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RESEARCH ARTICLE

Efficient Ultrasound Synthesis, Characterizations and Antimicrobial Screening of Novel Cyclic *β*-Diketones

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Abstract: 1-(2-Hydroxyphenyl)-3-propane,1,3-diones **4(L_A-L_F)** 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 elemental and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, UV/Vis, Mass). 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-Venkataraman 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 the chelation with metals, as intermediate in the synthesis of core heterocycles such as flavones[3], benzodiazepine[4], pyrazole[5], isoxazole[6] and pyrimidine[7] and triazole[8]. *β*-Diketones have been pharmacological activities like prophylactic antitumor[9], antiviral[10], antibacterial[11], systematic insecticidal[12] and antioxidant[13]. It has been used as an anti-sunscreen 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 chemopreventative blocking agent[17], anticarcinogenic agent[18] and antiestrogenic agent[19].

Owing to *β*-diketones having such varying pharmacological activities, we became interested to synthesize a series of novel *β*-diketones. However, in most cases, synthesis of

β-diketone by ultrasound irradiation method has received less attention. With this view here we report the synthesis of novel cyclic *β*-diketones **4(L_A-L_F)** under ultrasound irradiation using Baker-Venkatraman rearrangement and the synthesized compounds were evaluated for antibacterial and antifungal screening.

Ultrasound irradiation assisted organic synthesis is an efficient and eco-friendly synthetic strategy. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide 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 used were of synthetic grade.

Measurements

Melting points were determined in open glass capillaries and were uncorrected. ^{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. UV/Vis spectra were recorded on UV/Vis spectrophotometer model UV-1601, SHIMADZU, Japan. Elemental analyses were done using Perkin Elmer 2400CHN analyzer.

*Preparation of 2-acetylphenyl benzoate **(3A-F)***

To the mixture of *o*-hydroxyacetophenone (1.36 g, 0.01 mol) and 4-methoxy benzoic acid (1.52 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 (1M) containing 50 g of crushed ice and solid obtained was filtered and washed with 10 mL ice-cold methanol and then with 10 mL of water. It was recrystallized from ethanol, filtered and dried.

*Preparation of 2-hydroxyphenyl-3-phenylpropane-1,3diones **4(L_A-L_F)***

Compound **3A** (2.7 g, 0.01 mol) was dissolved in dry pyridine (10 mL). To this powdered 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_A-L_F)** are given in Table 1. The spectral data for various **4(L_A-L_F)** are described below.

Table 1. The analytical data of compounds **4(L_A-L_F)**

Compd.	Molecular Formula	Mol. Wt.	% Analysis			
			% C		% H	
			Cald	Found	Cald	Found
4L_A	$C_{16}H_{14}O_4$	270	71.10	71.01	5.22	5.13
4L_B	$C_{17}H_{16}O_4$	284	71.82	71.10	5.67	5.52
4L_C	$C_{15}H_{11}O_3Br$	319	56.45	56.09	3.47	3.20
4L_D	$C_{16}H_{13}O_4Cl$	304.65	63.06	62.98	4.30	4.11
4L_E	$C_{17}H_{15}O_4Cl$	318.5	64.06	63.93	4.74	4.60
4L_F	$C_{15}H_{10}O_3ClBr$	353.5	50.95	50.81	2.85	2.35

4L$_A$*:* FT-IR (KBr) cm^{-1}: 2912.98 (-OH), 1708.01 (C=O), 1487.74 (Ar C=C).^{1}H-NMR (300 MHz, $CDCI_3$,-d6): δ =7.9 (d, 3H, Ar-H), 6.8 (m, 5H, Ar-H),7.4 (q , 1H,=CH-), 3.9 (s,3H, OCH_3) ,12.2 (s, 1H, OH), 15.9 (s, 1H, Enolic-OH), **^{13}C**-NMR (300 MHz, $CDCl_3$), δ 190.0(s, C-1,C=O), 92.8 (s, C-2,-CH=), 185.1(S,C-3), 126.0(d, C-1',C-1''), 162.8 (s,C-2'), 118.4 (s,C-3'), 135.8 (s,C-4'), 119.3 (s,C-5'), 128.7 (s, C-6,'), 128.0 (d, C-2'',C-6''), 114.1(d, C-3'', C-5''), 162.0 (s, C-4''), 55.8 (s,C-7'',0CH_3). UV/Vis (DMSO)nm: 370,410; EC-MS :270.28 (M+23).

4L$_B$*:* FT-IR (KBr) cm^{-1}: 2921.31 (-OH), 1741.68 (C=O), 1486.11 (Ar C=C).^{1}H-NMR (300 MHz, $CDCl_3$-d6); δ=7.85 (d,3H, Ar-H), 6.85(m,5H, Ar-H), 7.4 (q, 1H,=CH-),4.1 (q,2H,-OCH_2-), 1.7 (t,3H,-CH_3), 12.1 (s,1H,OH), 15.9 (s, 1H, Enolic-OH), ^{13}C-NMR (300MHz, $CDCl_3$), δ 189.5(s, C-1, C=O), 93.1(s,C-2, -CH=), 185.0(s,C-3), 124.5(s,C-1'), 162.5(s, C-2'), 118.0(s,C-3'), 136.0(s,C-4'), 118.5(s, C-5'), 127.5(s,C-6'), 126.0(s,C-1''), 127.0(d,C-2'',C-6''), 114.3(d, C-3'',C5''), 162.0(s,C-4''), 64.6(s,C-7'',-CH_2-),14.5(s,C-8'',-CH_3),UV/Vis(DMSO)nm:360,410 EC-MS: 284.31 (M+23).

4L$_C$*:* FT-IR (KBr) cm^{-1}: 3069.78 (-OH), 1702.02 (C=O), 1486.96 (Ar C=C). ^{1}H-NMR (300 MHz, $CDCl_3$-d_6); δ=6.8 (d,3H,Ar-H), 7.7 (m, Ar-H), 7.39 (s,1H, =CH-), 12.1 (s,1H, OH), 15.5 (s, 1H, Enolic-OH), 13C-NMR(300 MHz, $CDCl_3$) ,δ 190.0(s,C-1,C=O), 93(s,C-2,-CH=), 184.2(s,C-3), 126.5(s, C-1'), 162.0(s,C-2'), 119.0(s,C-3')136(s,C-4'), 119.5(s,C-5'), 131.3(s,C-6'),129.4(s,C-1''),128.6(d,C-2'',C-6''),131.6(d,C-3'',C5''),122.3(s,C-4''). UV/Vis(DMSO)nm:360,412; EC-MS: 319.15 (M+23).

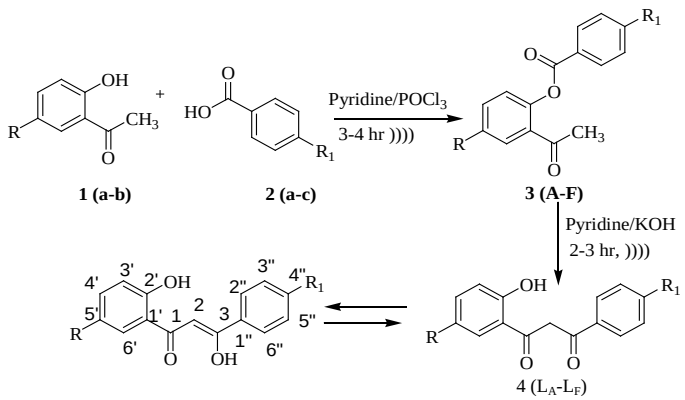
4L$_D$*:* FT-IR (KBr) cm^{-1}: 2919.67(-OH), 1743.31 (C=O), 1465.02 (Ar C=C). ^{1}H NMR (300MHz, $CDCI_3$-d_6);δ =7.0 (t,3H, Ar-H), 7.99 (d, 2H, Ar-H), 7.85 (s, 1H, Ar-H), 7.31 (m,1H, Ar-H), 6.9 (q, 1H,=CH-), 3.9 (s, 3H,-0CH_3), 12.1 (s, 1H,OH), 17.75 (s,1H,Enolic -OH), ^{13}C-NMR(300MHz,$CDCl_3$);δ 192.5(s,C-1,C=O). 91.2(s,C-2,-CH=), 179(s,C-3), 124.5 (s,C-1'), 161.0(d,C-2',C-4''), 120.0(s,C-3'), 134.9(s,C-4'), 128.4(t,C-5',C-2'',C-6''), 131.5 (s,C-6'), 128.0(s,C-1'')114.2(d,C-3'',C-5''), 55.1(s,C-7'',OCH_3), UV/Vis(DMSO) nm: 374, 412; EC-MS : 304.73 (M+23).

4L$_E$*:* FT-IR (KBr) cm^{-1}: 2977.54 (-OH), 1718.10 (C=O), 1471.16 (Ar C=C). ^{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,-OCH2),1.45 (q, 3H,-CH3),12.1 (s,1H,OH), 15.7 (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).

4L$_F$*:* FT-IR (KBr) cm^{-1} 2916.32 (-OH), 1720.28 (C=O), 1469.22 (Ar C=C). ^{1}H-NMR (300MHz, $CDCl_3$-d_6); δ=7.8 (m,5H, Ar-H), 7.35 (q, 1H, Ar-H), 7.01 (m, 1H, Ar-H), 6.65 (s,1H, =CH-), 11.95 (s, 1H,OH), 15.45 (s,1H, Enolic-OH), ^{13}C-NMR(300MHz, $CDCl_3$), δ 192.5(s,C-1,C=O), 92(s,C-2,-CH=), 176.8(s,C-3), 124.1(s,C-1'), 161.9(s,C-2'), 118.8(s,C-3'), 136.0(s,C-4'), 127.6(s,C-5'), 132.0(s,C-6'), 128.6(t,C-1'',C-2'',C-6''), 132(d,C-3'',C-5''), 121.6(s,C-4''), UV/Vis(DMSO)nm: 360,410; EC-MS: 353.6 (M+23).

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).



4L$_A$: R=H;R$_1$=OCH$_3$, 4L$_B$: R=H;R$_1$=OC$_2$H$_5$, 4L$_C$: R=H;R$_1$=Br, 4L$_D$: R=Cl;R$_1$=OCH$_3$, 4L$_E$: R= Cl;R$_1$=OC$_2$H$_5$, 4L$_F$: R= Cl;R$_1$=Br

Scheme 1. Synthesis of ligands

1-(2-Hydroxyphenyl)-3phenylpropane-1,3-diones **4(L$_A$-L$_F$)** were prepared by Baker-Venkatraman transformation[21-22] of **3(A-F)** with KOH in pyridine. The ^{1}H NMR spectrum of **4L$_A$** exhibited a singlet at δ15.9 ppm due to enolic proton (since enol form in *β*-diketone is more stable), a singlet at δ12.2 ppm due to phenolic proton adjacent to the carbonyl group. ^{13}C NMR spectra gives singlet at δ190.0 ppm due to ketonic carbon C-1 and δ185.1 ppm due to enolic carbon C-3 confirming the keto-enol tautomerism in *β*-diketone **4L$_A$**. The IR spectrum showed absorption bands at 2912.98(OH), 1708.01(C=O) and 1487.74c m^{-1} (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-(4-methoxy phenyl) propane-1,3-dione **4L$_A$**. The EC-MS spectrum showed a molecular ion peak at 270.28(M+23), confirms the molecular formula $C_{16}H_{14}O_4$. UV/vis spectrum in DMSO generally showed intense peak in the region 360-412 nm confirms the α –β unsaturated carbonyl group of enol tautomerism indicating the presence of enolic structure[23].

Comparative study results obtained by ultrasonication synthesis, *versus* conventional stirring method was that reaction which required 590 min by conventional method, was completed within 120 min by ultrasonication technique and yields have been improved from 70% to 85% **4L$_A$**. 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 substituted 1-(2-hydroxyphenyl)-3-phenyl propane-1,3-dione **4(L$_A$-L$_F$)**

		With ultrasound[a]		Without ultrasound[b]	
Compd.	M.P. ^{0}C	Time, min	Yield[c], %	Time, min	Yield[c], %
4L$_A$	115-117	120	85	590	70
4L$_B$	146-148	120	85	590	73
4L$_C$	130-132	110	87	570	75
4L$_D$	164-166	120	82	600	74
4L$_E$	133-135	120	84	590	72
4L$_F$	138-140	110	88	570	71

[a]Reaction of diketones under ultrasonic waves. [b]Reaction of diketones under stir conditions. [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 *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 h. 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 rotated 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 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 °C for 24 h. 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 3.

Table 3. Antimicrobial activity of compounds **4 (L_A-L_F)**

Compd.	Conc., ppm	Antibacterial activity			Antifungal activity	
		Bacillus subtilis	*E. coli*	*Staphylococcus aureus*	*Aspergillus. niger*	*Fusarium. oxysporum*
4L_A	100	8	10	7	8	11
4L_B	100	11	8	8	7	8
4L_C	100	11	11	7	12	12
4L_D	100	10	7	10	11	11
4L_E	100	8	7	9	7	12
4L_F	100	10	9	9	7	13
Streptomycin	100	6	7	6	6	6

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

Conclusion

In the present work various1-(2-hydroxyphenyl)-3propane-1,3-diones **4(L_A-L_F)** 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_A-L_F)** 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 for the synthesis of novel cyclic *β*-diketones **4(L_A-L_F)** under ultrasound irradiation and result obtained confirmed the superiority of ultrasound irradiation method over the conventional method.

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