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Alum Catalyzed Green Methodology For The Synthesis Of Substituted Pyrazole Curcumin Analogues

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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 [K, Al (SO4)2.12H2O] 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: Curcumin, Pyrazole analogues, Alum Catalyzed, Green methodology

1. Introduction

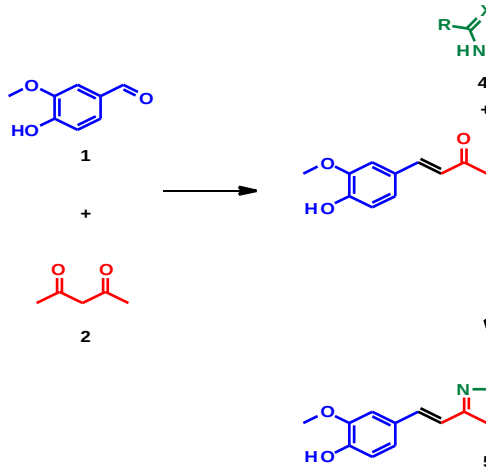
The naturally occurring Curcumin [(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione] found wide spectrum of biological activity. Curcumin is also known as 'Indian Saffron', cultivated in most part of India. Curcumin traditionally recognized for its medicinal property in several Asian 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. 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).



Reaction Scheme 1. Green methodology for Curcumin pyrazole derivatives by conventional and microwave irradiation method using Alum:water as catalyst:solvent combination.

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

Entry	-R	Conventional[a]		MWI[b]		Melting point in °C	
		Time in hr.	Yield	Time	Yield[c]	Obs.	Lit. [18]
5a	-NH_2	8	61	120 sec.	70	208	210
5b	-Ph	8	80	120 sec.	89	198	----
5c	-(*2*-OH)Ph	10	58	180 sec.	66	210	209
5d	-(*4*-OH)Ph	10	65	180 sec.	70	221	220
5e	-(*4*-NH_2) Ph	10	71	180 sec.	84	200	198
5f	-(*4*-NMe_2)Ph	8	83	120 sec.	91	235	237

5g	$NH_2CNNH\text{-}NH_2$	8	60	120 sec.	80	219	220
5h	$NH_2CSNH\text{-}NH_2$	8	57	120 sec.	55	194	192

General Procedure for synthesis of compounds 5a-h

Conventional Method

Curcumin 3 (1 eq.), hydrazide derivative (1.5 eq.) were taken in 10% Alum in water 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.

MWI Method

Curcumin 3 (1 eq.), hydrazide derivative (1.5 eq.) were taken in 10% Alum in water and irradiated at 600W for appropriate time, irradiation discontinue for 10 sec. after every 30 sec. (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; 1H 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; 1H 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

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 acetic acid. Alum (10%) exhibits pH range 3.3, hence, keep constant thought out set of experiment. While exploring best solvent combination possibility of various mixtures, mixture of solvents also has been tried along with alum. However, when alcohol was used with water as for better solubility, no significant change in yield of product was observed, it was observed that keeping alcohol as single solvent obtained pure product, only after difficulty. For model reaction Semicarbazide 4a (1.5 eq.) and Curcumin 3a (1 eq.) were used for both, conventional and MWI method. By increasing reflux time to 12 and 15 hr. it was observed that product yield raised by 1 and 3% respectively. For microwave method, intentionally 10 sec. interval time was included after 30 sec. of successful irradiation to sidestep bumping of reaction.

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. This method residing many attractive feathers like water as solvent and cost effective naturally occurring Alum as 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 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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