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Silica Catalyst Promoted One-Pot Synthesis of 4-[(Dialkylamino)methyl]-1,7-diphenylhepta-1,6-diene-3,5-dione

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Silica (SiO_2) catalyzed one-pot synthesis of 4-[(dialkylamino)methyl]-1,7-diphenylhepta-1,6-diene-3,5-dione. An expeditious synthesis under microwave irradiation method for curcumin Mannich base derivatives are known for its biological activity. 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. Present methodology offers silica catalyzed one pot, productive technique to obtain curcumin Mannich base. Both, conventional and microwave irradiation methods were found productive. The final products were characterized by ^{1}H NMR.

Keywords: Curcumin, Mannich reaction, One-pot, Conventional and Microwave irradiation method.

INTRODUCTION

The naturally occurring curcumin [(1*E*,6*E*)-1,7-*bis*(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione] and nitrogenous containing curcumin 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 colour pigment is everyday practice. Modern study reveals curcumin for its antioxidant [1], anti-inflammatory [2], antitumor [3] and antiangiogenic [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 antimicrobial 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 drug for treatment of wide spectrum of diseases. Outstanding advantage of curcumin molecule is exceptionally safe at high dose. Clinical trial exhibits that 12 g per day is well tolerated quantity [15-17]. Major problem of approving curcumin as 'drug' and its bioavailability, to overcome this limitation one way is to prepare curcumin analogues. Studies have been reported for the synthesis of curcumin Mannich base derivatives [18,19].

Curcumin is symmetric molecule consisting α,β-unsaturated di-ketone 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 done consisting synthesis of curcumin [28], pyrazole analogues of curcumin [29] and rapid synthetic methodology of mono-carbonyl [30] curcumin derivatives.

EXPERIMENTAL

All the compounds used in synthesis were 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^1 NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in DMSO-d_6. 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). The silica catalysts were characterized by FTIR spectroscopy data.

Characterization of SiO_2 catalyst

FT-IR: The distinctive band around 1665-1660 cm^{-1} and 832 cm^{-1} due to Si-O-Si stretching of silica catalyst. The intense absorbance band in FT-IR spectrum were observed in range between 460 cm^{-1} due to single Si-O bond and Cu-O shows at

604 cm^{-1} which were attribute to the Si–O stretching vibrations (Fig. 1).

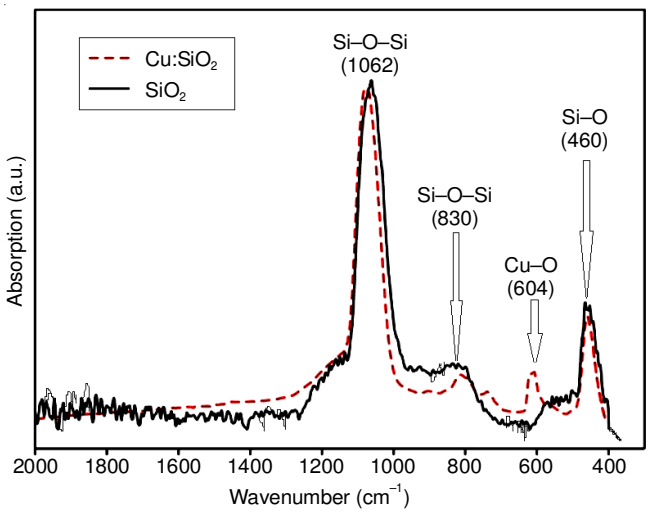


Fig. 1. FTIR spectra of SiO_2 catalyst

Synthesis of compound 3 [26] and (1*E*,6*E*)-4-((dimethylamino)-methyl)-1,7-*bis*(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-diones

Conventional method: Equimolar di-alkyl amine and formaldehyde (2 mmol) were taken in xylene (5 mL), Silica (3 mmol) were added and stirred resulting mixture for 30 min. at room temperature. Curcumin (1 mmol) in xylene (20 mL) were added and allowed to reflux for appropriate time (Table-1) (TLC). Reaction mixture was filter at hot condition to removed silica, allowed to stand in an ice bath until crystals obtained and filter. The products were recrystallized by 95 % of alcohol to offered pure product.

TABLE-1
OPTIMIZATION OF SOLVENT USED FOR THE REACTION OF CURCUMIN, FORMALDEHYDE AND DIMETHYL AMINE USING SILICA AS CATALYST

S. No.	Solvents and SiO_2	Yield of product (%)[a]	
		Conventional	MWI
1	Ethanol	16	33
2	Methanol	14	20
3	PEG	45	40
4	DMF	55	61
5	DMSO	38	55
6	Toluene	72	79
7	Xylene	85	80
8	THF	68	55
9	DCM	40	36
10	$CHCl_3$	41	30

[a]Isolated yield; Reaction condition: Formaldehyde (2 mmol), dimethyl amine (2 mmol), silica (3 mmol) and solvent 5 mL. (1) Conventional: Reflux for 3 h and (2) MWI: stirred at 30 min then microwave irradiation power at 300 W for 1-2 min.

Microwave irradiation method: Equimolar di-alkyl amine and formaldehyde (2 mmol) were taken in xylene (5 mL), silica (3 mmol) were added and stirred resulting mixture for 30 min at room temperature. Curcumin (1 mmol) in xylene (10 mL) were added and allowed to irradiate for 300 Watt for appropriate time Table-1 (TLC). Reaction mixture was filter at hot condition to removed silica, allowed to stand in an ice bath until crystals obtained and filter. The products were recrystallized by 95 % of alcohol to offered pure product.

Spectral characterization data of some synthesized product

(1*E*,6*E*)-4-[(Dimethylamino)methyl]-1,7-*bis*(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione: Yield 85 %. m.p. 166 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.55 (s, 2H, ArOH), 7.43 (d, 2H), 7.21-6.51 (m, 6H), 6.62 (d, 2H), 3.36 (s, 6H, OCH_3), 3.10 (t, 1H), 2.86 (d, 2H, CH_2N), 2.55 (s, 6H, NCH_3)

(1*E*,6*E*)-4-[(Diethylamino)methyl]-1,7-*bis*(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione: Yield 91 %, m.p. 154 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.59 (s, 2H, ArOH), 7.44 (d, 2H,), 7.24-6.52 (m, 6H), 6.69 (d, 2H), 3.39 (s, 6H, OCH_3), 3.16 (t, 1H), 3.50 (d, 2H, CH_2N), 2.66-2.58 (m, 2H, CH_2), 1.11-1.07 (m, 6H, CH_3);

(1*E*,6*E*)-1,7-*Bis*(4-hydroxy-3-methoxyphenyl)-4-(morpholinomethyl)hepta-1,6-diene-3,5-dione: Yield 90 %. m.p. 142 °C; 1H NMR (300 MHz, DMSO-d_6) δ: 9.56 (s, 2H, ArOH), 7.41 (d, 2H), 7.41-6.77 (m, 6H), 6.63 (d, 2H), 3.41 (s, 6H, OCH_3), 3.26 (t, 1H), 3.51 (d, 2H, NCH_2), 3.24-3.12 (m, 4H, O-CH_2), 2.12-2.06 (m, 4H, NCH_2).

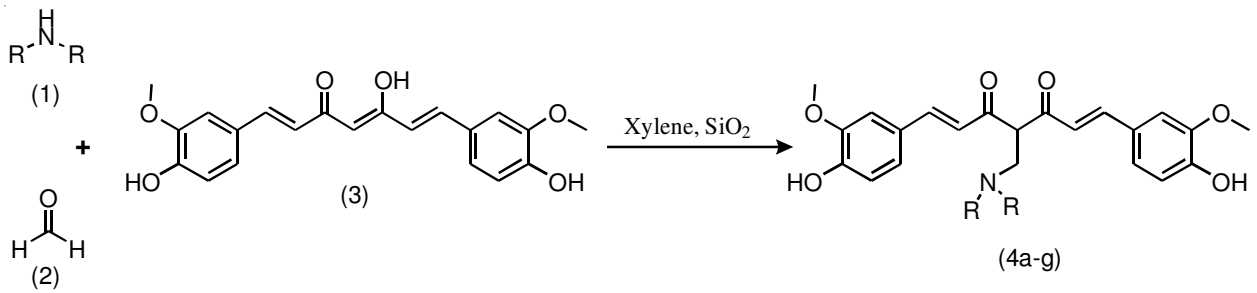
RESULTS AND DISCUSSION

A series of reactions were performed to optimized curcumin-Mannich reaction. Literature survey exhibits rare reports on curcumin Mannich base reaction [18]. Microbial activity of curcumin Mannich base was promising and underlines the need for further exploration along with experimental simplicity. Focus were kept on successive formation of iminium ion, hence first step consists of addition of formaldehyde and secondary amine in presence of silica. This step was kept constant during conventional as well as non-conventional method.

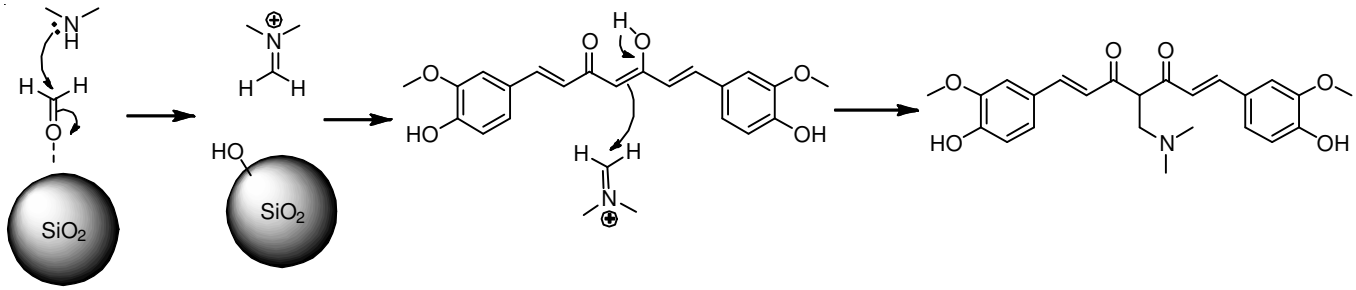
Firstly, formaldehyde (2 mmol) and dimethyl amine (2 mmol) were mixed in presence of silica (SiO_2) (3 mmol) as representative reaction (**Scheme-I**). Various solvents have been tried such as alcohol, Polyethylene glycol, DMF, DMSO, THF, water, toluene and xylene in both conventional and non-conventional method (Table-1). The silica (SiO_2) helps to generate imine (Schiff base) having acidic in nature as shown in mechanistic path (**Scheme-II**). Here in we observed that, non-polar-aprotic solvent found to more productive over polar and protic solvents (Table-1, entry no. 7). Good to better yield was obtained under both conventional and microwave irradiation method but a rapid reaction carried out under microwave irradiation method. After stirring condition the reaction of products were obtained in very less time of reaction (1-2 min) using microwave energy in xylene as non-polar-aprotic solvent.

Thus, selection of non-polar solvents found more productive may be because of tendency of curcumin to exhibits 1,3-dicarbonyl structure in presence of nonpolar solvent. All the derivatives of curcumin were synthesized reasonably good to better yield (Table-2).

These final products were isolated by simple filtration, due to their low solubility in aqueous medium. The products were recrystallized from mixture of ethanol-chloroform to afforded analytically pure samples, hence avoiding extraction and chromatographic separations.



Scheme-I: Synthesis of curcumin Mannich base using SiO_2 catalyst and xylene as solvent



Scheme-II: Probable mechanism for the formation of curcumin-Mannich base using silica as catalyst

TABLE-2
SYNTHESIS OF 4-((DIALKYLAMINO)METHYL)-1,7-DIPHENYLHEPTA-1,6-DIENE-3,5-DIONE

S. No.	Amine	Yield of product[a]		m.p. (°C)
		Conventional	MWI	
1	Dimethyl amine	85	80	166 [18]
2	Diethyl amine	91	77	154 [18]
3	Morpholine	90	61	142 [18]
4	Piperidine	82	55	182 [18]
5	N-methylaniline	94	78	131 [18]
6	1-Methylpiperazine	80	64	174 [18]
7	2,2'-Azanediylbis(ethan-1-ol)	55	32	200 [18]

[a]Reaction condition: Formaldehyde (2 mmol), dimethyl amine (2 mmol), silica (3 mmol) and Xylene 5 mL. (1) Conventional: Reflux for 3 h and (2) MWI: stirred at 30 min then microwave irradiation power at 300 W for 1-2 min.

Conclusion

In conclusion, we developed one-pot synthesis of nitrogen containing curcumin (curcumin Manich base) derivatives from easily available starting reactant molecule. An eco-friendly catalyst as non-toxic, non-hazardous easily available used for the synthesis of curcumin analogue under conventional and microwave irradiation method. An expeditious reaction carried out under the microwave method with good to better yield.

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