A Green Approach: For the Synthesis of Curcumin and Its Derivatives

J. M. Pawara

Abstract: Here in the present research work we have developed newer method for the synthesis of curcumin C. Barium Hydroxide was found to be an effective and mild base synthesis of curcumin and its derivatives obtained by reaction of one equivalent of acetyl acetone with two equivalent of corresponding aromatic aldehyde in microwave. The current scheme offers various benefits such as high yield, less time, and environmentally friendly.

Keywords: Curcumin, Barium Hydroxide, acetyl acetone, aromatic aldehyde, microwave

1. Introduction

Curcumin, (I) a polyphenol derived from Curcuma longa (commonly known as turmeric) is an ancient spice and therapeutic used in India for centuries to induce color in food and to treat a wide array of diseases [1]. Curcumin a major yellow pigment and active component of turmeric powder extracted from Curcuma longa L. 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 Ayurveda 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.[2] It has attracted a lot of attention due to its promising biological properties to treat cancer,[3] Alzheimer’s disease,[4] HIV,[5-6] chronic inflammations,[2] oxidative stress,[7] and cystic fibrosis[8]. Curcumin underwent clinical trial for cancer owing to its prominent activity as an antitumor and chemo preventive agent [9] However, this trial ceased due to poor bioavailability of the molecule [10-11]. Clinical trials are ongoing to test the efficacy of curcumin against Alzheimer’s disease [12] and cystic fibrosis [13]. Intense research is also being undertaken to modify the structure of curcumin so as to increase the bioavailability and potency while maintaining the relative non-toxic nature of this natural product [14-17].

During the past era, synthetic modifications of curcumin, which were aimed at enhancing its bioactivities, have been intensively studied. One sustainable strategy for green synthesis of organic compounds is microwave irradiation. Since, microwaves will not affect molecular structure in the excitation of molecules, the effect of microwave absorption is purely kinetic. Compared to traditional methods, microwave synthesis is more suitable to synthesize and can be carried out in greater yields in short reaction times under mild reaction conditions.[18-21] The current scheme offers various benefits such as high yield, short time, efficient, and environmentally friendly.

Figure 1: Tautomeric structure of curcumin (I)

2. Experimental Section

M.P points were determined by open glass capillary method. All chemicals used were reagent grade and were used as received. A Laboratory Microwave Oven (Model BP 310/50) operating at 2450 MHz and power output of 600 W was used for all the experiments. The completion of reactions was monitored by TLC (Merck silica gel). IR spectra were recorded on a Shimadzu FTIR-420 spectrophotometer. 1H NMR and 13C NMR spectra were recorded at 400C on a Bruker AVANCE DPX (400 MHz) FT spectrometer in CDCl3 using TMS as an internal reference (chemical shift in δ, ppm) and mass spectra.

A- General procedure for the synthesis of curcumin derivatives. (Conventional Method)

In a mixture of 2 equivalent of substituted benzaldehyde (10 mmol), 1 equivalent of acetyl acetone (5 mmol) dissolved in 20 mL of DMF was added 3 equivalents of calcium hydroxide (15 mmol), and the reaction mixture was stirred at 110 °C for about 15-16 hour. The progress of the reaction was monitored by TLC. After completion of the reaction, it was poured into cold water, neutralized with cold dil. HCl up to pH 4 to 5. The solid precipitated was filtered, washed with cold water and purifie by crystallization from ethanol.

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B- Procedure for synthesis of curcumin derivatives
(Microwave method)
In a microwave assisted method in 250 ml beaker we have taken 2 equivalent of substituted benzaldehyde (20 mmol), and one of acetyl acetone (10 mmol) 20 ml water and 3 equivalent of Barium hydroxide was added. The reaction mixture was stirred for room temperature and then irradiated for 4-6 min in microwave at 240 W (40%) power. Then the reaction mixture was poured into ice cold water neutralized with HCl The solid product was filtered on sanction pump, washed with cold water and purified by crystallization from methanol.

3. Result and Discussion
Acetyl acetone having terminal two methyl group and it also having active methylene group 1 equivalent of barium hydroxide form complex with acetyl acetone in its enol form. It blocks that active methylene group and other two equivalent of barium hydroxide take proton form terminal -CH₃ and generate carbanion. That generated carbanion react with aromatic aldehyde, Workup using dil. HClcleaved Ba complex to give curcumin derivatives. The reaction was monitored by TLC and purified from alcohol. From experimental result is was observed that traditional method time required to get product in 12-16 hour and yield is also less. The microwave assisted method gives high yield in short time. Surprisingly we get product within 4-6 minutes very high yield. It is very important to mention aromatic aldehyde bearing both electron donating and electron withdrawing groups easily undergo condensation to give corresponding curcumin analogues. While study on effect of substitution on aromatic rings it was observed that reaction is prone to steric hindrance and yield suffer from othosubstituted aldehyde.

| Sr. No | Compound Code | R¹ | R² | R³ | Traditional method | Microwave method | Melting Point
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IR (KBr): ν 3412, 2932, 1627, 1603, 962, 814 cm⁻¹

Data of Cb:
IR (KBr): ν 3080

Data of Cl:
IR (KBr): ν 3080

Data of Cm:
IR (KBr): ν 3080

Data of Co:
IR (KBr): ν 3080

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815
IR (KBr): v 3417, 2920, 1664, 1362, 962, 814 cm⁻¹ 1 H NMR (300 MHz, CDC13): δ 3.03 (12H, s, 2 Ar(NH3)2), 6.25 (1H, s, H-4), 6.72 (4H, d, J = 8.7 Hz, H-3, 5, 3”, 5”), 6.84 (1H, d, J = 16 Hz, H-7), 6.91 (1H, d, J = 16 Hz, H-6), 7.05 (1H, d, J = 16 Hz, H-2), 7.42 (4H, d, J = 8.7 Hz, H-2’, 6’, 2”, 6”), 7.63 (2H, d, J = 16 Hz, H-1) 13C NMR (75MHz, CDC13): δ 42.4 (N(CH3)2), 101.6 (C-2), 123.1 (C-1), 128.2 (C-4, 6, 6”), 135.3 (C-3’, 5’, 3”, 5”), 182.4 (C-3’, 4’, 4”), 182.5 (C-3, 5’, 5”) ppm

Data of Cg:
IR (KBr): v 3417, 2920, 1664, 1362, 962, 814 cm⁻¹ 1 H NMR (300 MHz, CDCl3): δ 3.92 (s, 6H), 3.97 (s, 6H, Ar(NH3)2), 6.78 (1H, s, H-4), 6.87 (1H, d, J = 16 Hz, H-2), 7.10 (1H, d, J = 16 Hz, H-2), 7.32 (1H, d, J = 16 Hz, H-7), 7.73 (2H, m, H-5’, 5”), 7.91 (2H, m, H-4’, 4”), 8.02 (2H, d, J = 8, 2 Hz, H-6’, 6”), 8.14 (2H, d, J = 8, 2 Hz, H-3’, 3”), 8.27 (2H, d, J = 15.8 Hz, H-6’, 6”), 7.71 (1H, d, J = 16 Hz, H-1) ppm

Data of Cm:
IR (KBr): v 3374, 2932, 1627, 1683, 1173 cm⁻¹ 1 H NMR (300 MHz, CDC13): δ 6.57 (1Hs, H-4), 6.82 (1H, d, J = 16 Hz, H-7), 6.88 (1H, d, J = 16 Hz, H-6), 7.08 (1H, d, J = 16 Hz, H-2), 7.32 (2H, d, J = 8, 2 Hz, H-3’, 5’, 3”), 7.52 (4H, d, J = 8 Hz, H-2’, 6’, 2”, 6”), 7.71 (1H, d, J = 16 Hz, H-1) ppm

Data of Cn:
IR (KBr): v 3417, 2920, 1664, 1362, 962, 814 cm⁻¹ 1 H NMR (300 MHz, CDCl3): δ 3.84 (s, 6H, 2 Ar(OCH3)), 6.06 (s, 1H), 6.71 (d, 2H, J = 16 Hz, H-6), 6.82 (d, 2H, J = 8.22 Hz, ortho coupling), 7.16 (d, 2H, J = 8.03 Hz, ortho coupling), 7.33 (s, 2H), 7.55 (d, 2H, J = 15.35 Hz), 9.74 (s, 2H, 2 × phenolic OH), 10.13 (s, 1H, enol OH) ppm

Data of Ck:
IR (KBr): v 3374, 2932, 1627, 1683, 1173 cm⁻¹ 1 H NMR (300 MHz, CDC13): δ 6.61 (1H, s, H-1), 6.87 (1H, d, J = 16 Hz, H-6), 6.87 (1H, d, J = 16 Hz, H-2), 7.09 (1H, d, J = 16 Hz, H-7), 7.28 (2H, d, J = 8, 2 Hz, H-4’, 4”), 7.33 (2H, J = 8, 2 Hz, H-5’, 5”), 7.37 (2H, dd, J = 8, 2 Hz, H-6’, 6”), 7.48 (2H, dd, J = 8 Hz, H-3’, 3”), 7.84 (2H, d, J = 16 Hz, H-1) ppm

Data of Cl:
IR (KBr): v 3417, 2920, 1664, 1362, 962, 814 cm⁻¹ 1 H NMR (300 MHz, CDCl3): δ 3.92 (s, 6H, 2 Ar(OCH3)), 6.06 (s, 1H), 6.71 (d, 2H, J = 16 Hz, H-6), 6.82 (d, 2H, J = 8.22 Hz, ortho coupling), 7.16 (d, 2H, J = 8.03 Hz, ortho coupling), 7.33 (s, 2H), 7.55 (d, 2H, J = 15.35 Hz), 9.74 (s, 2H, 2 × phenolic OH), 10.13 (s, 1H, enol OH) ppm

Data of Cj:
IR (KBr): v 3412, 3391, 1615, 1255, 1142, 961, 752 cm⁻¹ 1 H NMR (300 MHz, DMSO-d6): δ 6.16 (1H, s, H-4), 6.64 (1H, d, J = 16 Hz, H-6), 6.87 (2H, d, J = 7.5 Hz, H-3’, 5’)
3´), 6.95 (2H, d, J = 16 Hz, H-2), 7.05 (1H, d, J = 16 Hz, H-7), 7.25 (4H, m, H-4´, 5´, 4´´, 5´´), 7.67 (2H, d, J = 7.5 Hz, H-6´, 6´´), 7.89 (1H, d, J = 16 Hz, H-1) ppm 13C NMR (75 MHz, DMSO-d6): δ 101.3 (C-1´, 1´´), 117.2 (C-3´, 3´´), 118.9 (C-6´, 121.1 (C-5´, 5´´), 122.2 (C-1´, 1´´), 122.9 (C-2), 127.3 (C-5´, 5´´), 128.8 (C-6´, 6´´), 129.4 (C-4´, 4´´), 140.1 (C-7), 142.6 (C-1´), 157.3 (C-2´, 2´´), 182.4 (C-3, C-5) ppm

Data of Ch:
IR (KBr): ν 3452, 2933, 1692, 1608, 1177, 1028, 977, 826 cm⁻¹ 1 H NMR (300 MHz, CDCl3): δ 6.83 (1H, s, H-1), 6.91(1H, d, J = 16 Hz, H-7), 7.08 (2H, d, J = 15.7 Hz, H-6), 7.28 (1H, d, J =16 Hz, H-2), 7.92 (2H, d, J = 15.7 Hz,H-1), 8.12 (4H, d, J = 8.7 Hz, H-2´, 6´, 2´´, 6´´), 7.98 (4H, d, J = 8.7 Hz, H-3´, 5´, 3´´, 5´´) ppm 13C NMR (75 MHz, CDCl3): δ 101.8 (C-4´), 118.3 (C-6´), 123.6 (C-2´, 2´´), 123.8 (C-3´, 5´, 3´´, 5´´), 129.2 (C-2´, 6´, 2´´, 2´´), 140.6 (C-7), 141.3 (C-1´, 1´´), 142.6 (C-1´), 147.4 (C-4´, 4´´), 182.8 (C-3, C-5) ppm

4. Conclusion
In the conclusion the present work describes simplistic method to synthesize curcumin and its congeners using a cheap Barium hydroxide by microwave method. Compared to literature methods the present method is mentionable in terms of reaction condition, high yield, energy efficient, and less time.

5. Acknowledgement
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References

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