ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 08 | August - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

SILICA SUPPORTED PERCHLORIC ACID CATALYZED SYNTHESIS OF SUBSTITUTED PYRAZOLE CURCUMIN ANALOGUES

Chemistry

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ABSTRACT

Curcumin is naturally occurring yellow pigments isolated from Curcuma longa, structurally it is polyphenolic compounds consisting spectacular biological activity. However, clinical utility of curcumin is limited due to its poor bioavailability. Synthesis of heterocyclic curcumin analogues is major attempt to overcome such limitations. Heterocyclic analogues of Curcumin prepared by one pot green methodology by using naturally occurring Alum [KAl $(SO_4)_2.12H_2O$] as catalyst. Both, conventional and microwave irradiation methods were found productive. In summary, present methodology offers rapid synthesis of pyrazole analogues of curcumin ins short course of time with many advantages like environmentally benign catalyst and solvent, cost effective, easy product separation and clean reaction profile

KEYWORDS

INTRODUCTION

The naturally occurring Curcumin [*(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione*] found wide spectrum of biological activity. Curcumin is also known as 'Indian Saffron', cultivated in most part of India. Curcumin traditionally recognized for its medicinal property in several Asian countries like India and China. Finding shown that the frequently observed neoplasm like colon, lung, breast and prostate are less common in India, where using curcumin as curry color pigment is everyday practice. Modern study reveals curcumin for its anti-oxidant [1], anti-inflammatory [2], anti-tumor [3] and anti-angiogenic [4] properties. Curcumin has found significant preventive against Aβ aggregation, [4-8] the major threats for memory loss. Systematic study of curcumin also confirms its biological utility as anti-microbial activity [9-10]. Study also established curcumin as hepato- and nephron-protective [11-13], in thrombosis suppressing [14]. Many studies proven curcumin has unique ability as potential drugs for treatment of wide spectrum of diseases. Beauty of curcumin molecule is, it is exceptionally safe at high dose. Clinical trial exhibits that 12 gm per day is well tolerated quantity [15-17]. Major problem of approving curcumin as 'drug' is its bioavailability, to overcome this limitation one way is to prepare curcumin analogues. Few studies have been reported for the synthesis of pyrazole curcumin derivatives. [18-19]

Curcumin is symmetric molecule consisting an α, β- unsaturated diketone moiety exhibiting keto-enol tautomerism. Various attempts have been made for the synthesis of diketone and monoketone analogues of curcumin and its heterocyclic derivatives. [20-27]. Present study is extended part of our previous work synthesis of curcumin [28] and pyrazole analogues of curcumin [29] and rapid synthetic methodology of mono-carbonyl [30] curcumin derivatives.

MATERIALS AND METHODS

Experimental Section

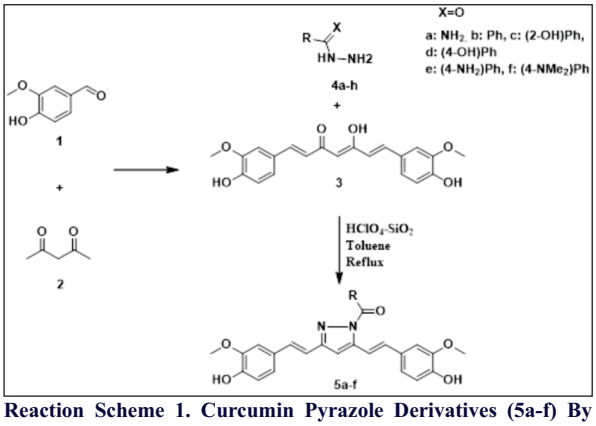
All the compounds used in synthesis were purchase of analytical grade; the melting points of the compounds were determined in open head capillary in paraffin bath and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm-1 by using KBr pallet on FT-IR Perkin spectrophotometer. H^1NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in *D6*-DMSO. The values of chemical shift are expressed in δ ppm as a unit. All the compounds were checked for purity by thin layer chromatography (TLC).

Preparation of Silica supported perchloric acid catalyst

A 70% aqueous perchloric acid (1.8 g, 12.5 mmol) was added to a suspension of SiO2 (230–400 mesh, 23.7 g) in ether (70 ml). The mixture was concentrated and the residue was heated at 100°C for 72 h under vacuum to give HClO4-SiO2 (0.5 mmol/g) as free flowing powder (50 mg, 0.025 mmol of HClO4).

Experimental procedure for synthesis of compound 3 [26]

Acetyl acetone (1 mmol.), boric acid (1 mmol.) and anhydrous Sodium sulfate (0.5mmol.) were taken in moisture free toluene as solvent and stirred for 60 min. at 50°C in water bath. Substituted aromatic aldehydes (Table 1) (2 eq.) was added to reaction mixture, finally drop wise with continuous stirring n-$BuNH_2$ (2 eq.) was added, reaction mixture was irradiated at 600 W for 6-8 min. (Table 1). Filter to removed solvent, cold 1 N hydrochloric acid was added (20 ml) to residue and stirred for 2 hr. Filter, wash with cold water several times, air dried and purified by Column chromatography.



Reaction Scheme 1. Curcumin Pyrazole Derivatives (5a-f) By Silica-perchloric Acid Catalyst.

Table 1. Preparation of Curcumin-pyrazole derivatives. Reaction condition; 3 (369 mg; 1 mmol, 1 eq.), 4 (1.5 mmol, 1.5 eq.) catalyst (5mol%) were reflux in Toluene for appropriate time; [a]isolated yield.

Entry	-R	Time in min.	Yield[a]
5a	-NH_2	180	61
5b	-Ph	230	90
5c	-(*2*-OH)Ph	130	57
5d	-(*4*-OH)Ph	180	61
5e	-(*4*-NH_2) Ph	180	66
5f	-(*4*-NMe_2)Ph	180	80

General Procedure for synthesis of compounds 5a-f

Curcumin **3** (1 eq.), hydrazide derivative (1.5 eq.) and catalyst (5mol%) were taken in 20ml of toluene and reflux for appropriate time (**Table 1**), on completion of reaction (TLC, DCM:MeOH; 7:3) allowed to cool, filter washed several time with water and recrystallized from alcohol.

NMR spectra of some represented compounds, products validation done by matching with reported one [18]

(5a) m.p. 208°C; ^{1}H NMR (300 MHz, DMSO-d6) δ: 12.60 (s, 2H, CONH2), 9.02 (s, 2H, ArOH), 6.88 (d, 2H,), 7.00-6.88 (m, 6H), 6.69 (d, 2H,), 6.45 (s, 1H), 3.68 (s, 6H,); IR (KBr) ν: 3533, 3110, 2900, 2847, 1630, 1570, 1520, 1480, 1376, 1240, 1020 cm^{-1};

(5c) m.p. 210 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ: 8.19 (s, 2H), 8.08 (s, 1H), 7.60-7.00 (m, 2H), 7.40 (d, 2H), 7.20 (d, 2H), 7.25-7.04 (m, 2H), 6.98-6.62 (m, 6H), 6.14 (s, 1H), 3.73 (s, 6H); IR (KBr) ν: 3510,

3440, 2990, 2920, 2860, 1740, 1680, 1570, 1510, 1430, 1360, 1190, 1135, 1080 cm^{-1}

RESULTS AND DISCUSSIONS

Series of reactions were performed to optimize catalyst-solvent combination. Literature survey reveals that 1,3-dicarboyl moiety undergo cyclisation with hydrazine in presence of various acid catalyst. While exploring best catalyst-solvent combination, various possibilities has been check carefully. It was found that polar protic solvents offers readily homogeneous reaction mixture but work up done only after difficulties. For model reaction Semicarbazide 4**a** (1.5 eq.) and Curcumin **3a** (1 eq.) were used. By increasing reflux time to 12 and 15 hr. it was observed that product yield rose by 1 and 3% respectively.

It was observed that, using equimolar **3a** and **4a** requisite column chromatography for purification. Minimum molar ratio for **4a** is 1.5 eq., during execution of series of reactions various molar ratios up to 5 eq. for **4a** were tried and found promising productivity with ease of product isolation. Upon completion of reaction (TLC) 10 ml of ethyl acetate were added and allowed catalyst settle down. Supernatant reaction mixture were decant off, water washing given to removed unreacted **4a**. In observation, **5c** and **5d** products unexpectedly obtained with low percentage of yield, this may be due to presence of hydrophilic hydroxy group, while workup procedure, inevitable loss would have possible.

CONCLUSION

Herein, report a green methodology for the synthesis of Curcumin-pyrazole analogues. This method residing many attractive feathers like cost effective green catalyst, easy reaction methodology, etc. Nontoxic, non-corrosive set of reaction has its own environmental importance. This methodology fulfills all criterions essential for classified as 'Novel' green methodology in the field of organic synthesis. Curcumin derivatives often need column chromatograph for purification of product, especially hydroxy substituted analogues, present methodology dwindle need of column for product purification. Present methodology, we further explore for 1,3-dicarbonyl and α,β-unsaturated carbonyl moieties and results will be publish during the course of time.

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