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RESEARCH ARTICLE

Efficient Ultrasound Synthesis,Characterisation and Biological Screening of Novel Cyclic *β*-Diketones

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Abstract: 1-(2-Hydroxyphenyl)-3-propane,1,3-diones **4(L_1-L_6)** have been synthesized by a simple and convenient method employing Baker-Venkatraman transformation on corresponding 2-acetylphenyl benzoate by conventional as well as ultrasound irradiation method. The structure of synthesized compounds has been assigned on the basis of spectral analysis such as IR, ^{1}H NMR, ^{13}C NMR, UV/Vis, mass and elemental analysis. The synthesized compounds were evaluated for antibacterial and antifungal activities. Utilization of ultrasound irradiation, simple reaction conditions, isolation and purification makes this manipulation very interesting from an economic and environmental perspective.

Keywords: 2-Acetylphenyl benzoate, Cyclic *β*-diketones, Baker-Venkatraman rearrangement, Antimicrobial screening, Ultrasound irradiation

Introduction

Cyclic *β*-diketones have gained a lot of interest due to their importance as good ligands[1,2] for chelation with metals. *β*-Diketones have shown pharmacological activities like antibacterial[3], antioxidant[4], systematic insecticidal[5], antiviral[6], prophylactic antitumor[7]. Cyclic *β*-diketones are used as an intermediate in the synthesis of isoxazole[8], flavones[9], pyrazole[10], triazole[11], benzodiazepine[12], pyrimidine[13]. It has been used as an anti sun-screen agent[14]. *β*-Diketones are well known to have keto-enol tautomerism[15] and recently it is reported that they have the important pharmacophores for the HIV-integrase (1N) inhibitors[16]. Further, it has been reported recently that a number of *β*-diketones has warrant examination as breast cancer chemopreventive blocking agent[17], anticarcogenic agent[18] and antiestrogenic agent[19]. The *β*-diketones ligands are considered as potential ligands due to their enolising ability.

Due to purpose of varying pharmacological activities of *β*-diketones, we decided to synthesize a series of novel *β*-diketones. It is found that synthesis of *β*-diketones by ultrasound irradiation method has received less attention. By considering this fact in mind, here we report the synthesis of novel cyclic *β*-diketones **(L_1-L_6)** under ultrasound irradiation using Baker-Venkatraman rearrangement and the synthesized compounds were evaluated for antibacterial and antifungal screening.

Synthesis of *β*-diketones through ultrasound irradiation method is an efficient and eco-friendly synthetic strategy. The sonication method provides improved yields and increased selectivities[20]. Therefore, ultrasound irradiation has been established as an important technique in organic synthesis.

Experimental

2-Hydroxy acetophenone **1(a)** was prepared by Fries migration of phenyl acetate using anhydrous $AlCl_3$. All the solvents and reagents were of synthetic grade.

Measurements

Melting points were determined in open glass capillaries and were uncorrected. ^1H 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. UV/Vis spectra were recorded on UV/Vis spectrophotometer model UV-1601, SHIMADZU, Japan. Elemental analysis were done using perkin Elmer 2400CHN analyser.

*Preperation of 2-acetylphenyl benzoate **3(a-f)***

To the mixture of *o*-hydroxyacetophenone (1.36 g, 0.01 mol) and benzoic acid (1.22 g, 0.01 mol) a dry pyridine (5 mL) and $POCl_3$ (1 mL) were added drop wise with constant stirring at 0 ^oC. The reaction mixture was irradiated for about 3-4 h under ultrasound. After completion of the reaction (monitored by TLC), the reaction mixture was poured into 100 mL HCl (1 M) containing 50 g of crushed ice and solid obtained was filtered and washed with 10 mL of water. It was recrystallized from ethanol, filtered and dried.

*Preperation of 2-hydroxyphenyl-3-phenylpropane-1,3diones **4(L_1-L_6)***

2.7 g of compound **3a** (0.01 mol) was dissolved in dry pyridine (10 mL). To this powered KOH (1.12 g, 0.02 mol) was added and the reaction mixture was irradiated for about 2-3 h under ultrasound. After completion of reaction (monitored by TLC), the reaction mixture was poured into ice cold water and acidified with conc. HCl. The yellow solid obtained was filtered off and crystallized from absolute ethanol to obtain pure product. The analytical data of the compounds **4(L_1-L_6)** are described below (Table 1).

Table 1. The analytical data of compounds **4(L_1-L_6)**

Compd.	Molecular Formula	Mol.Wt	% Analysis			
			%C		%H	
			Calcd.	Found	Calcd.	Found
L_1	$C_{15}H_{12}O_3$	240	74.99	74.78	5.03	4.80
L_2	$C_{16}H_{14}O_3$	254	75.57	75.42	5.55	5.41
L_3	$C_{15}H_{10}Cl_2O_3$	309	58.28	58.12	3.26	3.15
L_4	$C_{15}H_{11}O_3Cl$	274.5	70.46	70.38	4.80	4.64
L_5	$C_{16}H_{13}O_3Cl$	288.6	66.56	66.59	4.54	4.60
L_6	$C_{15}H_9O_3Cl_3$	343.5	52.43	52.36	2.64	2.48

L_1: FT-IR: (KBR) cm^{-1}: 3120.25 (OH), 1725.36 (C=O), 1540.12 (Ar C=C). ^1H-NMR (300 MHz, $CDCl_3$-d_6); δ=6.8-7.1 (m,4H, Ar-H), 7.2-7.4 (m, 3H, Ar-H), 7.5-7.8 (m, 3H, Ar-H), 12.1 (s, 1H, OH), 15.1 (s,1H, Enolic-OH). ^{13}C-NMR (300MHz, $CDCl_3$); δ=188.3 (s, C-

12,C=O), 94.5 (s, C-2, -CH=), 185.3 (s, C-3), 114.1 (s, C-1'), 156.4 (s, C-2'), 113.6 (s,C-3'), 127.3 (d,C-4'), 124.4 (s, C-5'), 126.3 (s, C-6'), 139.3 (s, C-1"), 130.1 (d, C-2",C-6"), 134.2 (s, C-4"), 129.4 (d, C-3",C-5"). UV/Vis (DMSO)nm: 372,419. EC-MS: 241.12 (M+1).

L_2: FT-IR: (KBR) cm^{-1}:3096.25 (OH), 1715.20 (C=O), 1528.16 (Ar C=C). ^{1}H-NMR (300 MHz, $CDCl_3$-d_6); δ=2.3 (s, 3H, CH_3) 6.8-7 (m, 3H, Ar-H), 7.2-7.4 (m, 3H, Ar-H), 7.5-7.9 (m, 3H, Ar-H). 12.2 (s, 1H, OH), 15.6 (s, 1H, Enolic-OH). ^{13}C-NMR (300MHz, $CDCl_3$); δ=194.1 (s, C-1, C=O), 92.4 (s, C-2, -CH=), 180.2 (s, C-3), 112.5 (s, C-1'), 161.1 (s, C-2'), 117.3 (s, C-3'), 128.4 (d, C-4'), 120.2 (d, C-5'), 126.4 (s, C-6'), 135.4 (d, C-1"), 131.4 (d, C-2",C-6"), 143.1 (s, C-4"), 130.3 (,C-3",C-5"), 22.6 (s,C7",CH_3). UV/Vis (DMSO)nm: 380,420. EC-MS: 255.13 (M+1).

L_3: FT-IR: (KBR) cm^{-1}: 3050.33 (OH), 1685.67 (C=O), 1424.18 (Ar C=C), ^{1}H-NMR (300 MHz, $CDCl_3$-d_6): δ=6.8-7.2 (m, 3H,Ar-H), 7.3-7.7 (m, 5H, Ar-H), 11.9 (s, 1H, OH), 15.2 (s,1H, Enolic-OH). ^{13}C-NMR (300MHz, $CDCl_3$); δ=191.3 (s, C-1, C=O), 94.1 (s, C-2, -CH=), 184.6 (s,C-3), 112.2 (d, C-1'), 162.3 (d,C-2'), 118.3 (s, C-3'), 128.4 (d, C-4'), 122.6 (d,C-5'), 126.6 (s, C-6'), 134.2 (d, C-1"), 135.6 (s, C-2"), 131.2(s, C-3"), 145.2 (s, C-4"), 125.6 (s, C-5"), 130.3 (s, C-6"). UV/Vis(DMSO)nm: 372,410. EC-MS: 310.05 (M+1).

L_4: FT-IR: (KBR) cm^{-1}: 3023.45(-OH), 1713.28(C=O), 1522.36 (Ar C=C).^{1}H-NMR (300 MHz, $CDCl_3$-d_6): δ=6.9-7.1(m, 3H, Ar-H), 7.2-7.5 (m, 3H, Ar-H), 7.6-7.9 (m, 3H, Ar-H),12.3 (s,1H, OH),15.2 (s, 1H, Enolic-OH), ^{13}C-NMR (300MHz, $CDCl_3$), δ=191.2(s, C-1, C=O), 92.1 (s,C-2, -CH=), 186.5 (s, C-3), 110.4 (d, C-1'), 153.3 (s, C-2'), 119.5 (s, C-3'), 130.6 (d, C-4'), 125.5 (s, C-5'), 127.1 (d, C-6'), 138.2 (s, C-1"), 129.5 (d, C-3", C-5"), 136.5 (d, C-4"), 128. 4 (d C-2"-C-6"). UV/Vis (DMSO)nm: 356,417. EC-MS:275.2(M+1).

L_5: FT-IR: (KBR) cm^{-1}: 3010.17 (OH), 1707.32 (C=O), 1515.11 (Ar C=C). ^{1}H-NMR (300 MHz, $CDCl_3$-d_6); δ=2.2 (s, 3H,CH_3), 6.8 (s, 1H), 7.1 (s, 1H), 7.4-7.6 (t,3H,Ar-H), 7.7-7.9 (m, 3H, Ar-H), 12.1 (s, 1H, OH), 15.6 (s, 1H, Enolic-OH), ^{13}C-NMR (300MHz, $CDCl_3$); δ=189.4 (s, C-1, C=O), 93.3 (s, C-2, -CH=), 183.7 (s, C-3), 112.2 (s, C-1'), 160.6 (s, C-2'), 119.2 (s, C-3'), 129.5 (d, C-4'), 126.2 (d,C-5'), 127.3 (s, C-6'), 135.1 (d, C-1"), 130.5 (d,C-2",C-6"), 143.1 (d, C-4"), 131.3 (d,C-3",C-5"), 25.2 (s,C-7",CH_3) UV/Vis (DMSO)nm: 360,412. EC-MS: 289.5.

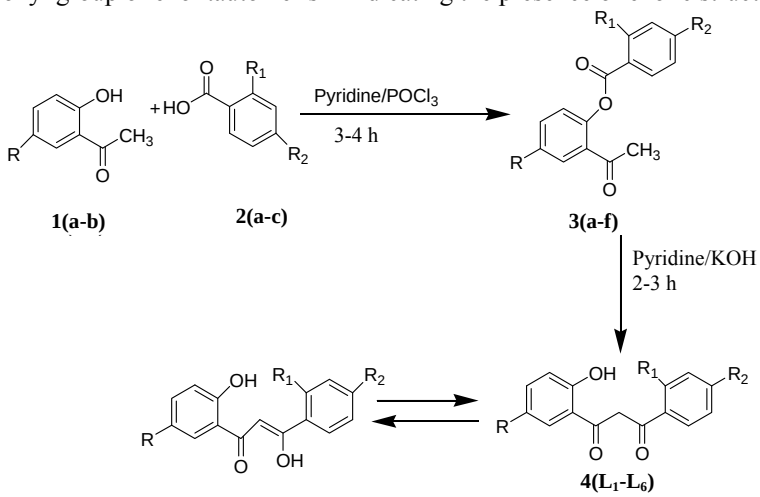
L_6: FT-IR: (KBR) cm^{-1}: 3001.96 (OH), 1680.26 (C=O), 1497.83 (Ar C=C). ^{1}H-NMR (300 MHz, $CDCl_3$-d_6); δ=6.8 (s, 1H, =CH-), 7.1 (s,1H, Ar-H), 7.4-7.7 (m,5H, Ar-H), 11.9 (s, 1H, OH), 15.1(s, 1H, Enolic-OH), ^{13}C-NMR (300MHz, $CDCl_3$); δ=187.3 (s, C-1, C=O), 94.1 (s, C-2, -CH=), 185.6 (d, C-3), 115.2 (s, C-1'), 160.4 (s, C-2'), 119.2 (d, C-3'), 129.5 (d, C-4'), 125.5 (s, C-5'), 128.3 (d, C-6'), 135.2 (s, C-1"), 136.5 (d, C-2"), 131.5 (d, C-3"), 141.3 (s, C-4"), 127.2 (s, C-5"), 132.6 (s, C-6"). UV/Vis (DMSO)nm: 370,415. EC-MS: 344.91(M+1).

Results and Discussion

The 2-acetylphenyl benzoate **3(a-f)** were prepared by the esterification of 2-hydroxy acetophenone **1(a-b)** with aromatic carboxylic acids **2(a-c)** in the presence of $POCl_3$ (Scheme 1).

1-(2-Hydroxyphenyl)-3phenylpropane-1,3-dione **4(L_1-L_6)** were prepared by Baker-Venkatraman transformation[21-22] of **3(a-f)** with KOH in pyridine. The ^{1}H NMR spectrum of **L_1** exhibited a singlet at δ15.1 ppm due to enolic proton (since enol form in *β*-diketone is more stable), a singlet at δ12.1 ppm is due to phenolic proton adjacent to the carbonyl group. ^{13}C NMR spectra gives singlet at δ188.3 ppm due to ketonic carbon C-1 and δ185.3 ppm due

to enolic carbon C-3 confirming the keto-renol tautomerism in *β*-diketone. The IR spectrum showed absorption at 3120.25 (OH), 1719.36 (C=O) and 1540.12 (C-O). The negative test for ester, the presence of characteristic ^{1}H-NMR peaks and ^{13}C-NMR peaks are consistent with the structure of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione. The EC-MS spectrum showed a molecular ion peak at 241.12 (M+1), confirms the *α-β* unsaturated carbonyl group of enol tautomerism indicating the presence of enolic structure[23].



L_1: R=H, R_1=H; R_2=H, L_2: R=H; R_1=H; R_2=CH3, L_3: R=H; R_1=Cl; R_2=Cl, L_4 : R=Cl; R_1=H; R_2=H
L_5 : R=Cl; R_1=H; R_2=CH_3, L_6: R=Cl;;R_1=Cl;R_2=Cl

Scheme 1. Synthesis of ligands

Comparative study results obtained by ultrasound synthesis versus conventional stirring method was that reaction which required 580 min by conventional method, was completed within 115 min by ultrasound technique and yields have been improved from 70% to 80% **L_1**. The comparison study data of ultrasonication and conventional method with physical data of the compounds are presented in Table 2.

Table 2. Physical data of 1-(2-hydroxyphenyl)-3-phenyl propane-1,3-dione 4(L_1-L_6)

Compd.	M.P.	[a]Without ultrasound		[b]With ultrasound	
		Time, min	Yield[c], %	Time, min	Yield[c], %
L_1	105-115	580	65	115	70
L_2	110-120	570	70	120	80
L_3	120-130	574	70	130	80
L_4	107-117	583	68	125	75
L_5	125-135	574	78	125	86
L_6	150-160	582	73	135	80

[a]Reaction of diketone under stir condition. [b]Reaction of diketones under ultrasonic waves. [c]Isolated yield

The reaction yield was improved with short time under sonication compared to that of conventional method[24].

Antimicrobial screening

Antibacterial screening[25] of cyclic *β*-diketones has been tested against one gram negative bacteria *E.coli* and two gram positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis* and

antifungal screening[26] has been tested against two species of fungi, *aspergillus niger* and *Tricoderma* by Kirby'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 h old culture 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 rotated to ensure the uniform mixing of the microorganisms 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 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 h. After incubation the inhibitory zones around the disc were observed. The diameter on inhibition zones were measured in terms of mm. The observed data of antimicrobial activity of compounds and the standard drugs are given in Table 3.

Table 3. Antimicrobial activity of compounds **4(L_1-L_6)**

Compd.	Conc., ppm	Antibacterial Activity			Antifungal Activity	
		Bacillus subtilis	*E.coli*	*Staphylococcus aureus*	*Aspergillus niger*	*Tricoderma*
L_1	100	9	11	9	9	16
L_2	100	12	9	7	7	17
L_3	100	12	11	9	8	9
L_4	100	11	9	10	9	7
L_5	100	8	7	9	10	6
L_6	100	11	10	9	6	15
Streptomycin	100	6	7	6	6	6

The screening results indicate the compounds **4(L_1-L_6)** showed moderate to excellent antimicrobial activities against the selected pathogens.

Conclusion

In the present work 1-(2-hydroxyphenyl)-3propane-1,3-diones **4(L_1-L_6)** were synthesiszed by Baker-Venkatraman transformation with KOH in pyridine by conventional as well as ultrasound irradiation and their structures confirmed on the basis of spectral analysis. ^{1}H NMR and ^{13}C NMR and UV/Vis spectra revealed that the prepared compounds **4(L_1-L_6)** possess characteristic peaks due to presence of enolic proton (enol form of β-diketone) and phenolic proton adjacent to carbonyl group. These synthesized compounds were screened for in vitro antimicrobial activity and found to be promising candidate as new antibacterial as well as antifungal agents. In summary, this work demonstrates a rapid, efficient and environmentally friendly method of novel cyclic *β*-diketones **4(L_1-L_6)** under ultrasound irradiation and results obtained confirmed the superiority of ultrasound irradiation method over the conventional method.

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