less attention. With this view here we report the synthesis of 1-(5-chloro,2-hydroxyphenyl)-3-(4-ethoxyphenyl)propane-1,3-dione and its transition metal complexes by ultrasound irradiation method and evaluated for their biological activities.

Ultrasound irradiation assisted organic synthesis is an efficient and eco-friendly synthetic strategy. Many homogeneous and heterogeneous reaction can be conducted smoothly by sonication to provide improved yields and increased selectivities[10]. Therefore ultrasound irradiation has been established as an important technique in organic synthesis.

MATERIALS AND METHODS

Experimental Section

5-chloro,2-hydroxy acetophenone(1)was prepared by Fries reaction from 4-chloro phenol and acetic anhydride. Melting points were determined in open glass capillaries and were uncorrected. All the elemental analyses were done using the Perkin Elmer2400 CHN analyzer. . ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian – NMR-mercury 300 using tetra methyl silane as an internal standard and $CDCl_3$ as solvent. FT-IR spectra were recorded using (KBr) disc on Bruker spectro-photometer. Mass spectra were taken on a Macro mass spectrometer.The magnetic susceptibility of the complexes were measured at room temperature using a Gouy balance.

5-chloro,2-acetylphenyl 4-ethoxy benzoate (3): To the mixture of 5-chloro,2-hydroxyacetophenone (1.70g, 0.01mol) and 4-ethoxy benzoic acid (1.66g, 0.01mol), a dry pyridine (5mL) and $POCl_3$ (1ml) were added drop wise with constant stirring at 0 ^{o}C. Then reaction mixture was irradiated for about 4-5hrs under ultrasound. After completion of the reaction (monitored by TLC), the reaction mixture was poured into 100ml 1M HCl containing 50g of crushed ice and solid obtained was filtered and washed with 10ml ice-cold methanol and then with 10ml of water. It was recrystallized from ethanol, filtered and dried.Yield:82%; mp :78°C

1-(5-chloro,2-hydroxyphenyl)-3-(4-ethoxyphenyl)propane-1,3-dione ($4L_E$): Compound 3 (3.18 g, 0.01mol) was dissolved in dry pyridine (10 ml). To this powdered KOH (1.12 g, 0.02mol) was added and the reaction mixture was irradiated for about 1-2 hrs . After completion of the reaction (monitored by TLC), the reaction mixture was poured on ice cold water and acidified with conc.HCl. The yellow solid obtained was filtered off and crystallized from absolute ethanol to obtain pure product.Yield:80%; mp :132°C. IR(KBr) cm^{-1}: 2977.54(-OH),1718.10(C=O),1471.16(C-O), ^{1}H-NMR (300MHz, $CDCI_3$-d_6); δ =7.89 (q, 4H,Ar-H), 7.05 (m, 3H, Ar-H), 6.61 (s,2H,=CH-), 4.1(t,2H,-OCH_2),1.45 (q, 3H,-CH_3),12.15 (s,1H,OH), 15.75 (s,1H,Enolic-OH),^{13}C-NMR (300MHZ,$CDCl_3$),δ 193.8(s,C-1,C=O), 91.2(s,C-2,-CH=),179.0(s,C-3), 124(s,C-1'), 163.6(s,C-2'), 120(s,C-3'), 135.9(s,C-4,), 128(s,C-5'), 131.9(s,C-6'), 121.5(s,C-1''),129.5(d,C-2'',C-6''), 114.4(d,C-3'',C-5''), 161.5(s,C-4'')64.0(s,C-7'',-CH_2-), 14.6(s,C-8'',-CH_3), UV/Vis(DMSO)nm:360,410; EC-MS : 318.75 (M+23). Elemental analysis Calcd. for $C_{17}H_{15}O_4Cl$, C,64.06; H,4.74 Found :C,63.93; H,4.60.

Bis(-diketonato) Fe(III) complex ($5E_1$): The mixture of (6.36g, 0.02mol) of compound $4L_E$ and (4.04g, 0.01mol) of anhydrous Fe (III) nitrate and 20 ml anhydrous ethanol was added and irradiated for about 1-2 hrs under ultrasound . The brown solid which precipitated was washed with boiling ethanol and recrystallised from ethyl acetate to give brownish crystals of Fe(III)β- diketonate.Yield: 85% ; mp :338°C.

RESULTS AND DISCUSSION

5-chloro,2-acetylphenyl4-ethoxybenzoate(3) was prepared by the esterification of 5-chloro,2-hydroxy acetophenone with 4-ethoxy benzoic acid in presence of $POCl_3$(scheme1). 5-chloro,2-acetylphenyl,4-ethoxybenzoate(3) undergoes Baker-Venkataraman transformation[11] to offered pale yellow needles of 1-(5-chloro,2-hydroxyphenyl)-3-(4-ethoxyphenyl)propane-1,3-dione($4L_E$). The negative test for ester confirms the absence of ester group. The structure was further confirmed by spectral analysis.

In the ^{1}H-NMR spectra it gives characteristic peak at δ 15.7 which corresponds to enolic proton and at 12.1 which is being due to phenolic proton adjacent to carbonyl group. It confirms the formation of β-diketone and in the ^{13}C-NMR spectra it gives characteristic peak at δ 193.8, 91.8 and 179 confirms the formation of β-diketone. The compound in enolic form is more stable than that of ketonic one.The complex of synthesized compound ($4L_E$) gives browned coloured Fe(III) diketonate($5E_1$)in high yield. The structure was then confirmed by spectral analysis: IR (KBr)cm^{-1}:1650.19(C=O), 1512.54(C-O), 2982.53(-OH),835.40(M-O);The C=0 bond in complex($5E_1$) shifted to lower frequency as compared to that of free ligand which indicates the coordination of metal atom with the carbonyl group of diketone[12].

Similarly, other transition metal complexes were prepared by the same method. The ligand and its metal complexes are quite stable. All the complexes are insoluble in water but soluble in DMSO and DMF. The complexes are non-electrolytic in nature[13] .

It was observed that the reaction under ultrasonic irradiation had significantly improved yield[14].

Magnetic Measurements: Magnetic moments of complexes were measured at room temperature and the values are given in Table 1.The observed magnetic moment value of Fe(III) complex is 6.37BM, Co(II) complex is 4.46BM, Ni(II) complex is 2.80BM, Cu(II) complex is 2.10BM and Cr(III) complex is 3.72 BM at room temperature has octahedral geometry[15-16].

Table-I Molar conductivity, Magnetic and Infrared spectral data of synthesized compounds

compound	μeff(BM)	Molar conductance ohm-$^{-1}$cm^{2}mol^{-1}	IR(cm^{-1})				
			ν(C=O)	ν(C-O)	ν(-OH)	ν(M-O)	ν(-OH) coordinated H_2O molecule
Ligand $4L_E$			1718.10	1471.16	2977.54	---	---
Fe (III) complex	6.37	65.6	1650.19	1512.54	2982.53	835.40	3244.13
Co (II) complex	4.46	24.3	1679.57	1493.37	3294.32	804.87	3324.26
Ni(II) complex	2.80	51.2	1680.75	1563.61	3369.49	636.05	3185.17
Cu(II) complex	2.10	27.5	1679.48	1493.59	3342.15	767.24	---
Cr(III) complex	3.72	26.4	1647.29	1512.55	2982.13	835.30	---

The antimicrobial screening of ligand and its metal complexes shows that it possesses antibacterial activity with respect to pathogenic bacteria like Bacillus subtilis and Staphylococcus aureus(Gram +ve); Escherichia coli(Gram -ve) and antifungal activity with fungi such as Aspergillus niger and Fusarium Oxysporum. From the antimicrobial study, it was observed that complexes showed highest antimicrobial activity than ligand.

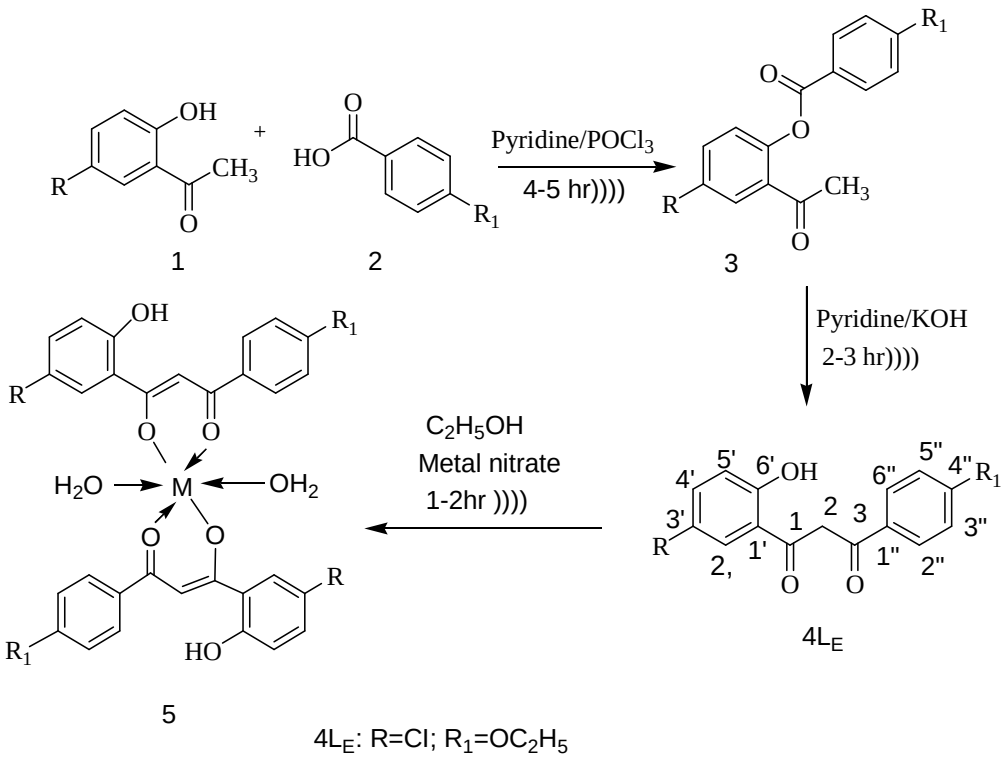
Antimicrobial Screening: Antimicrobial screening [17] of prepared compounds were tested against bacteria as *Staphylococcus aureus* and *Bacillus subtilis* (Gram +ve); Escherichia coli(Gram -ve) and against *fungi*, *Aspergillus niger* and *Fusarium Oxysporum* by Kirby Baur's disc diffusion technique using dimethyl sulfoxide as a solvent. The streptomycin was used as reference in case of antibacterial and antifungal activity.

A uniform suspension of test organism of 24 hrs old cultures was prepared in test tube containing sterile saline solution. A sterile nutrient agar was then added in each of the petri plates. The plates were related to ensure the uniform mixing of the micro organism in the agar medium which was then allowed to solidify. Sterile Whatmann filter paper disc were dipped in the solution of each compound and placed on the labeled plates. The DMSO was used as a control of the solvent. The *streptomycin* was used as a standard compound for comparison. Plates were kept in refrigerator for half an hour for diffusion and then incubated at 37^{o}C for 24 hrs. After incubation the inhibitory zones around the discs were observed. The diameter on inhibition zones were measured in terms of mm. Activity of each compound was compared with streptomycin as standard. The observed data of antimicrobial activity of compounds and the standard drugs are given in Table 2 .

Table 2 Antimicrobial activity of synthesized compounds

Compd No.	Conc. (ppm)	Antibacterial activity (inhibition in mm)			Antifungal activity(inhibition in mm)	
		Bacillus subtilis	*E. coli*	*Staphylococcus aureus*	*Aspergillus. niger*	*Fusarium oxysporum*
Ligand$4L_E$	100	8	7	9	12	7
Fe Complex	100	6	8	7	8	7
Co Complex	100	9	16	20	28	11
Ni Complex	100	8	7	7	15	9
Cu Complex	100	20	9	8	16	8
Cr Complex	100	7	9	7	8	7
Streptomycin	100	6	7	6	6	6

Among all the compounds screened Co(II)and Cu(II)complexes showed highest antibacterial activity than other compounds whereas Co(II), Ni(II) and Cu(II) showed more antifungal activity. Although with respect to standard, all the tested compounds were found to be moderately active.



M : Fe(III), Co(II)and Ni(II),however in case of Cu(II)and Cr(III) water of coordination is absent

Scheme 1. Synthesis of ligand and metal complexes

CONCLUSION

In the present work 1-(5-chloro,2-hydroxyphenyl)-3-(4-ethoxyphenyl)propane-1,3-dione ($4L_E$) and its transition metal complexes were synthesized and their structures elucidated on the basis of spectral analysis. The ^{1}H-NMR and ^{13}C-NMR spectra revealed that the prepared diketone possess charecterestic peaks due to the presence of enolic proton(enol form of β-diketone) and phenolic proton adjacent to carbonyl group. These synthesized compounds were screened for in vitro antibacterial and antifungal activity and found to be promising candidates as new antibacterial and antifungal agents.

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