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EXPEDITIOUS MICROWAVE-ASSISTED ZIRCONIUM CHLORIDE CATALYSED SYNTHESIS OF CURCUMIN ANALOGUES

Mahesh Shioorkar[1], Sangeeta Pawar[1], Milind Ubale[2]*

[1]Department of Chemistry, Vivekanand College, Aurangabad.
[2]Post graduate department of Chemistry, Vasantrao Naik College, Aurangabad.

Email of corresponding author: drmilindubale@gmail.com

ABSTRACT

Curcumin (*1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione*) -4-substituted analogues synthesis describe with microwave irradiation method. Curcumin and aromatic aldehydes in presence of water:ethanol (1:1) as solvent and Zirconium Chloride ($ZnCl_4$) as catalyst exposed to microwave irradiation, to obtained product in good yields, six derivatives **(3a-f)** was prepared with satisfactory yield. Present methodology consists of simple working procedure, environmental friendly, easy workup procedure and cost effective starting materials. Derivatives **(6a-f)** was obtained by this were characterized for spectral analysis and found good agreement with reported.

Keywords: Curcumin analogues, Green reaction, Zirconium Chloride catalyzed, Microwave assisted synthesis.

INTRODUCTION

Curcumin commonly known as turmeric, obtained from the rhizomes of *Curcuma longa*, one of the species from *Zingiberaceae* family and exhibits characteristic golden yellow colour. Today there are some 120 known species of turmeric. Curcumin used as yellow colour curry pigment in all over Indian subcontinent. Several research groups have investigated and compare their activity as antioxidant, cardio-protective, neuro-protective, antidiabetic, antitumor and chemopreventive activities, either as pure compound or as mixtures **[1-4].** It helps prevent cell weakening and rebuild the cellular genetic codes to life levels [**5-8**]. Curcumin found useful in human prostate cancer cells [9], and release of cytochrome [**10, 11**]. On the other hand, one of the predominant targets of curcumin is the NF-kB cell signaling pathway [**12, 13**], curcumin has found active to proteasomes *26S* [**14, 15**]. Curcumin has been introduced to many clinical trials in different human cancer therapy [**16-18**], the clinical potential of curcumin remains

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limited because of its relatively poor bioavailability [**19**].

Curcumin consisting central methylene moiety with most reactive proton held by carbon atom. Aromatic benzaldehyde in presence of ethanolic sodium hydroxide offers 4-arylidene substituted curcumin. Pharmaceutically these analogues were synthesized and found more active than curcumin **[20, 21].** Replacement of an acidic proton from the central methylene with benzylidene derivatives proved to be as effective antimalarial as curcumin. The 4-hydroxy-3-methoxy-benzaylidene derivative of curcumin was more active than curcumin. This suggested that the presence of electron donating group (-OMe) at *meta* position of 4-hydroxy-3-methoxy-benzylidene derivative of curcumin appears to play an important role for the potency of antimalarial compounds. **[20, 21].**

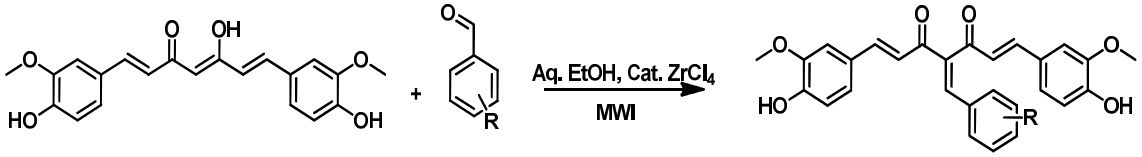
RESULTS AND DISCUSSIONS

Describe new methods for the synthesis of 4-substituted curcumin analogues (**Reaction Scheme 1**). For synthesis of 4-substituted curcumin analogues, aqueous ethanol (50%) and Zirconium Chloride ($ZnCl_4$) were used as catalyst-solvent and MWI condition.

A model reaction was performed to optimized reaction condition. Curcumin and 4-methoxy benzaldehyde were kept as fixed reacting partner. Various reaction conditions were tried including non-conventional techniques like Microwave irradiation and solvent free method. 4-methoxy benzaldehyde was preferred as one fix component to avoid workup difficulties after completion of reaction, which usually occurs with free hydroxyl (–OH) aldehydes. Addition preference does not show any significant effect on yield of product. **Table 1** shows numbers of solvent catalyst combinations were used to achieve optimum yield of reaction. Curcumin is unstable in alkaline *p*H [**25**]. Two phenolic –OH and one enolic –OH susceptible for alkaline *p*H, KOH catalyzed reaction, not surprisingly, gave low productivity.

Reaction Scheme 1

Synthesis of 4-arylidine curcumin analogues from Curcumin and aromatic aldehydes



(1) (2) (3a-f)

Table 1 Optimization of reaction condition for Scheme 1, Curcumin and 4-methoxy benzaldehyde as model reaction.

Sr. No.	Reaction condition	Time	Yield[a] of products
1.	EtOH, KOH, rt.	12 hours	38%
2.	Toluene, pyridine, reflux	18 hours	27%
3.	Toluene, NaH, stirred at rt	12 hours	17 %
4.	DMF, AcOH, pyridine, stirred at rt	24 hours	27%
5.	DMF, AcOH, AcONa, reflux	12 hours	49%
6.	DMF, Alum, $CH_3CO_2NH_4$, reflux	4 hours,	73%

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7.	DMF, AcOH, $CH_3CO_2NH_4$, reflux	9 hours	68%
8.	Toluene, pyridine, MWI	2 min.	Sticky mass
9.	DMF, Alum, $CH_3CO_2NH_4$, MWI	2 min.	53%
10.	Absolute EtOH; $ZnCl_2$: MWI (600W)	2 min.	69%
11.	**EtOH (50%); $ZrCl_4$: MWI** (600W)	**2 min.**	**88%**

[a] Isolated yield

This explanation for low productivity may extend upto workup stage, after product formation, pour to ice-water and neutralized, this water-alcohol solvent mixture not allowed all products to precipitate out. Workup procedure for alcoholic KOH when was modified with evaporation of alcohol from reaction mixture in reduce pressure, offers dark red-brown coloured sticky product. This required reaction condition was achieved by using absolute ethanol, as it works as excellent solvent and mainly due to its dehydrating nature (**Table 1; Entry 10**). Present methodology with model reaction was subjected for Microwave irradiation with verity of irradiating power (**Table 2**).

Table 2. Optimization of reaction condition with respect to Microwave irradiation power

Sr. No.	Products No.		Aq. EtOH, $ZrCl_4$	
		Time in Min.	MWI	Yield (%)
1	**(3a)**	2	600W	88%
2	**(3b)**	2	600W	69%
3	**(3c)**	3	600W	87%
4	**(3d)**	2	600W	84%
5	**(3e)**	2	600W	89%
6	**(3f)**	2	600W	90%

[a] Isolated yield

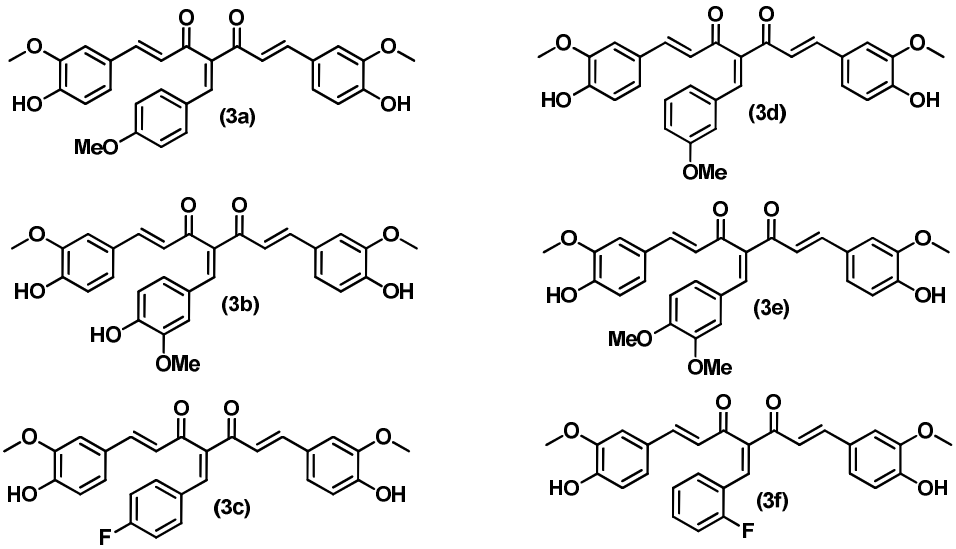

Figure 1. Structure of 4-substitiuted curcumin derivatives.

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Second methodology describes offers choice of diarylheptanoid backbone selection. Three moles of Aromatic aldehydes and one mole of acetylacetone (**Scheme 2**) react to obtain desired curcumin-4-arylidine analogues. 4-methoxy benzaldehyde and acetylacetone was taken as fix starting materials for model reaction. Various reaction conditions were applied to optimized reaction condition with respect to yield, easy handling procedure and time. Reaction conditions were applied as shown in **Table 2.**

Microwave technique was used and found productive (**Table 2; Entry 6**). As microwave methods found more fruitful used further for derivatisation reactions. As continuation of previous research work [**26-27**], developed new methods consisting more green impact in form of using Zinc Chloride as catalyst and absolute EtOH as solvent with non-conventional method.

EXPERIMENTAL

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. ^{1}H NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in$CDCl_3$ using TMS as Internal standard. Chemical shifts (δ) are reported in ppm. The IR spectra were recorded using Perkin Elmer spectrometer (KBr plates).The reaction was carried out in a scientific microwave oven (Sineo, MASS-II, Microwave Synthetic Workstation, China). All the compounds were checked for purity by thin layer chromatography (TLC). Column chromatographic separation was performed with 60-120 mesh size silica gels. Melting points were recorded in an oil bath with open head capillary and are uncorrected. All products were shown good agreements with reported spectral values and physical constant. [20, 21]

General procedure for synthesis of substituted Curcumin

Curcumin (2 mmol), 4-methoxybenzaldehyde (2.2 mmol) was added in 50% aqueous ethanol (10mL) containing $ZrCl_4$ (10 mmol) in single lot. Reaction was subjected to MWI for appropriate time and progress of reaction was monitor by TLC. After completion of reaction, allowed contain to attained room

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temperature and ethanol was removed in reduced pressure and pour into crush-ice-water mixture with gentle stirring and left in ice-water bath for few minutes. Thus obtained crude product was filter off and purified with column chromatography.

SPECTRAL ANALYSIS

1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(4-methoxybenzylidene)hepta-1,6-diene-3,5-dione: (3a) Yield 88%; NMR (300MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.89 (d, 1H), 7.51 (d, 1H), 7.48 (d, 1H), 7.18-7.23 (d, 2H), 7.09-7.13 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (d, 2H), 6.71-6.68 (d, 2H), 5.87-5.93 (broad, 2H), 3.88 (s, 3H), 3.64 (s, 3H), 3.55 (s, 3H).

CONCLUSIONS

Curcumin is established biologically active naturally occurring yellow colour pigments and utility restricted due to its limited solubility, thus easy derivatisation; one step reaction is highly demanded. Present methodology is environmental friendly, consisting cost effective starting material, easy working procedure and significant productivity. We believe that, this method may excellent replacement of long time required, acid containing Curcumin analogues methodologies.

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