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# SYNTHESIS OF CURCUMIN AND ANALOGUES USING THIAMINE HYDROCHLORIDE AS AN EFFICIENT CATALYST

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## ABSTRACT

A highly efficient, mild simple and single pot protocol is described for the synthesis of curcumin and analogues in PEG-400 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 a valuable alternatives to traditional curcumin synthesis methods.

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

## 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*, founds with two isomers demothoxy curcumin (DMC) and bisdemethoxy curcumin (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].

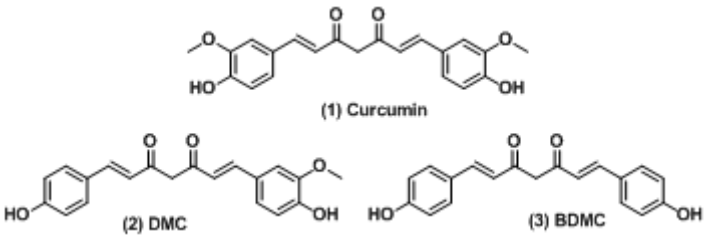



**Figure 1: Structure of Curcuminoids, (2) Demthoxy curcumin (DMC) and (3) Bisdemethoxy curcumin are differ from Curcumin (1) by absence of methoxy (-OMe) group.**

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 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 trial and error basis.

## EXPERIMENTAL

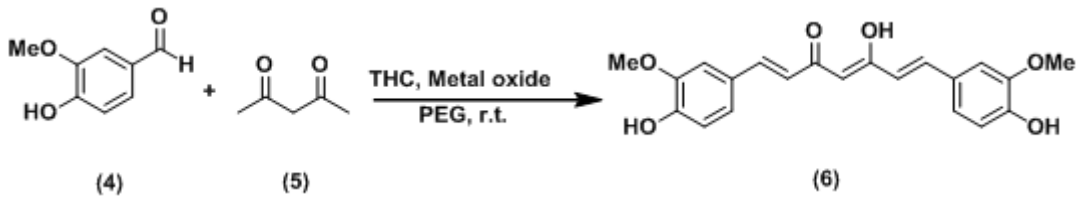
All the compounds used in synthesis were of analytical grade; the melting points of the compounds were determined in open head capillary and are uncorrected. The reaction was carried out without further purification of solvent or chemicals. $H^1$ NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer 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 round bottom flask containing 10 ml of PEG-400, aromatic aldehyde (0.02 mol), acetylacetone (0.01 mol, 1gm) and calcium oxide (0.01 mol, 560mg) was added, reaction contains was stir for next few minutes just to obtained homogeneous mixture. To this Thiamine hydrochloride (10mol%, 265mg) was added in single portion. Reaction contains was stirred at room temperature for appropriate time (TLC). After completion of reaction, contains pour to distilled water (150 ml) with stirring. 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.

**Reaction Scheme 1: Optimization of reaction condition for model reaction**

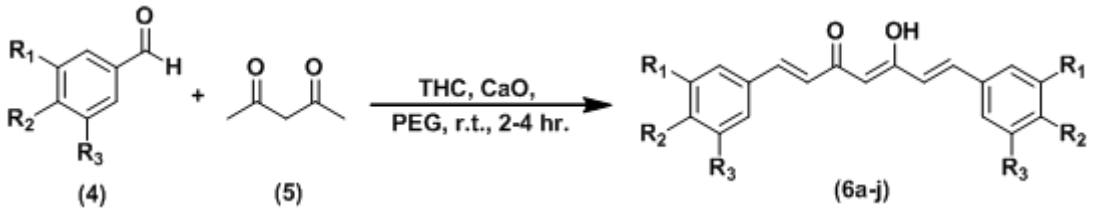



(4) (5) (6)

**Reaction condition: 4 (2eq.), 5 (1 eq.), Metal oxide (1eq.) and THC (10 mol %) was stirred at room temperature in PEG (10 ml).**

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 Scheme 2: Derivative preparation of Curcumin analogues using THC, CaO as catalyst and PEG as solvent**




**SPECTRAL DATA OF REPETITIVE COMPOUNDS**

**(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)

**(1E,4Z,6E)-5-hydroxy-1,7-bis(4-hydroxyphenyl)hepta-1,4,6-trien-3-one (6b)**
IR (KBr): 3455, 3241, 1623, 1590, 1269, 1164 $cm^{-1}$, $^1$H-NMR (DMSO-*d6*) 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)-5-hydroxy-1,7-bis(4-methoxyphenyl)hepta-1,4,6-trien-3-one (6c)**
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 (6h)**
IR (KBr): 3447, 2891, 1704, 1212, 962, $cm^{-1}$, $^1$H NMR (300 MHz, $CDCl_3$) δ 3.03 (s,12H, -N(CH3)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 (6i)**
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)

## RESULTS

Sodium hydroxide (Table 1; Entry 3) and Calcium hydroxide (Table 1; Entry 5) used offers 19% and 66% of yields, respectively. Sodium hydroxide was introduced for its basic nature, in search of compatible partner for THC and offers only 19% of yield of product. Calcium hydroxide, one of the meritorious catalyst for this reaction, As previous reports reveal its ability to work as base as well as chelating agent (24), obtained yield was good (Table 1; Entry 6). Previous reports of Calcium oxide (25) consists of microwave irradiation techniques, which in fact expeditious method, but report was described to offers product after long 12 hours long workup procedure. In present study CaO was used with THC gives 89% of yield (Table 1; Entry4). Other metal oxides like Zink, Copper and Magnesium when used result obtained was not satisfactory hence eliminated from further experimentation.

**Table 1: Optimization of catalyst for the synthesis of Curcumin using model reaction**

| Entry | Catalyst used THC (10mol%): Metal oxide (1 eq) | Yield (%)[a] | Time in min. |
|---|---|---|---|
| 1) | THC without metal | ---- | 120 |
| 2) | THC: MgO | 30% | 120 |
| 3) | THC: NaOH | 19% | 120 |
| 4) | THC: CaO | 89% | 120 |
| 5) | THC: $Ca(OH)_2$ | 66% | 120 |
| 6) | THC: ZnO | 32% | 120 |
| 7) | THC: CuO | 29% | 120 |
| 8) | CaO | ---- | 120 |

**[a] Isolated yield**

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

| Entry | THC: CaO | Yield (%)[a] |
|---|---|---|
| 1) | 5mol%:1eq. | 23 |
| 2) | 10mol%:1eq. | 89 |
| 3) | 15mol%:1eq. | 37 |
| 4) | 5mol%:50mol%. | ---- |
| 5) | 10mol%:10mol% | 11 |
| 6) | 15mol%:10mol% | ---- |

**[a] Isolated yield**

To optimized amount of THC, sets of reactions were performed with varying its amount. When amount of THC was changes to 5mol%, [**Table 2**] TLC shown aromatic aldehydes in the reaction mixture remain as it is after 6 hours. In search of optimum productivity THC was added 15%, which gives multisport on TLC were not separated. Amount of calcium oxide were also alter for model reaction [**Table 2, Entry 4-6**].

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

| Entry | $R_1$ | $R_2$ | $R_3$ | Time in min. | Yield in %[a] | M.P. (°C) [24,26]* |
|---|---|---|---|---|---|---|
| **6a** | $-OCH_3$ | -OH | -H | 240 | 89 | 179-180 |
| **6b** | -H | -OH | -H | 240 | 73 | 174-176 |
| **6c** | -H | $-OCH_3$ | -H | 90 | 92 | 162-163 |
| **6d** | -H | -Br | -H | 90 | 94 | 152-145 |
| **6e** | -H | $-OCOCH_3$ | -H | 90 | 90 | 171-173 |
| **6f** | -H | $-NO_2$ | -H | 180 | 77 | 152-153 |
| **6g** | -H | -Cl | -H | 180 | 71 | 150-151 |
| **6h** | -H | $-N(CH_3)_2$ | -H | 180 | 77 | 170-172 |
| **6i** | -H | $-CH_3$ | -H | 90 | 93 | 112-113 |
| **6j** | -H | -H | -H | 240 | 72 | 140-142 |

**[a] Isolated yield, * Literature reports.**

Calcium oxide (1 eq.) and THC (10mol%) 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].

## DISCUSSIONS

Thiamine hydrochloride founds versatile ability to acts as catalyst in various elementary transformations, mainly in oxidative condensation reactions. But no reports were found concern with curcumin synthesis. 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 use was necessary with compatible solvent. Use of boron was reported in literature but was not included in present study, as boron-dicarbonyl complex broken down at highly acidic condition which reduces its green impact. Solvent choice was done on the basis of easy workup producer and environmentally benign nature. Alcohol was the first choice, but after completion of reaction, thus formed curcumin will soluble in alcohol, and to remove solvent it will

be necessary to evaporate alcohol first, so we, kept alcohol on least preferable solvent for curcumin synthesis methodology. Our focus was on simple workup procedure at room temperature. 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.

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].

## CONCLUSIONS

In conclusion, herein we describe environmentally benign, cost effective, mild 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 in nature. No high temperature is required, productive at room temperature and finally no acid or base workup to obtained final product enhance significant utility of present methodology.

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