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Simple and effective microwave assisted one pot synthesis of symmetrical Curcumin analogues

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ABSTRACT

A simple, one pot, time efficient and productive method is reported with simple work up for the synthesis of Curcumin and its symmetrical analogues by application of Microwave irradiation techniques using Toluene as solvent, Boric acid used as chelating reagent and anhydrous Sodium Sulfate as effective mild dehydrating agent.

INTRODUCTION

Curcumin ((1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one) is natural product and isolated from plant *Curcuma longa*[1]. Curcumin, found with its isomers demothoxy curcumin (DMC) and bisdemethoxy curcumin (BDMC) as yellow colour mixture. Curcumin is molecule impart by traditional wisdom, popularly used as curry color pigment in India, likewise among other various Asian countries such as China and Nepal, Curcumin is socially accepted as naturally gifted medicine. Modern science authenticated that Curcumin inhibits induction of nitric oxide [2], 5-Chloro curcumin exhibits anti-oxidant[3] properties, due to presence of phenolic unit curcumin exhibits anti-oxidant properties in water [4]. Curcumin found to be excellent inhibitor for various type of cancer[5] such as gastrointestinal cancer [6],breast cancer [7],pancreatic cancer [8],lung cancer [9],blood cancer properties[10], anti-oral and anti-cervical cancer.[11-12] Curcumin, now also reported for possessing anti-inflammatory[13], anti-bacterial[14], anti-diabetic[15], anti-Alzheimer [16](AD) and anti-HIV[17] properties. Curcumin found useful natural product for treatment of psychiatric disorder like depression [18], many other studies underline pharmacokinetic importance of curcumin. [19-20]

Bioavailability of curcumin [21] is major hurdle, which prevent curcumin to establish as super drug. Many attempts were made, by synthesizing of curcumin and its analogues in the laboratory, in search of novel pharmacokinetic properties. Most of such methods involving one mole of Acetyl acetone and two moles of vanillin along with suitable base. Conventionally synthesis of Curcumin required longer time [22],Success of the reaction depends upon condensation of terminal methyl groups with aromatic aldehydes. Due to presences of more active methylene moiety at centre of acetyl acetone, it reacts first and reduce yield of product.

Attempts were made for the synthesis of Curcumin and its analogues by MWI techniques[23-24]. Practically, curcumin analogues with non-hydroxyl aromatic aldehydes do react to obtained satisfactory yield. But during the reaction of synthesis of Curcumin or bisdemethoxy curcumin (BDMC) yield of product fall down. One way is to protect hydroxyl groups followed by Claisen-Schmidt reaction. Another way is modification in reaction condition by

using better chelating techniques of dicarbonyl moieties. Present study reports useful modification in the synthetic procedure pathway.

MATERIALS AND METHODS

All the compounds used in synthesis were of analytical grade, the melting points of the compounds were determined in open head capillary and are uncorrected. The reaction was carried out in a domestic microwave oven (Samsung output energy 900W) H^1 NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in $CDCl_3$/DMSO-d_6 using TMS as internal standard. Chemical shifts (δ) are reported in ppm. The IR spectra were recorded using Perkin Elmer spectrometer (KBr plates). All the compounds were checked for purity by thin layer chromatography (TLC).

General experimental procedure

Acetyl acetone (1 mmol.), boric acid (1 mmol.) and anhydrous Sodium sulfate (0.5mmol.) were taken in moisture free toluene as solvent and stirred for 60 min. at 50°C in water bath. Substituted aromatic aldehydes (Table 1) (2 eq.) was added to reaction mixture, finally drop wise with continuous stirring n-$BuNH_2$ (2 eq.) was added, reaction mixture was irradiated at 600 W for 6-8 min. (Table 1). Filter to removed solvent, cold 1 N hydrochloric acid was added (20 ml) to residue and stirred for 2 hr. Filter, wash with cold water several times, air dried and purified by recrystalization (3e-3i) or Column chromatography (3a-3d).

***Spectral data of Compounds* (3a-3i)**

(1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one (3a)

IR (KBr): 3530, 1640, 1618, 1020, 980 cm^{-1}, ^{1}H-NMR (DMSO-d_6) δ 3.88 (s,6H, OCH_3), 6.04 (s,1H, H-4), 6.71(d,1H, H-7), 6.77 (d, 2H, Ar), 6.82 (d, 1H, H-6), 7.09(d, 2H, Ar), 7.14(d,1H, H-2), 7.33 (s, 2H, Ar), 7.61 (d, 1H, H-1), 9.71 (s, 2H, OH), 10.11(s, 1H, enol OH)

(1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxyphenyl)hepta-1,4,6-trien-3-one (3b)

IR (KBr): 3455, 3241, 1623, 1590, 1269, 1164 cm^{-1}, ^{1}H-NMR (DMSO-d_6) δ 6.11(s, 1H, H-4), 6.69 (d,1H, H-7), 6.83 (d,1H, H-6), 6.87 (d,4H, Ar), 7.63 (d, 4H, Ar), 7.67 (d, 1H, H-1), 7.81(d, 1H, H-2), 9.42(s,2H, OH)

(1E,4Z,6E)-1,7-bis(3,4-dihydroxyphenyl)-5-hydroxyhepta-1,4,6-trien-3-one (3c)

IR (KBr): 3561, 3312, 1680, 1630, 1154 cm^{-1}, ^{1}H-NMR (DMSO-d_6) δ 6.32(s, 1H, H-4), 6.39 (d,1H, H-7), 6.75 (d,1H, H-6), 6.80 (d,2H, Ar), 6.83(d,2H, Ar) 7.63 (s, 2H, Ar), 7.73 (d, 1H, H-1), 7.83(d, 1H, H-2), 9.61(s,4H, OH)

(1E,4Z,6E)-5-hydroxy-1,7-bis(2-hydroxyphenyl)hepta-1,4,6-trien-3-one (3d)

IR (KBr):3451, 3410, 1610, 1231, 1142, 1074 cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.20 (s,1H, H-4), 6.51(d,1H, H-6), 6.89 (d, 2H, Ar), 6.98 (d, 2H, H-2), 7.11 (d,1H,H-7), 7.29 (m,4H, Ar),7.67 (d,2H, Ar), 7.89 (d,1H, H-1)

(*1E,4Z,6E)-5-hydroxy-1,7-bis(4-methoxyphenyl)hepta-1,4,6-trien-3-one (3e)*

IR (KBr): 3453, 2889, 1641, 1588, 1121, 1028, 826 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl^3$) δ 3.84 (s,6H,OCH_3), 6.71 (s,1H, H-4), 6.79 (d,1H, H-7), 6.88 (d,1H,H-6), 6.92 (d,4H, Ar), 7.11 (d, 1H,H-2), 7.46 (d, 4H, Ar),7.69 (d 1H, H-1)

(1E,4Z,6E)-1,7-bis(4-(dimethylamino)phenyl)-5-hydroxyhepta-1,4,6-trien-3-one(3f)

IR (KBr): 3447, 2891, 1704, 1212, 962, cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s,12H, $N(CH_3)_2$), 6.19 (s,1H, H-4), 6.68 (d, 4H, Ar), 6.72 (d,1H,H-7), 6.91 (d,1H,H-6), 7.11 (d,1H,H-2), 7.40 (d, 4H, Ar),7.61 (d, 2H,H-1)

(1E,4Z,6E)-5-hydroxy-1,7-di-p-tolylhepta-1,4,6-trien-3-one(3g)

IR (KBr): 3459, 2892, 1651, 1595, 1102,980 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl^3$) δ2.46 (s,6H, $-CH_3$), 6.58 (s,1H, H-4), 6.91 (d,1H, H-7), 6.97 (d,1H, H-6), 7.11 (d,1H, H-2) 7.16 (dd, 2H, Ar), 7.51 (dd,4H, Ar), 7.69 (d,1H, H-1)

(1E,4Z,6E)-5-hydroxy-1,7-bis(4-nitrophenyl)hepta-1,4,6-trien-3-one(3h)

IR (KBr): 3512, 2867, 1678, 1612, 1157, 1048, 838 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (s,1H, H-4),6.79(d,1H, d, H-7), 7.14 (d,2H, H-,6), 7.23 (d,1H, d,H-2), 7.81 (d,2H, d,H-1), 8.04 (d, 4H, Ar), 8.13 (d,4H,Ar)

(1E,4Z,6E)-1,7-bis(4-bromophenyl)-5-hydroxyhepta-1,4,6-trien-3-one(3i)
IR (KBr): 3445, 2890, 1614, 1543, 844 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ6.41 (s,1H, H-4), 6.64 (d,1H,H-7), 6.89 (d,1H, H-6), 7.11 (d, 1H, H-2), 7.41 (dd,2H,Ar), 7.61 (dd,4H, Ar), 7.81 (d,1H, H-1).

RESULTS AND DISCUSSION

Herein we reported a modified Claisen-Schmidt condensation reaction for the synthesis of curcumin and analogues. Fruitful synthesis needs to hold acetyl acetone in keto-enol form. (Fig.1) instead of keto-keto form. Boron complex formation with acetyl acetone 'trap' acetyl acetone in keto-enol form. During the experiment, it was observed that using dehydrating agent enhanced yield of reaction anhydrous sodium sulfate was found to be compatible for this reaction purpose. Slow and drop wise addition of n-butyl amine to the reaction mixture with continuous stirring has been made followed with microwave irradiation at 600W for 6-8 min. (Table 2) with 30 second cooling period after one minutes. Dark red colored mass was filter to removed solvent, residue left in ice cold 2M hydrochloric acid with stirring for 2 hour. Obtained solid was filter, air dried. Curcumin and bisdemethoxy curcumin (BDMC) and other hydroxyl curcumin analogues were further purified by column chromatography.

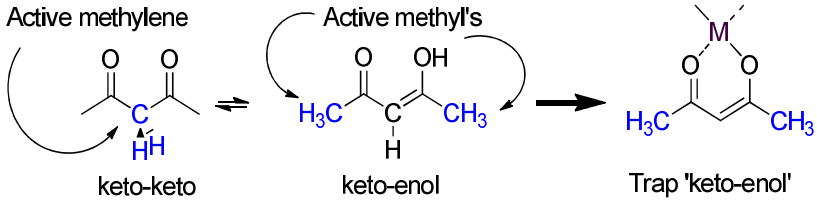

Fig. 1 Acetyl acetone with interfering keto-keto form and preferable keto-enol form for the synthesis of Curcumin

Table 1.Optimization of solvents for the synthesis of Curcumin

Entry	Solvent	Yield[a]
1	DMF	63%
2	Ethanol	31%
3	PEG-400	67%
4	Toluene	73%
5	CH_3CN	58%
6	Ethyl acetate	28%

[a]*Isolated yields*

Reaction Scheme 1.One pot MWI synthesis of symmetrical curcumin analogues

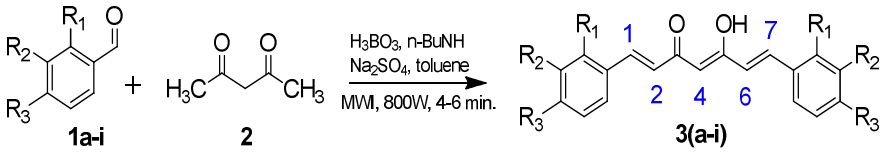

Table 2.Reaction of Aldehydes and Acetyl acetone for the Synthesis of Curcumin analogues

Entry	R_1	R_2	R_3	Time (min.)	Yield[a]	M.P.
3a	-H	$-OCH_3$	-OH	8	73%	180-181
3b	-H	-H	-OH	8	71%	179-180
3c	-H	-OH	-OH	8	59%	131-132
3d	-OH	-H	-H	8	62%	185-186
3e	-H	-H	$-OCH_3$	6	86%	160-161
3f	-H	-H	$-N(Me)_2$	6	65%	152-153
3g	-H	-H	-Me	6	81%	110-111
3h	-H	-H	$-NO_2$	6	91%	148-149
3i	-H	-H	-Br	6	92%	150-151

[a]*Isolated yields*

CONCLUSION

Present method is efficient, simple and one step protocol for the synthesis of curcumin analogues. Utility spectrum of this method is sufficiently wide, by means of using cheaper dehydrating agent as well as chelating agent. In conclusion, this method of curcumin synthesis by MWI method is productive, time efficient and easy to workup.

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