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A HIGHLY EFFICIENT ONE STEP GREEN PROCEDURE FOR BAKER-VENKATARAMAN REARRANGEMENT IN AQUEOUS MEDIUM

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Abstract
A highly efficient procedure for the synthesis of 2-hydroxydibenzoylmethanes and 2-hydroxybenzoylcinnamoylmethanes is described. 2-Hydroxyacetophenones on reaction with aroyl chloride/ cinnamoyl chloride and potassium carbonate homogenized with few drops of water on microwave irradiation give required β-diketones directly. The formation of 2-aroyloxyacetophenones/ 2-cinnamoyloxyacetophenones followed by their Baker-Venkataraman rearrangement take place simultaneously in a single step. It is a green procedure as it avoids the use of organic solvents at any stage of the reaction.

Keywords: Baker-Venkataraman rearrangement, 2-hydroxyacetophenones, 2-hydroxydibenzoylmethanes, 2-hydroxybenzoylcinnamoylmethanes, microwave irradiation, aqueous medium.

Introduction
1-(2-Hydroxyphenyl)-3-phenylpropane-1,3-diones, commonly known as 2-hydroxy dibenzoylmethanes are the required key intermediates for the synthesis of flavones: a class of naturally occurring compounds[i], 3-aroylcoumaranones[ii], pyrazoles[iii], isoxazoles[iv], benzodiazepine[v] and pyrimidines[vi] while 1-(2-hydroxyphenyl)-3-styrylpropane-1,3-diones (2-hydroxybenzoylcinnamoylmethane) are required for the synthesis of 2-styrylchromones[vii]. These β-diketones have been found to exhibit varying degree of pharmacological activities like antibacterial[viii], antiviral[ix], insecticidal[x], antioxidant[xi], potential prophylactic antitumor activity[xii], and have also been used as sunscreen agent[xiii]. Dibenzoylmethane has potent chemopreventive activity against DMBA-induced carcinogenesis in rats[xiv, xv] and also β-ketoenols are important pharmacophores of HIV-1 integrase inhibitors[xvi].

These β-diketones are generally obtained by base catalyzed Baker-Venkataraman rearrangement of 2-aryloxyacetophenones. Due to high synthetic value of these β-diketones, number of attempts have been made to simplify the procedures which include use of $NaNH_2$ in dry ether[xvii], KOH in pyridine[xviii], NaOH or KOH in DMSO[xix, xx], KOH under grinding[xxi]. 2-Aroyloxyacetophenones required for Baker-Venkataraman rearrangement are generally obtained by the reaction of 2-hydroxyacetophenones with acid chlorides or anhydrides in pyridine[xxii] by

reaction of 2-hydroxyacetophenones with acids with $POCl_3$ in pyridine[xxiii] or in DCC in pyrolidine-CH_2Cl_2 medium[xxiv].

Results and Discussion

These days, much emphasis is being laid by the chemists to develop the synthetic procedures which could avoid the use of toxic and hazardous chemicals including organic solvents and the use of eco-friendly solvents is being encouraged as the medium for the reactions[xxv]. Use of microwave heating has been employed in a number of reactions when water is being used as reaction medium[xxvi].

Herein, we report a highly rapid aqueous mediated one step green synthesis of these 2-hydroxydibenzoylmethanes (1-7) and 2-hydroxybenzoylcinnamoyl methanes (8-10). A mixture of 2-hydroxyacetophenone, benzoyl chloride and potassium carbonate homogenized with a few drops of water was subjected to microwave irradiations as shown in scheme I. The reaction was found to be completed after 30-40 seconds when was checked by TLC. The presence of small amount of water was found necessary as no reaction was found to take place in its absence. The product was recovered by acidification of the reaction mixture in ice cold water and was identified as 2-hydroxydibenzoylmethane based on its IR and NMR spectra. Structure of the compound was further confirmed by comparison with authentic sample prepared by the reaction of 2-benzoyloxyacetophenone with NaOH in DMSO [xx].

The general nature of the reaction was shown by preparing differently substituted 2-hydroxydibenzoylmethanes. The reaction was also repeated using acid anhydride in place of aroyl chloride, when similar results were obtained. The use of aroyl chloride was preferred because the preparation of acid anhydride itself requires the use of $POCl_3$ in pyridine or expensive reagents like DCC in DMSO. Moreover, after the reaction half of the acid goes waste.

The present method was further extended successfully for the preparation of 2-hydroxybenzoylcinnamoylmethanes from 2-hydroxyacetophenones and cinnamoyl chloride following similar procedure.

Table 1. Synthesis of 2-hydroxydibenzoylmethanes/ 2-hdroxybenzoylcinnmoylmethanes (1-7/8-10)

Compd	R_1	R_2	R_3	R_4	Time (sec.)	M.P. (^{0}C)	Lit. M.P. (^{0}C)	Yield (%)[a]
1	H	H	H	H	30	117-18	118[xxi]	80
2	CH_3	H	H	H	40	80-82	82 [xxi]	85
3	H	OCH_3	H	H	40	100-01	102[xxvii]	90
4	H	H	H	OCH_3	35	109-10	112 [xxi]	95
5	CH_3	H	H	OCH	30	94-96	96 [xxi]	90
6	H	OCH_3	H	OCH_3	40	107-08	107 [xxi]	80
7	H	H	OCH_3	H	45	79-81	82-83[xxviii]	85
8	H	H	H	H	40	132-33	131 [xxi]	80
9	CH_3	H	H	H	30	133-35	137-39 [xxi]	95
10	H	OCH_3	H	H	30	149-50	148 [xxi]	85

[a] Yield after crystallization

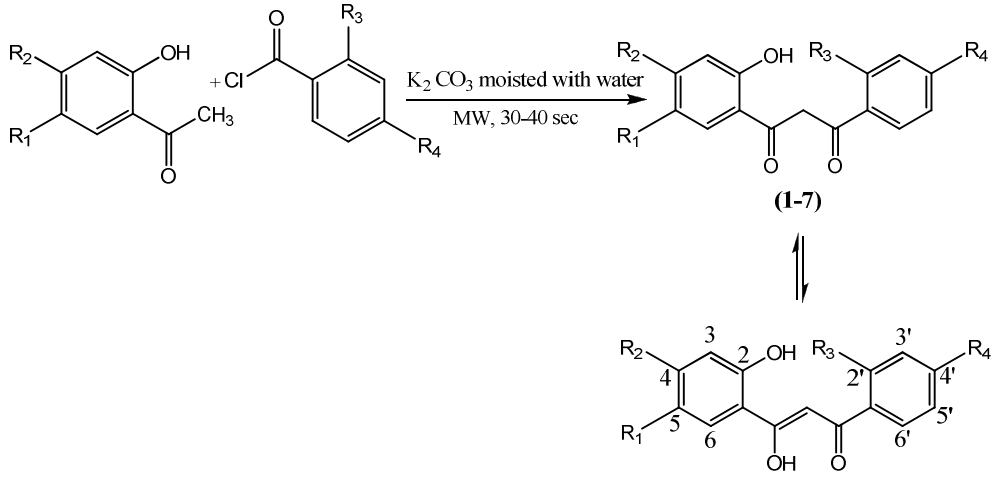
Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer Spectrum BX-series FT-IR spectrophotometer and ^{1}H NMR spectra on a Bruker Avance II 400MHz NMR spectrometer using tetramethylsilane as an internal standard.

General experimental procedure

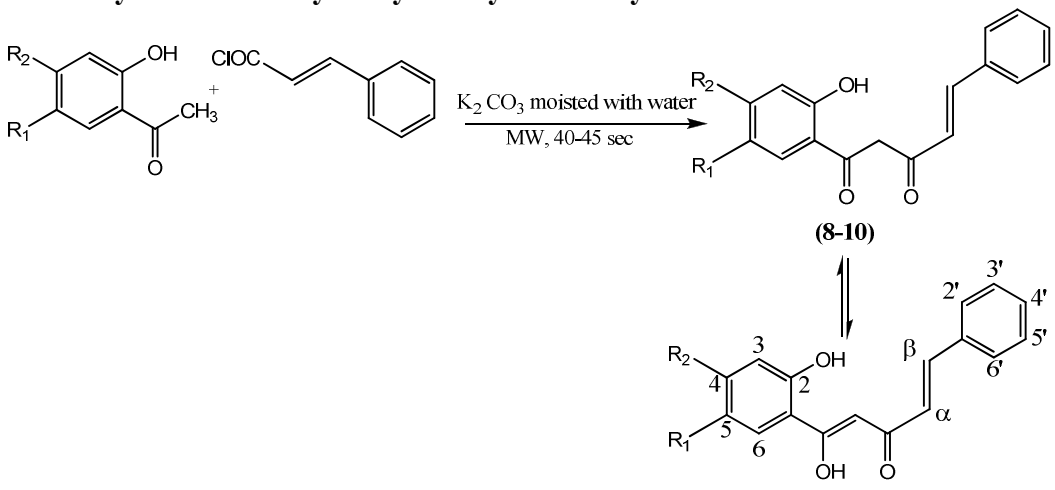
A mixture of substituted 2-hydroxyacetophenone (2 mmol), aroyl chloride/ cinnamoyl chloride (2 mmol) and potassium carbonate (10 mmol) homogenized with 8-10 drops of water was subjected to microwave irradiation for 30 (5×6) sec. The completion of reaction was checked by thin layer chromatography. The reaction mixture was diluted with ice cold water, acidified with conc. HCl (pH 5.5- 6.0), solid that separated was filtered, washed with water and recrystallized from aqueous ethanol to afford 2-hydroxydibenzoylmethane/ 2-hydroxybenzoylcinnamoylmethane.

Scheme 1. Synthesis of 2-hyroxydibenzoylmethanes



Scheme 1

Scheme 2. Synthesis of 2-hydroxybenzoylcinnamoylmethanes



Scheme 2

Spectral data of compounds (1-10)

1. IR (KBr): 3433 cm^{-1} (OH str), 1606 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 6.85 (s, 1H, -C**H**=C(OH)-), 6.90-7.89 (m, 6H, H-3, H-4, H-5, H-3', H-4', H-5'), 7.95-8.26 (m, 3H, H-6, H-2', H-6'), 12.10 (s,1H, Ar-O**H**), 15.50 (s, 1H, enolic O**H**).

2. IR (KBr): 3379 cm^{-1} (OH str.), 1597 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H, CH_3), 6.47 (s, 1H, -C**H**=C(OH)-), 6.66 (d, 1H, J= 8.24 Hz, H-3) 7.02 (d, 2H, J=8.24 Hz, H-4), 7.29-7.48 (m, 3H, H-3', H-4', H-5'), 7.87 (s, 1H, H-6), 7.93 (m, 2H, H-2', H-6'), 12.26 (s, 1H, Ar-O**H**).

3. IR (KBr): 3428 cm^{-1} (OH str.), 1610 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 6.36-6.55(m, 2H, H-3, H-5), 6.71 (s, 1H, -C**H**=C(OH)-), 7.39-7.58 (m, 3H, H-3', H-4', H-5'), 7.85-7.98 (m, 2H, H-2', H-6'), 8.02 (d, 1H, J=7.2 Hz, H-6), 12.58 (s, 1H, Ar-O**H**), 15.36 (s, 1H, enolic O**H**).

4. IR (KBr): 3540 cm^{-1} (OH str.), 1608 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 3.9 (s, 3H, OCH_3), 6.75 (s, 1H, -C**H**=C(OH)-), 6.88-7.46 (m, 5H, H-3, H-4, H-5, H-3', H-5'), 7.75 (dd, 1H, J= 8.08 Hz, J= 1.48 Hz, H-6), 7.85-7.95 (m, 2H, H-2', H-6'),12.14 (s, 1H, Ar-O**H**), 15.76 (s, 1H, enolic O**H**).

5. IR (KBr): 3440 cm^{-1} (OH str.), 1610 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 6.75 (s, 1H, -C**H**=C(OH)-), 6.89 (d, 1H, J= 8.44 Hz, H-3), 6.95-7.04 (m, 2H, H-3', H-5'), 7.26 (dd, 1H, J= 6.68 Hz, J=2 Hz, H-4), 7.53 (d, 1H, J=1.4 Hz, H-6), 7.85-7.96 (m, 2H, H-2', H-6'), 11.94 (s, 1H, Ar-O**H**), 15.83 (s, 1H, enolic O**H**).

6. IR (KBr): 3468 cm^{-1} (OH str.), 1605 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, 4'-OCH_3), 3.88 (s, 3H, 4-OCH_3), 6.37-6.52 (m, 2H, H-3, H-5), 6.64 (s, 1H, -C**H**=C(OH)-), 6.9-7.02 (m, 2H, H-3', H-5'), 7.68 (d, 1H, J= 9.72 Hz, H-6), 7.81-7.91 (m, 2H, H-2', H-6'), 12.62 (s, 1H, Ar-O**H**), 15.55 (s, 1H, enolic O**H**).

7. IR (KBr): 3480 cm^{-1} (OH str.), 1602 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): 3.99 (s, 3H, OCH_3), 6.90-7.92 (m, 9H, H-3, H-4, H-5, H-6, -C**H**=C(OH)-, H-3', H-4', H-5', H-6'), 12.16 (s, 1H, Ar-O**H**), 15.64 (s, 1H, enolic O**H**).

8. IR (KBr): 3380cm^{-1} (OH str.), 1628 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 6.32 (s, 1H, -C**H**=C(OH)-), 6.60 (d, 1H, J= 15.76 Hz, α –C**H**=CH-), 6.91(dd, 1H, J=7.08 Hz, J=1.04 Hz, H-3), 6.97-7.50 (m, 5H, H-4, H-5, H-3', H-4', H-5'), 7.57 (dd, 2H, J=7.9 Hz, J=2 Hz, H-2', H-6'), 7.66 (d, 1H, J= 15.76 Hz, β –CH=C**H-**), 7.70 (dd, 1H, J= 8.08 Hz, J= 1.52 Hz, H-6), 12.22 (s, 1H, Ar-O**H**), 14.64 (s, 1H, enolic O**H**).

9. IR (KBr): 3385 cm^{-1} (OH str.), 1636 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 6.32 (s, 1H, -C**H**=C(OH)-), 6.61 (d, 1H, J= 15.48 Hz, α–C**H**=CH-), 6.90 (d, 1H, J= 8.44 Hz, H-3), 7.28 (dd, 1H, H-4), 7.34- 7.45 (m, 3H, H-3', H-4', H-5'), 7.48 (d, 1H, J= 1.44Hz, H-6), 7.56 (dd, 2H, J= 9.4 Hz, J= 2.76 Hz, H-2', H-6'), 7.65 (d, 1H, J= 15.48 Hz, β–CH=C**H-**), 12.03 (s, 1H, Ar-O**H**), 14.68 (s, 1H, enolic O**H**).

10. IR (KBr): 3382 cm^{-1} (OH str.), 1628 cm^{-1} (C=O str.)
^{1}H NMR ($CDCl_3$): δ 3.84 (s, 3H, OCH_3), 6.20 (s, 1H, -C**H**=C(OH)-), 6.37-6.50 (m, 2H, H-3, H-5), 6.58 (d, 1H, J= 15.8 Hz, α –C**H**=CH-), 7.31-7.44 (m, 3H, H-3', H-4', H-5'), 7.55 (dd, 2H, J= 8Hz, J= 1.64 Hz, H-2',H-6'), 7.63 (d, 1H, J= 7.04 Hz, H-6), 12.69 (s, 1H, Ar-O**H**), 14.51 (s, 1H, enolic O**H**).

Conclusion

It appears to be the first report where 2-hydroxydibenzoylmethanes/ 2-hydroxybenzoylcinnamylmethanes have been obtained directly from the reaction of 2-hydroxyacetophenone and aroyl chlorides/ cinnamoyl chloride in aqueous medium in one step without isolating the 2-aoryloxyacetophenone/ 2-cinnamoyloxyacetophenone intermediate. Moreover, it avoids the use of organic solvents at any stage of the reaction, making the procedure greener in nature.

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