Solid-Phase Microwave Assisted Synthesis of Curcumin Analogs

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Abstract: Turmeric contains three important analogs, curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC), collectively called as curcuminoids. Curcumin, the most abundant of these curcuminoids is reported to have antioxidant, anti-inflammatory, neuroprotective, antimicrobial, nematocidal, antimutagenic, anticarcinogenic, antiretroviral and chemopreventive activities. Curcumin (a symmetric β diketone) analogs **3a-e** were synthesized from β-diketones and aromatic aldehydes using solid phase microwave irradiation method in presence of boric acid in diethanolamine, acetic acid (1:1) with reduced reaction time and enhanced %yield. Various clays like Alumina (neutral), Silica gel and Montmorillonite K_{10} were used as solid phase catalysts where alumina was found to be efficient in the synthesis of curcumin analogs.

Keywords: Aldol condensation, boron-assisted, curcumin analogs, microwave irradiation, regioselective, solid-phase.

INTRODUCTION

Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphenol derived from the rhizome (turmeric) of the herb *Curcuma longa* (Zingiberaceae). Turmeric has been used for thousands of years in ayurvedic and traditional medicine of Chinese and Indians. In modern days, curcumin continues to be used as an alternative medicinal agent in many parts of South East Asia for the treatment of many ailments such as stomach upset, flatulence, jaundice, arthritis, sprains, wounds and skin infections.

Turmeric contains three important analogs, curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC), collectively called the curcuminoids. Structures of curcuminoids are presented in Fig. (**1**). Of the three curcuminoids, curcumin is the most abundant in turmeric, followed by DMC and BDMC. Commercially available curcumin mixture contain 77% curcumin, 17% DMC, and 3% BDMC. Chemically, it is a bis-α, β-unsaturated β-diketone-(1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadien- 3, 5-dione), that exhibits keto-enol tautomerism presented in Fig. (**2**).

Curcumin has been shown to exhibit antioxidant [1], anti-inflammatory [2], neuroprotective, antimicrobial, nema-tocidal, antimutagenic, anticarcinogenic [3], antiretroviral [4] and chemopreventive activities. It also has hepatoprotective and nephroprotective activities, suppresses thrombosis, protects against myocardial infarction and has hypoglycemic [5] and antirheumatic properties. The curcuminoids have been shown to be scavengers of free radicals and reactive oxygen species (ROS), such as hydroxyl radicals [1], superoxide radicals, singlet oxygen, peroxyl radicals, and peroxynitrite, whose production is implicated in the induction of oxidative stress [1, 6-9].

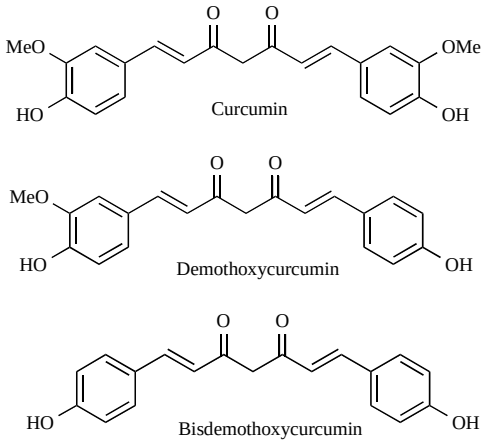

Fig. (1). Structures of curcuminoids.

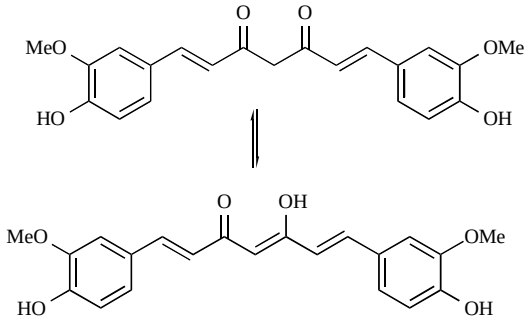

Fig. (2). Keto-enol tautomerism of Curcumin.

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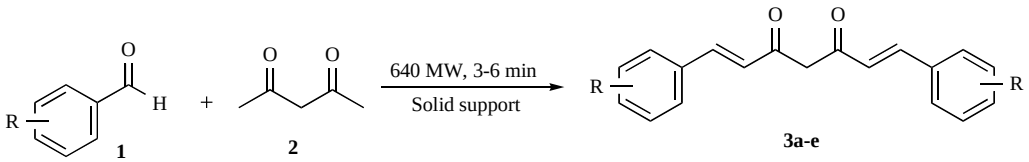


Scheme 1. Microwave assisted synthesis of Curcumin analogs on solid-support.

Curcumin is synthesized majorly by the aldol condensation of β-diketones and aromatic aldehydes. The microwave-assisted aldol condensations using boric acid was already reported to synthesize curcumin [10, 11]. However, the solid supported microwave synthesis of curcumin with boron-assisted regioselective aldol condensation is not yet investigated.

One of the major current challenges before chemists is to develop synthetic methods that are less polluting, i.e., to design clean or 'green' chemical transformations. An important family of catalysts that has received considerable attention of the synthetic chemist in recent times is derived from the soil, i.e. clays and zeolites. During microwave induction of reactions under dry conditions, the reactants adsorbed on the surface of clay, absorb the microwaves and accelerate the reaction.

Clays are solid acidic catalysts which can function as both Bronsted and Lewis acids in their natural and ion-exchanged form. Modified smectite clays are very selective for a wide range of organic transformations [12-16]. Clay minerals are alluminosilicates and classified as phyllosilicates, having layered structures comprising tetrahedral silicate and octahedral aluminate sheets. Higher acid strength of the catalyst generally leads to greater catalytic activity, but poorer product selectivity [17-21]. Lewis acidity may persist under dehydrated conditions [21].

In the present study, we designed a novel, green solid-phase synthetic method (Scheme **1**) for the preparation of curcuminoids (**3**) using the microwave irradiation and various clays like Alumina (neutral), Silica gel and Montmorillonite K_{10} as catalysts. Several analogs of curcumin were prepared (**3a-e**) from various substituted aromatic aldehydes (**1**) using the novel method.

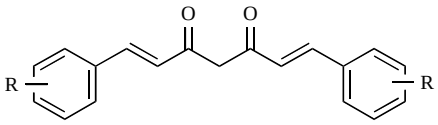
RESULTS AND DISCUSSION

Although curcumin is a simple symmetrical β- diketone, its synthesis is complex and involves double aldol condensation on 2, 4-pentadione (acetyl acetone) (**2**). Since C_3 of 2, 4-pentadione is more acidic than terminal C_1 and C_5 - methyl groups, it undergoes Knoevenagel condensation leading to the formation of side products [22]. To overcome this condensation, Boron-based protection is reported to facilitate aldol condensations at C-1 and C-5 of acetyl acetone. A boron-based reagent such as boric acid, DMF and diethyl amine and acetic acid acts as Lewis acids with the β-diketone systems and consequently reduces the nucleophilicity of the C-3 position and the reaction occurs selectively at the terminally active methylenes, resulting in diarylheptanoids [23].

More accessible, convenient and efficient inorganic solid supports like silica gel, neutral alumina, and montmorillonite K_{10} were chosen as catalysts. The organic compounds were adsorbed on the surface of inorganic oxides which do not absorb or restrict the transmission of microwaves [24]. These clays were found to fasten the rate of reaction and thus decrease the time of reaction by twice.

Here, the compounds were subjected to 640 MW power with 10 sec interval leading to the completion of reaction. Moderate to excellent yields of the desired compounds were obtained when the reaction mixture was irradiated for 3-6 minutes by microwaves. The yields of the compounds made in this investigation under microwave-assisted conditions are consistently higher than those reported under conventional conditions. The reaction times and % yields of various curcumin derivatives at varied reaction conditions were presented in Table **1**.

Table 1. Reaction Times and % Yield of Synthesized Compounds (3a-f)



Compound Code	Substitution R	Reaction Time (min)			% yield[a]		
		Alumina	Silica	Montmorillonite K_{10}	Alumina	Silica	Montmorillonite K_{10}
3a	H	2.5	5.8	5.2	89	68	82
3b	2-OH	2.6	5.6	5.8	92	74	86
3c	3-OCH_3	2.3	5.8	5.6	87	72	76
3d	4-OCH_3	2.8	5.2	5.6	85	69	72
3e	4-Cl	2.2	5.3	4.8	95	73	76

[a]Isolated yields after column chromatography.

NMR spectra revealed that the compounds exist in enol form in solution. The H-bonded hydroxyl proton of the enol form expected in highly desheilded region (>δ 13) was seen; the active methine (-COCHCO-) of the diketo tautomer was observed. Elemental analyses of these compounds were with in ±0.4 range from the calculated value.

The enhanced yields and reduction in time with alumina may be attributed to the acidic nature of alumina. The good reaction conditions with K10 clay may be due to bulky organic alkyl ammonium ion which carries out ion exchange reactions with inorganic exchangeable cations between the clay unit layers, leading to the increase of the distance between the clay layers.

EXPERIMENTAL

Melting points were recorded on an electro-thermal apparatus and are uncorrected. Column chromatography purifications were carried using silica gel (230-400 mesh) obtained from Silicycle.^{1}H NMR spectra were obtained using a Bruker 400-MHz spectrophotometer in $CDCl_3$, and chemical shift values are expressed in δ values (ppm) relative to tetramethylsilane (TMS) as internal standard. Reaction progress was monitored by analytical thin-layer chromatography (TLC) on precoated glass plates (silica gel 60 F254 plate), and the spots were visualized by ultraviolet (UV) light. The structures of novel compounds were identified by infrared spectra obtained from Thermo Nicolet Nexus 670 spectrometer and EI-MS spectra obtained from CEC 21-110B sector instrument. CHN analyses were recorded on a Vario EL analyzer.

General Procedure for Synthesis of Compounds (3a-e)

10 mmole of acetyl acetone is reacted with 22 mmole of various aromatic aldehydes in the presence of boric acid (10 mmoles) and diethyl amine: acetic acid (1:1) were subjected to microwave irradiation in the presence of various catalysts like Alumina (neutral), Silica gel and Montmorillonite K_{10} clay with 10s pulse at 640 MW, resulting in a reddish yellow viscous liquid which, upon purification by column chromatography, yielded reddish brown gummy solid.

1, 7-Diphenylhept-1, 6-diene-3, 5-dione (3a)

Reddish brown gummy solid; $C_{19}H_{16}O_2$; IR (cm^{-1}, KBr): 3625 (enolic OH), 1708.24 (C=O), 1660.65 (C=C); 1H NMR (400MHz, $CDCl_3$, δppm): 15.0 (br, 1H, enolic -OH), 7.66 (s, 1H, CH=C), 7.26–7.49 (m, 10H, Ar-H), 7.03 (s, 1H, CH=C), 6.85 (s, 1H, CH=C), 6.7 (s, 1H, CH=C), 6.65 (s, 1H, CH=C); MS (EI) 70eV, *m/z* (rel. intensity): 276 (M+, 100), 277 (21.5), and 278 (2.7); Elemental analysis (cal/obser) C 82.58/82.54, H 5.84/5.86, O 11.58/11.60.

1, 7-Bis (2-hydroxyphenyl) hept-1, 6-diene-3, 5-dione (3b)

Reddish brown gummy solid; $C_{19}H_{16}O_4$; IR (cm^{-1}, KBr): 3630 (enolic OH), 1705.24 (C=O), 1670 (C=C); 1H NMR (400MHz, $CDCl_3$, δppm) 15.0 (s, 1H, enolic -OH), 7.93 (s, 1H, CH=C), 7.13 (m, 2H, Ar-H), 6.97 (m, 2H, Ar-H), 6.92 (s, 1H, CH=C), 6.86 (s, 1H, CH=C), 6.84 (s, 1H, CH=C) 6.77-6.7 (m, 4H, Ar-H), 6.68 (s, 1H, CH=C), 4.11 (q, 2H, Ar-OH). MS (EI) 70eV, *m/z* (rel. intensity): 308 (M+, 100), 309 (19.3), and 310 (3.9); Elemental analysis (cal/obser) C 74.01/74.06, H 5.23/5.21, O 20.76/20.73.

1, 7-Bis (3-methoxyphenyl) hept-1, 6-diene-3, 5-dione (3c)

Reddish brown gummy solid; $C_{21}H_{20}O_4$; IR (cm^{-1}, KBr): 3628 (enolic OH), 1720.24 (C=O), 1645.65 (C=C); 1H NMR (400MHz, $CDCl_3$, δppm): 15.0 (s, 1H, enolic -OH), 7.66 (s, 1H, CH=C), 7.46 (s, 2H, Ar-H), 7.44 (s, 2H, Ar-H), 7.39 (d, 2H, Ar-H), 7.03 (s, 1H, CH=C), 6.95 (d, 2H, Ar-H), 6.85 (s, 1H, CH=C), 6.7 (s, 1H, CH=C), 6.65 (s, 1H, CH=C), 3.869 (s, 6H, 2-OCH_3). MS (EI) 70eV, *m/z* (rel. intensity): 336 (M+, 100), 337 (23.7), and 338 (3.9); Elemental analysis (cal/obser) C 74.98/74.92, H 5.99/5.99, O 19.03/19.66.

1, 7-Bis (4-methoxyphenyl) hept-1, 6-diene-3, 5-dione (3d)

Reddish brown gummy solid; $C_{21}H_{20}O_4$; IR (cm^{-1}, KBr): 3638 (enolic OH), 1705 (C=O), 1640 (C=C); 1H NMR (400MHz, $CDCl_3$, δppm): 15.0 (s, 1H, enolic OH), 7.84 (d, 4H, Ar-H), 7.66 (s, 1H, CH=C), 7.03(s, 1H, CH=C), 7.0 (d, 4H, Ar-H), 6.85 (s, 1H, CH=C), 6.7 (s, 1H, CH=C), 6.65 (s, 1H, CH=C), 3.8 (s, 6H, 2-OCH_3); MS (EI) 70eV, *m/z* (rel. intensity): 336 (M+, 100), 337 (23.5), and 338 (2.7); Elemental analysis (cal/obser) C 74.98/74.83, H 5.99/5.96, O 19.03/19.21.

1, 7-Bis (4-chlorophenyl) hept-1, 6-diene-3, 5-dione (3e)

Reddish brown gummy solid; $C_{19}H_{14}Cl_2O_2$; IR (cm^{-1}, KBr): 3648 (enolic OH), 1708 (C=O), 1660 (C=C); 1H NMR (400MHz, $CDCl_3$, δppm): 15.0 (s, 1H, enolic OH), 7.82 (d, 4H, Ar-H), 7.66 (s, 1H, CH=C), 7.51 (d, 4H, Ar-H), 7.03 (s, 1-H, CH=C), 6.7 (s, 1H, CH=C), 6.85 (s, 1H, CH=C), 6.65 (s, 1H, CH=C); MS (EI) 70eV, *m/z* (rel. intensity): 344 (M^+, 100), 346 (66.5), 345 (20.7), 347 (21.9); Elemental analysis (cal/observed) C 66.10/66.25, H 4.09/4.04, O 9.27/9.25.

CONCLUSION

A series of curcuminoid analogs (**3a-e**) was synthesized on the solid support using microwave irradiation with boron assisted regioselectivity. Among the used clays, Alumina fastened the reaction and reduced the reaction times twice when compared with others. All the reported compounds had given the best yields with greater purity.

CONFLICT OF INTEREST

Declared none.

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