

A facile synthesis of 1-(2, 4-dihydroxyphenyl)-3-aryl-propane-1,3-diones via Baker-Venkataraman rearrangement under solvent free conditions at room temperature

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A simple and highly efficient method for the synthesis of 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones via Baker-Venkataraman rearrangement involving grinding of 2-aryloxy-4-hydroxyacetophenones with pulverized potassium hydroxide at room temperature under solvent free conditions has been described. The structures of these compounds were identified from their spectral data (FT IR, ¹H NMR, ¹³C NMR, Mass). This protocol avoids the use of hazardous chemicals and organic solvents at any stage of the reaction.

Keywords: 2-aryloxy-4-hydroxyacetophenones, 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones, Baker-Venkataraman rearrangement, solvent free conditions, grinding technique

INTRODUCTION

1-(2,4-Dihydroxyphenyl)-3-aryl-propane-1,3-diones, commonly known as 2,4-dihydroxy dibenzoylmethanes are the required key intermediates for the synthesis of various naturally occurring compounds [1] such as flavones [2], pyrazoles [3], isoxazoles [4], pyrimidines [5], benzodiazepine [6] and also possess a broad spectrum of pharmacological activities like antibacterial [7], antiviral [8], insecticidal [9], antioxidant [10], antitumor [11] and antimutagenic [12] activity. Further these compounds have been found to be potent anticarcinogenic [13,14], antiestrogenic [15], breast cancer chemopreventive blocking agent [14] and also used as anti sunscreen agents [16]. In recent studies, β -ketoenols has been reported to be important pharmacophores for the HIV-1 integrase inhibitors [17]. Their metal complexes also exhibited good biological properties [18,19].

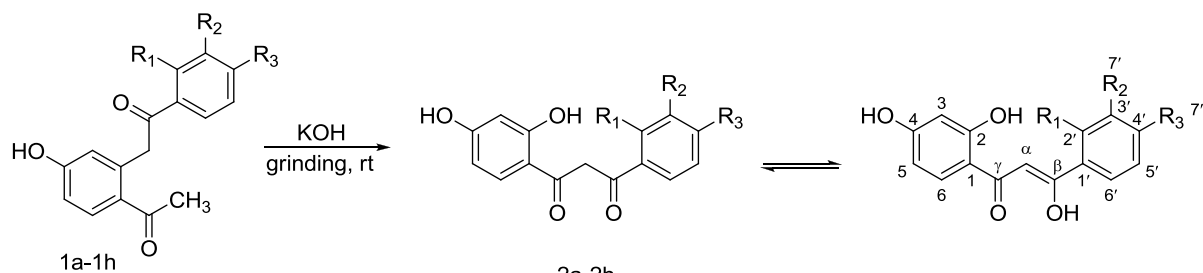
The most common method for the synthesis of these β -diketones is by Baker-Venkataraman rearrangement of 2-aryloxyacetophenones. Due to their important role in various fields, continuous efforts have been made to simplify

the procedures for their synthesis which include the use of potassium hydroxide in pyridine medium [20] or by heating with barium hydroxide in dimethylsulphoxide medium [21]. The above transformation has also been carried out in aqueous-benzene biphasic medium using phase transfer catalysis [22]. Other bases which have been used for this rearrangement include sodamide [23], sodium hydride [24], sodium hydroxide in dimethylsulphoxide [25], and potassium carbonate in aqueous medium under microwave irradiations [26].

Some of the above mentioned conditions possess shortcomings, such as use of harsh or hazardous chemicals, longer reaction time and elevated temperature. The shortcomings led us to develop a safe, environmentally benign, and more efficient condition for Baker-Venkataraman rearrangement.

In continuation of our work to develop eco-friendly procedures for the synthesis of organic compounds under solvent free conditions [27], we report herein a simple and efficient method for the synthesis of 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones via Baker-Venkataraman rearrangement under solvent free conditions using grinding technique (Scheme 1).

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2a-2h			
2	R ₁	R ₂	R ₃
a	H	H	OCH ₃
b	Cl	H	H
c	H	H	H
d	H	CH ₃	H
e	H	Cl	H
f	H	OCH ₃	H
g	H	H	CH ₃
h	H	H	Cl

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded on Perkin-Elmer spectrum BX series FT-IR Spectrophotometer with KBr pellets. NMR spectra were recorded on Bruker Avance (400 MHz) instruments using TMS as an internal standard. Mass spectra were recorded on Bruker-Daltonich mass spectrometer. A mortar and pestle of porcelain was used for all the experiments. All the chemicals were obtained commercially and used as received. Resacetophenone was prepared by the Nencki reaction as reported in the literature [28].

General Procedure for the synthesis of 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones 2a-2g

The substituted 2-aryloxy-4-hydroxyacetophenones (1.95 mmol) was ground with pulverized potassium hydroxide (1.95 mmol) in a mortar by pestle for 5 minutes and the reaction mixture was left at room temperature for another 5-10 minutes. The completion of the reaction was checked by TLC. The reaction mixture was diluted with ice cold water and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallized from aqueous ethanol to afford 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones.

1-(2,4-Dihydroxyphenyl)-3-phenylpropane-1,3-dione 2a.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3428 (OH), 1710 (C=O); ^1H NMR (CDCl_3) δ/ppm : 5.10 (s, 1H, Ar-OH), 6.35-6.65 (m, 2H, H-3, H-5), 6.75 (s, 1H, -CH=C-), 7.40-7.50 (m, 3H, H-3', H-4', H-5'), 7.85-8.0 (m, 2H, H-2', H-6'), 8.05 (d, 1H, $J=8.0$ Hz, H-6), 12.35 (s, 1H, Ar-OH), 15.50 (s, 1H, enolic OH); ^{13}C NMR (CDCl_3): δ/ppm : 94.0 (C- α), 104.3 (C-3), 109.1 (C-5), 115.1 (C-1), 126.1 (C-2'), 126.1 (C-6'), 128.1 (C-4'), 128.5 (C-3'), 128.5 (C-5'), 130.7 (C-1'), 132.5 (C-6), 163.4 (C-2), 165.5 (C-4), 184.6 (C- β), 190.1 (s, C- γ); MS (ESI): m/z 256.056 (M^+).

1-(2,4-Dihydroxyphenyl)-3-(3'-methoxyphenyl)propane-1,3-dione 2b.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3422 (OH), 1708 (C=O); ^1H NMR (CDCl_3) δ/ppm : 3.95 (s, 3H, OCH₃), 5.20 (s, 1H, Ar-OH), 6.75 (s, 1H, -CH=C-), 6.80-7.45 (m, 4H, H-3, H-5, H-4', H-5'), 7.80 (dd, 1H, $J=8.0$ Hz & 2.0 Hz, H-6), 7.80-7.95 (m, 2H, H-2', H-6'), 12.35 (s, 1H, Ar-OH), 15.55 (s, 1H, enolic OH). ^{13}C NMR (CDCl_3): δ/ppm : 55.5 (C-7'), 93.6 (C- α), 104.0 (C-3), 109.5 (C-5), 110.0 (C-2'), 113.2 (C-4'), 115.5 (C-1), 118.2 (C-6'), 129.4 (C-5'), 131.1 (C-1'), 132.5 (C-6), 160.2 (C-3'), 163.5 (C-2), 164.0 (C-4), 184.6 (C- β), 190.1 (C- γ); MS (ESI): m/z 286.056 (M^+).

1-(2,4-Dihydroxyphenyl)-3-(4'-methoxyphenyl)propane-1,3-dione 2c.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3420 (OH), 1705 (C=O); ^1H NMR (CDCl_3) δ/ppm : 3.9 (s, 3H, OCH_3), 5.15 (s, 1H, Ar-OH), 6.75 (s, 1H, $-\text{CH}=\text{C}-$), 6.85-7.48 (m, 4H, H-3, H-5, H-3', H-5'), 7.75 (dd, 1H, $J= 8.0$ Hz & 2.0 Hz, H-6), 7.85-7.95 (m, 2H, H-2', H-6'), 12.32 (s, 1H, Ar-OH), 15.52 (s, 1H, enolic OH); ^{13}C NMR (CDCl_3): δ/ppm : 56.0 (C-7'), 94.0 (C- α), 104.2 (C-3), 110.6 (C-5), 114.6 (C-3'), 114.6 (C-5'), 116.0 (C-1), 122.2 (C-1'), 127.9 (C-2'), 127.9 (C-6'), 131.4 (C-6), 159.4 (C-4'), 164.0 (C-2), 165.9 (C-4), 184.6 (C- β), 190.1 (C- γ); MS (ESI): m/z 286.071 (M^+).

1-(2,4-Dihydroxyphenyl)-3-(3'-methylphenyl)propane-1,3-dione 2d.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3428 (OH), 1710 (C=O); ^1H NMR (CDCl_3) δ/ppm : 2.40 (s, 3H, CH_3), 5.12 (s, 1H, Ar-OH), 6.95-7.95 (m, 8H, H-3, H-5, H-6, $-\text{CH}=\text{C}-$, H-2', H-4', H-5', H-6'), 12.15 (s, 1H, Ar-OH), 15.60 (s, 1H, enolic OH); ^{13}C NMR (CDCl_3): δ/ppm : 24.6 (C-7'), 93.9 (C- α), 104.2 (C-3), 109.2 (C-5), 116.0 (C-1), 123.2 (C-6'), 126.4 (C-2'), 128.2 (C-4'), 128.6 (C-5'), 130.6 (C-1'), 131.8 (C-6), 138.1 (C-3'), 164.1 (C-4), 164.4 (C-2), 184.5 (C- β), 189.9 (C- γ); MS (ESI): m/z 270.056 (M^+).

1-(2,4-Dihydroxyphenyl)-3-(4'-methylphenyl)propane-1,3-dione 2e.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3425 (OH), 1710 (C=O); ^1H NMR (CDCl_3) δ/ppm : 2.45 (s, 3H, CH_3), 5.15 (s, 1H, Ar-OH), 6.72 (s, 1H, $-\text{CH}=\text{C}-$), 6.82-7.45 (m, 4H, H-3, H-5, H-3', H-5'), 7.72 (dd, 1H, $J= 8.0$ Hz & 2.0 Hz, H-6), 7.80-7.92 (m, 2H, H-2', H-6'), 12.30 (s, 1H, Ar-OH), 15.48 (s, 1H, enolic OH); ^{13}C NMR (CDCl_3): δ/ppm : 24.2 (C-7'), 94.1 (C- α), 104.2 (C-3), 109.4 (C-5), 116.1 (C-1), 126.6 (C-2'), 126.6 (C-6'), 127.4 (C-1'), 129.4 (C-3'), 129.4 (C-5'), 131.8 (C-6), 137.4 (C-4'), 164.2 (C-2), 165.4 (C-4), 184.7 (C- β), 190.1 (C- γ); MS (ESI): m/z 270.071 (M^+).

1-(2,4-Dihydroxyphenyl)-3-(2'-chlorophenyl)propane-1,3-dione 2f.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3435 (OH), 1715 (C=O); ^1H NMR (CDCl_3) δ/ppm : 5.05 (s, 1H, Ar-OH),

6.90-7.92 (m, 8H, H-3, H-5, H-6, $-\text{CH}=\text{C}-$, H-3', H-4', H-5', H-6'), 12.18 (s, 1H, Ar-OH), 15.57 (s, 1H, enolic OH); ^{13}C NMR (CDCl_3): δ/ppm : 93.4 (C- α), 104.1 (C-3), 109.2 (C-5), 115.8 (C-1), 126.6 (C-5'), 128.6 (C-3'), 129.6 (C-4'), 130.4 (C-6'), 131.1 (C-2'), 131.6 (C-1'), 133.2 (C-6), 163.8 (C-2), 165.1 (C-4), 185.4 (C- β), 190.3 (C- γ); MS (ESI): m/z 290.03 (M^+).

1-(2,4-Dihydroxyphenyl)-3-(3'-chlorophenyl)propane-1,3-dione 2g.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3425 (OH), 1707 (C=O); ^1H NMR (CDCl_3) δ/ppm : 5.10 (s, 1H, Ar-OH), 6.85-8.0 (m, 8H, H-3, H-5, H-6, $-\text{CH}=\text{C}-$, H-2', H-4', H-5', H-6'), 12.17 (s, 1H, Ar-OH), 15.60 (s, 1H, enolic OH); ^{13}C NMR (CDCl_3): δ/ppm : 93.6 (C- α), 104.5 (C-3), 109.1 (C-5), 116.0 (C-1), 124.6 (C-6'), 126.4 (C-2'), 128.2 (C-4'), 131.0 (C-5'), 131.6 (C-1'), 132.5 (C-6), 134.2 (C-3'), 163.4 (C-2), 164.4 (C-4), 185.0 (C- β), 190.2 (C- γ); MS (ESI): m/z 290.03 (M^+).

1-(2,4-Dihydroxyphenyl)-3-(4'-chlorophenyl)propane-1,3-dione 2h.

IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3425 (OH), 1712 (C=O); ^1H NMR (CDCl_3) δ/ppm : 5.20 (s, 1H, Ar-OH), 6.72 (s, 1H, $-\text{CH}=\text{C}-$), 6.88-7.45 (m, 4H, H-3, H-5, H-3', H-5'), 7.72 (dd, 1H, $J= 8.0$ Hz & 2.0 Hz, H-6), 7.85-7.95 (m, 2H, H-2', H-6'), 12.25 (s, 1H, Ar-OH), 15.45 (s, 1H, enolic OH); ^{13}C NMR (CDCl_3): δ/ppm : 94.2 (C- α), 104.3 (C-3), 109.4 (C-5), 116.2 (C-1), 127.2 (C-2'), 127.2 (C-6'), 128.2 (C-1'), 128.6 (C-3'), 128.6 (C-5'), 132.2 (C-6), 133.2 (C-4'), 163.3 (C-2), 164.6 (C-4), 185.1 (C- β), 190.1 (C- γ); MS (ESI): m/z 290.033 (M^+).

RESULTS AND DISCUSSION

2-Aroyloxy--4-hydroxyacetophenone prepared by esterification of resacetophenone with aromatic carboxylic acids was ground with pulverized potassium hydroxide in a mortar by pestle at room temperature in the absence of any solvent (Scheme 1). The progress of the reaction was checked by thin layer chromatography (TLC) when the reactants were found to have reacted almost completely in 5 minutes and it had to be kept at room temperature for another 5-10 minutes for the completion of the reaction. During grinding the

Table 1. Physical data of 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones synthesized

Compound	Yield / %	Time/min (a+b)	mp / °C	Lit. mp / °C [25]
2a	82	5+5	156-158	158-159
2b	80	5+10	190-192	189-190
2c	84	5+10	163-165	164-165
2d	90	5+5	135-136	136-137
2e	86	5+5	170-171	170-171
2f	80	5+5	149-151	151
2g	84	5+10	125	124-125
2h	80	5+10	210-212	210-211

a- Time for grinding

b- Time at which the reaction mixture was kept at room temperature

reaction mixture absorbed moisture which was found to be sufficient to make the reaction mixture homogeneous. The product is also recovered simply by acidification of the reaction mixture in ice-cold water and avoids the need for organic solvent extraction of the compound. Attempt was also made using other bases such as barium hydroxide, calcium hydroxide, and calcium oxide which proved to be futile.

The validity of the reaction was established by converting differently substituted 2-aryloxy-4-hydroxyaceto-phenones into 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones in high yield (Table 1).

CONCLUSION

In conclusion, it can be stated that the present protocol for the synthesis of 1-(2,4-dihydroxyphenyl)-3-aryl-propane-1,3-diones is highly efficient and eco-friendly as it avoids the use of organic solvents at any stage of the reaction.

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ПРОСТА СИНТЕЗА НА 1-(2,4-ДИХИДРОКСИФЕНИЛ)-3-АРИЛ-ПРОПАН-1,3-ДИОНИ ЧРЕЗ ПРЕГРУПИРАНЕ НА ВАКЕР-ВЕНКАТАРАМАН ПРИ ОБИКНОВЕНИ ТЕМПЕРАТУРИ БЕЗ РАЗТВОРИТЕЛ

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(Резюме)

Описан е прост и високоефективен метод за синтезата на 1-(2,4-дихидроксифенил)-3-арил-пропан-1,3-диони чрез прегрупирането на Baker-Venkataraman, включващ смилането на 2-ароилокси-4-хидроксиацетофенони с пулверизиран калиев хидроксид при стайна температура в отсъствие на разтворител. Структурата на тези съединения е идентифицирана от тяхните спектрални данни (FT IR, ¹H NMR, ¹³C NMR, мас-спектрометрия). Процедурата не избягва използването на опасни реактиви и органични разтворители при всеки етап от реакцията.