Silica Supported Boric Acid Catalyzed Green Methodology for The Synthesis of Substituted Pyrazole Curcumin Analogues

MAHESH SHIOORKAR
Vivekanand Arts, Sardar Dalipsingh Commerce and Science College, Chhatrapati Sambhajinagar

Abstract- ***Curcumin is naturally occurring yellow pigments isolated from Curcuma longa, structurally it is polyphenolic compound 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. Present study reveals the silica-boric acid (SiO_2-H_3BO_3) as an efficient catalyst for the preparation of pyrazole Curcumin derivatives. Propose method offers rapid one step synthesis of product with desire green profile. In summary, present methodology offers rapid synthesis of pyrazole analogues of curcumin in short course of time with many advantages like environmentally benign catalyst and solvent, cost effective, easy product separation and clean reaction profile***

I. INTRODUCTION

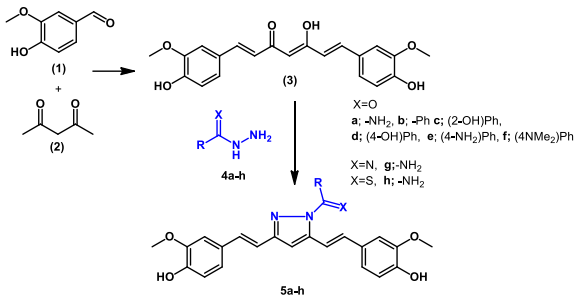
The naturally occurring Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione] found wide spectrum of biological activity. Curcumin is also known as '*Indian Saffron'*, cultivated in most part of India. Curcumin traditionally recognized for its medicinal property in several Asian countries like India and China. Finding shown that the frequently observed colon, lung, breast and prostate cancers diseases are less common in India, where as using curcumin as curry colour 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.

II. MATERIALS AND METHODS

A. 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. H1NMR 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).

C. Reaction Scheme:



Scheme 1. Reaction scheme depicted formation of Curcumin-pyrazole derivatives.

D. Preparation of silica supported boric acid:

Boric acid (3.0 g) was added to 50ml of water in one portion. To the same RBF Silica gel 60-120 (27g) was added portion wise with stirring. Reflux for 6 hrs and evaporated using rota evaporator till free flowing white power obtained.

E. 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-BuNH2 (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

Sr. No.	-R	Reflux[a]		Melting point in °C	
		Time in hr.	Yield	Obs.	Lit. [18]
5a	-NH_2	6	58	208	210
5b	-Ph	5	63	198	----
5c	-(*2*-OH)Ph	5	59	210	209
5d	-(*4*-OH)Ph	5	60	221	220
5e	-(*4*-NH_2) Ph	5	74	200	198
5f	-(*4*-NMe_2)Ph	5	80	235	237
5g	NH_2CNNH-NH_2	6	56	219	220
5h	NH_2CSNH-NH_2	6	47	194	192

Table 1. Showing isolated yield of products with physical constant.

F. General Procedure for synthesis of compounds (5a-h)

Curcumin 3 (1 eq.), hydrazide derivative (1.5 eq.) were taken in ethanol to this catalyst (SiO_2-H_3BO_3) (20 mol%) were added 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 compound, 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, $CONH_2$), 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};

III. RESULT AND DISCUSSION

Series of reactions were performed to optimize catalyst solvent combination. (Table 1) Literature survey reveals that 1,3-dicarboyl moiety undergo cyclisation with hydrazine in presence of acidic catalyst having typical pH range. Hence Silica boric acid was selected to maintained required reaction condition. As silica surface could have help binding 1,3-dicarbony moiety and enhance possibility of positive pathway of reaction. For model reaction Semicarbazide 4a (1.5 eq.) and Curcumin 3a (1 eq.) were used. For sample reaction time was increased up to 12 hrs. But was not found significant change in yield of product. 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, 1N HCl washing given to removed unreacted 4a, to avoid consecutive water washing, but yield of product fall down. Hence, repeatedly water washing workup strategy used for further reactions. 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. Present method residing many attractive feathers like alcohol as solvent and cost effective silica-boric acid as solid catalyst. 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 hydroxyl 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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