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One Pot Solvent Free Synthesis of Curcumin and Analogues Using Vitamin B1 as an Efficient Catalyst

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Abstract
A highly efficient, solvent free and simple single protocol is described for the synthesis of curcumin and analogues by grinding method using Thiamine hydrochloride (Vitamin B_1) and Calcium oxide as reagent. Two moles of aromatic substituted aldehydes with acetylacetone presented as starting component. This environmentally benign methodology may prove to be valuable alternatives to traditional curcumin synthesis methods.

Keywords: *Curcumin, synthesis of turmeric, Vitamin B_1, thiamine hydrochloride catalyzed, green reaction*

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I. INTRODUCTION

Curcumin is natural product and isolated from plant *Curcuma longa*, founds with two isomers demothoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) as yellow colour mixture, collectively called as Curcuminoids. [1]Modern science validate that Curcumin inhibit 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-cervical and anti-oral cancer. [11,12] Curcumin, 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]

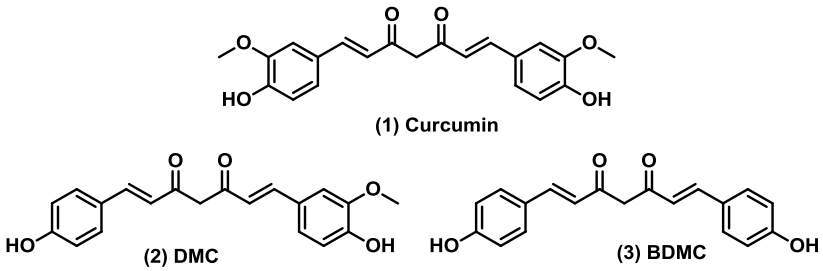


Figure 1.1 Structure of Curcuminoids, (2) Demthoxycurcumin (DMC) and (3) Bisdemethoxy curcumin are differ from Curcumin (1) by absence of methoxy (-OMe) group.

Bioavailability of curcumin [21] is major problem, 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. Majority of such methods involving one mole of Acetylacetone and two moles of vanillin along with suitable base. Conventional 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, it reacts first and reduce yield of product. Practically, curcumin analogues with non-hydroxyl aromatic aldehydes do react to obtained satisfactory yield. But during the reaction of synthesis of Curcumin or bis-demethoxycurcumin (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 trial and error basis.

Experimental

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 without further

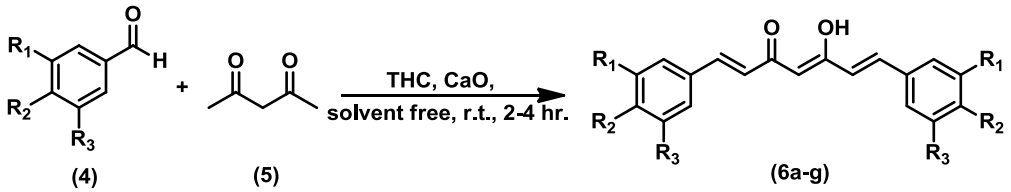
purification of solvent or chemicals. H^1 NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in $CDCl_3$/DMSO-*d6* as solvent using TMS as internal standard. Chemical shifts (δ) are reported in ppm. The IR spectra were recorded using Perkin Elmer spectrometer (KBr plates). All the compounds were checked for purity by thin layer chromatography (TLC). Mobile phase was used Methanol 3% in DCM. TLC visualization was done with UV chamber and other usual spray reagents.

General procedure

In a mortar, aromatic aldehyde (0.02 mol), acetylacetone (0.01 mol, 1gm) and calcium oxide (0.01 mol, 560mg) was added, Thiamine hydrochloride (10mol%, 265mg) was added in single portion, reaction contains was pestle for next few 30 minutes vigorously and further allowed to stand at room temperature forappropriate time (2 hrs.-4 hrs., TLC check) with occasional stirring to offer product. After completion of reaction (TLC) check, distilled water was added to reaction mixture. Yellow mass filter out washed with water and light petroleum repeatedly, dried under high vacuum to offered desired product. During optimization of amount of THC and metal oxide, products were separated by column chromatography using silica gel (60-120 mesh), mobile phase was Methanol (2%) in Chloroform.

Series of sets of reaction were performed to optimized reaction condition. Present work is extended part of our previously reported curcumin and analogues synthesis. [23]

Reaction Scheme1: Derivative preparation of Curcumin analogues using THC, CaO as catalyst and without solvent



Spectral data of representativecompound:

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

IR (KBr): 3542, 1635, 1622, 1046, 982 cm^{-1}, ^{1}H-NMR (DMSO-*d6*) δ 3.89 (s, 6H, -OCH_3), 6.12 (s, 1H, H-4), 6.73(d, 1H, H-7), 6.75 (d, 2H, Ar), 6.86 (d, 1H, H-6), 7.12(d, 2H, Ar), 7.16(d,1H, H-2), 7.27 (s, 2H, Ar), 7.65 (d,1H, H-1), 9.75 (s, 2H, -OH), 10.11(s, 1H, enol -OH)

II. RESULTS AND DISCUSSIONS

In our previous report [23 (a)] we synthesized Curcumin analogues using Thiamine hydrochloride as catalyst and PEG as solvent. Vitamin B1 mainly reported in oxidative condensation reactions. Present attempted was to check possibility of THC as catalyst in curcumin synthesis; hence THC and room temperature condition were kept as fixed factors throughout optimization of reaction.

Two molecules of Vanillin and one molecule of acetylacetone, thiamine hydrochloride stirring as room temperature were selected as fixed parameters for model reaction. To minimize byproduct, cheating metal used. Our focus was on simple workup procedure at room temperature, without any catalyst. Model reaction was performed without any metal chelating agent to ensured need of chelating, when THC was introduced without metal obtained result was not satisfactory.

Calcium hydroxide, one of the meritorious substances for this reaction. As previous reports founds its ability to work as base as well as chelating agent (24), obtained yield was good. Calcium oxide (25) was reported with microwave irradiation techniques, which in fact expeditious method, but report was described to offers product after long 12 hours workup.

Table 2. Optimization of Thiamine hydrochloride and metal oxide and yield of model reaction

Sr. No.	THC: CaO	Yield (%)[a]
1)	5mol%:1eq.	13
2)	10mol%:1eq.	59
3)	15mol%:1eq.	63
4)	5mol%:50mol%.	----
5)	10mol%:10mol%	Trace[#]
6)	15mol%:10mol%	----

[a]Isolated yield, [#] TLC check

Calcium oxide (1 eq.) and THC (15mol%) were found most productive and kept constant for further analogues synthesis of curcumin as shown in **Table 3**. It was found that $–OCH_3$, -Br, -F and methyl substituted benzaldehyde founds more productive. Whereas, Curcumin (6a), BDMC (6b) and other –OH containing curcumin (6d) analogues are less productive in nature. It was observed that –OH containing curcumin analogues are comparatively more water soluble and lost during workup [23].

Table 3. Table showing curcumin and substituent's of analogue and their melting point.

Sr. No.	R_1	R_2	R_3	Time in min.	Yield in %[a]	M.P. (°C) [23 (a)]*
6a	$-OCH_3$	-OH	-H	240	63	179-180
6b	-H	-OH	-H	240	50	174-176
6c	-H	$-OCH_3$	-H	90	67	162-163
6d	-H	-Br	-H	90	70	152-145
6e	-H	$-OCOCH_3$	-H	90	45	171-173
6f	-H	$-NO_2$	-H	300	13	152-153
6g	-H	-Cl	-H	240	46	150-151

[a] Isolated yield, * Literature reports.

Curcumin and analogues obtained as products were determined by Melting point and representative products were scan for IR and ^{1}HNMR. Thus obtained results were compared with reported one and found satisfactory. [24,26]

III. CONCLUSIONS:

In conclusion, we describe environmentally benign, solvent free, cost effective, mild work-up methodology for the synthesis of curcumin and analogues. Aromatic aldehydes and acetyl acetone are easily available, thiamine hydrochloride and calcium oxide are cheap and non-hazardous, and stirring at room temperature and finally no acid or base workup enhance significant utility of present methodology.

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