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Research Article

Microwave-Assisted Silica-Chloride Catalyzed Biginelli Approach for the Synthesis of Curcumin-3,4-Dihydropyrimidinones

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ABSTRACT

Describe method describes the synthesis of curcumin-3,4-dihydropyrimidinones using green reaction profile. Substituted aromatic aldehydes, urea, and (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Curcumin) added to polyethylene glycol-400 as solvent in presence of heterogeneous catalyst silica-chloride and exposed to microwave at 600W. During reaction care was taken to avoid overheating by cutting microwave with definite time interval. After completion of reaction, reaction mass transfer to ice cold water and extracted with ethyl acetate to obtained crude product. Hot ethanol used for crystallization to get pure product. Propose reaction method is expendious, cost effective. Non requirement of column chromatography for purification is another significant advantage of present method.

Key words: Curcumin, Dihydropyrimidinones, Microwave assisted, One pot, Silica-chloride.

1. INTRODUCTION

Heterocyclic molecules are well established for their therapeutic properties. Almost two-third compounds are heterocyclic among all reported drugs. Curcumin heterocyclic analogs are reported for their outstanding biological activity. Pyrazole analogs are curcumin, were synthesized, and reported for various biological activities. To improve biological activity of curcumin, medicinal chemists have exploited total four sites for chemical transformation consisting aryl side chain, central diketones functionality, carbon-carbon unsaturated bond, and central acidic methylene group. Heterocyclic modifications mainly involved with one or two keto groups. Molecular modeling was tried and obtained improved antimalarial curcumin analogs [1]. Pyrazole based heterocyclic analogues have been extensively reported as promising molecules with potent anticancer property [2-6]. Curcumin-pyrazole is well known for their pharmaceutical significance, such as antiproliferative [7], antimicrobial [8], anticancer [9], and antibacterial activity [10].

Curcumin-3,4-dihydropyrimidinones analogs have been known for their synergistic antimicrobial properties [11]. Further, exploration of analogs found promising antioxidant, anti-inflammatory [12], and anticancer activity [13]. Tetrahydrocurcuminoid dihydropyrimidinones derivatives have been found acetyl cholinesterase inhibitors [14]. Italian scientist Pietro Biginelli in 1891, from University of Florence, reports acid catalyzed condensation of ethyl acetoacetate (1,3-diketo), benzaldehyde, and urea in alcohol when refluxed obtained crystalline 3,4-dihydropyrimidine-2(1H)-one as pure product [15].

Multicomponent Biginelli approach for the synthesis of curcumin 3,4-dihydropyrimidine has been reported with Stannous chloride [11], chitosamine-hydrochloride as catalyst [12], Conc. sulfuric acid [13], and tetrahydrocurcumin Biginelli product obtained using Copper sulfate as a catalyst [14]. Classical Biginelli approach and its application in the synthesis of curcumin-dihydropyrimidinones are depicted in Figure 1.

2. EXPERIMENTAL SECTION

The commercial sample of curcumin was purchased from S. D. Fine Chemical Limited, Mumbai, Maharashtra. Solvents were used during experimentation which was of analytical grade purchased from Spectrochem of Loba, India and used further without purification. Separation of curcumin, demethoxycurcumin, and bisdemethoxycurcumin from commercial sample was performed by column chromatography whenever necessary.

2.1. Preparation of Catalyst

To a well-stirred silica gel (20 g) in DCM (50 mL) was added to this slow drop-wise $SOCl_2$ (20 g) introduced at room temperature with occasional shaking. After stirring for 1–2 h, the solvent was removed under reduced pressure to dryness. The silica chloride thus obtained was used in the describe experiments as catalyst [16]. During workup, aqueous layer was filter to obtained silica chloride as residue, further washed with water, and kept in oven at 110°C for 2 h. Reusability of catalyst study will be published during course of time.

2.2. General Experimental Procedure

Mixtures of curcumin (**1**; 2 mmol; 736 mg), substituted aromatic aldehyde (2 mmol), and urea (**2**; 2 mmol) were added to stir solvent

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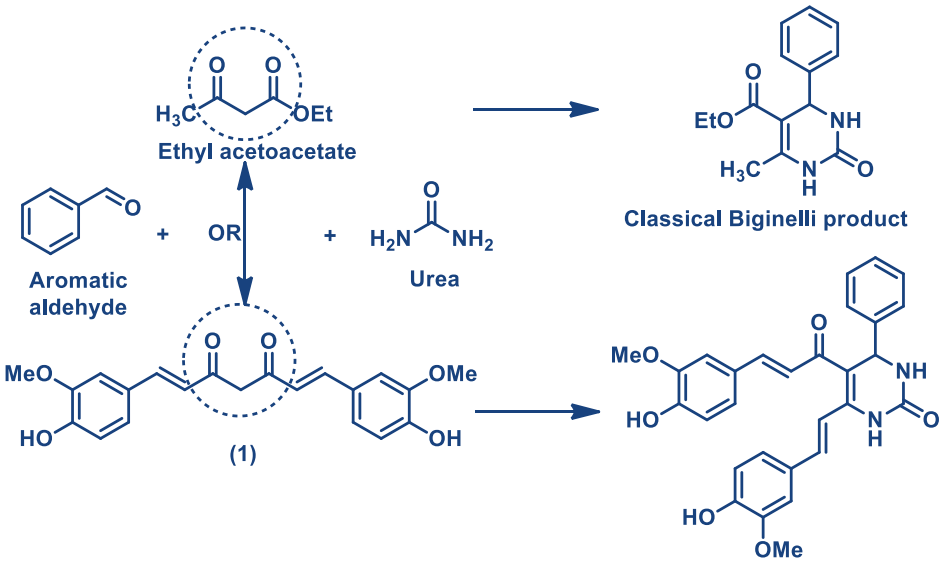

Figure 1: Classical Biginelli approach and replacement of β-diketo ester with curcumin.

polyethylene glycol (PEG)-400 (15 mL) in one portion (Scheme 1). To this reaction mixture silica chloride (10 mol %, 217 mg) was added. Thus, obtained reaction mixture describe with microwave irradiation (MWI) at power 600W. After every successive 1 min, irradiation 8–10 s interval period was set to avoid overheating. Progress of reaction was monitor by TLC (Acetone: Hexane; 4:6). After completion of reaction pour to ice cold water and extracted with ethyl acetate (25 mL × 2), collected organic layer evaporated in reduced pressure to obtained pure product after recrystallization.

2.3. Spectral Analysis

Prepared samples were previously reported [17]. Sample products (2a, 2b, and 2c) were scan for spectral analysis and found in agreement with reported data.

2.3.1. 5-((E)-3-(4-hydroxy-3-methoxyphenyl)acryloyl)-6-((E)-4-hydroxy-3-methoxystyryl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (2a)

IR (KBr) $cm^{-1:}$ 3564 (OH), 3154 (NH), 2912 (=C-H), 1631 (CO), 1503, 1414, 1342, 1042, 750cm^{-1};1H NMR (300 MHz, DMSO): δ3.80 (3H, s, OCH3), 3.87 (3H, s, OCH3), 5.43 (1H, s, C4-CH*), 6.71 (2H, d, H-2,7), 6.79-6.87 (5H, m, ArH), 7.11 (2H, s, ArH) 7.23–7.29 (5H, m, ArH).

2.3.2.5-((E)-3-(4-hydroxy-3-methoxyphenyl)acryloyl)-6-((E)-4-hydroxy-3methoxystyryl)-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (2b)

M.P. IR (KBr) $cm^{-1:}$ 3510 (OH), 3174 (NH), 2933 (=C-H), 1631 (CO), 1510, 1421, 1382, 1082, 813cm^{-1}; 1H NMR (300 MHz, DMSO): δ3.72 (3H, s, OCH3), 3.75 (3H, s, OCH3),5.23 (1H, s, C4-CH*), 6.76 (2H, d, H-2,7), 6.81-6.87 (4H, d, ArH), 7.20 (2H, s, ArH) 7.24–7.28 (5H, m, ArH).

2.3.3.5-((E)-3-(4-hydroxy-3-methoxyphenyl)acryloyl)-6-((E)-4-hydroxy-3methoxystyryl)-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (2c)

IR (KBr) $cm^{-1:}$ 3555 (OH), 3112 (NH), 2930 (=C-H), 1622 (CO), 1510, 1421, 1382, 1080, 766 cm^{-1};1H NMR (300 MHz, DMSO): δ3.84(3H, s, OCH3), 3.87 (3H, s, OCH3), 5.17 (1H, s, C4-CH*), 6.51 (1H, s, ArH-2"), 6.64-6.66 (2H, d, Ar-H), 6.79-6.81 (2H, d, H-6,7), 7.04–7.10 (2H, m, aromatic), 7.81(1H, d, H-2).

3. RESULTS AND DISCUSSION

In continuation of our efforts to investigate new synthetic methodologies, herein, we describe curcumin dihydropyrimidine synthesis from equimolar mixture of curcumin, substituted aromatic aldehydes, and urea. A model reaction strategy was used for optimization of reaction condition and stoichiometry. Curcumin, benzaldehyde, and urea were taken as model reactants and applied various proportions of silica-chloride as catalyst [Table 1]. During optimization of amount of catalyst, reaction was performed without catalyst [Table 1; Entry 1] to check need of any catalyst for this transformation. This attempted was ended with recovering starting materials. Gradual increases of amount of catalyst from 5 mol% to 25 mol% results are depicted in Table 1. When introduced 10 mol% of catalyst reaction offers 84% of product, no significant elevation observed when amount of catalyst were changes to 15 and 20 mol%. MWI power required for effective product formation was fixed by performing reaction at various Watt power [Table 1; Entry 3, 7 and 8], comparison of results was allowed us to fixed 600W as fixed irradiation power for further reactions. Ability of catalyst as recoverable and recyclable significantly increases its synthetic impact in methodology development.

On completion of first batch of reaction, silica-chloride was recovered by simple filtration of aqueous layer, washed with water, and dried in oven for 2 h before reused. This dried catalyst considered as 10 mol% throughout all further recirculation reactions, results are depicted in Table 2. Obtained results were shown slow fall down of yield of products, efforts were done until no significant product was obtained. From third recycle, times of reaction were increases in search of better yield of product by 15 min [Table 2; Entry 4] and by 20 minutes [Table 2; Entry 5, 6 and 7]

Further derivatization were performed by keeping 10 mol% of silica-chloride and 600W power as fixed parameters along with curcumin as one reactant and changing aromatic aldehydes with urea [Table 2]. Study of effect of substituent on yield of product was shown that electron donating moiety when present on aromatic aldehyde enhanced yield of product [Table 2; Entry b, d and e]. Comparatively, low productivity observed when aromatic aldehyde used with electron-withdrawing group like $–NO_2$. Model reaction [Table 2; Entry a] consists of urea as one of the reactant obtained 84% of product. Further derivatisation

were performed by keeping 10mol% of silica-chloride and 600W power as fixed parameters along with curcumin as one reactant and changing aromatic aldehydes with urea [Table 2]. Structure of prepared molecules 2a-2g is as shown in the Figure 2.

Relative changes in yields of product with respect to electron-donating or withdrawing substituent's present on aromatic aldehyde or with respect to involvement of urea could be explained by taking a closer look at mechanistic pathway. Recirculation of catalyst gradually yield lower yield of product may also explained by same mechanism [Figure 3]. Silica-chloride when involved as heterogeneous catalyst in presence of polyhydrated solvent like PEG-400, librates H^+ ion which changes reactions *p*H to acidic one. During each successive reaction, silica-chloride capacity of generation of H^+ gradually falls down, hence productivity also fall down.

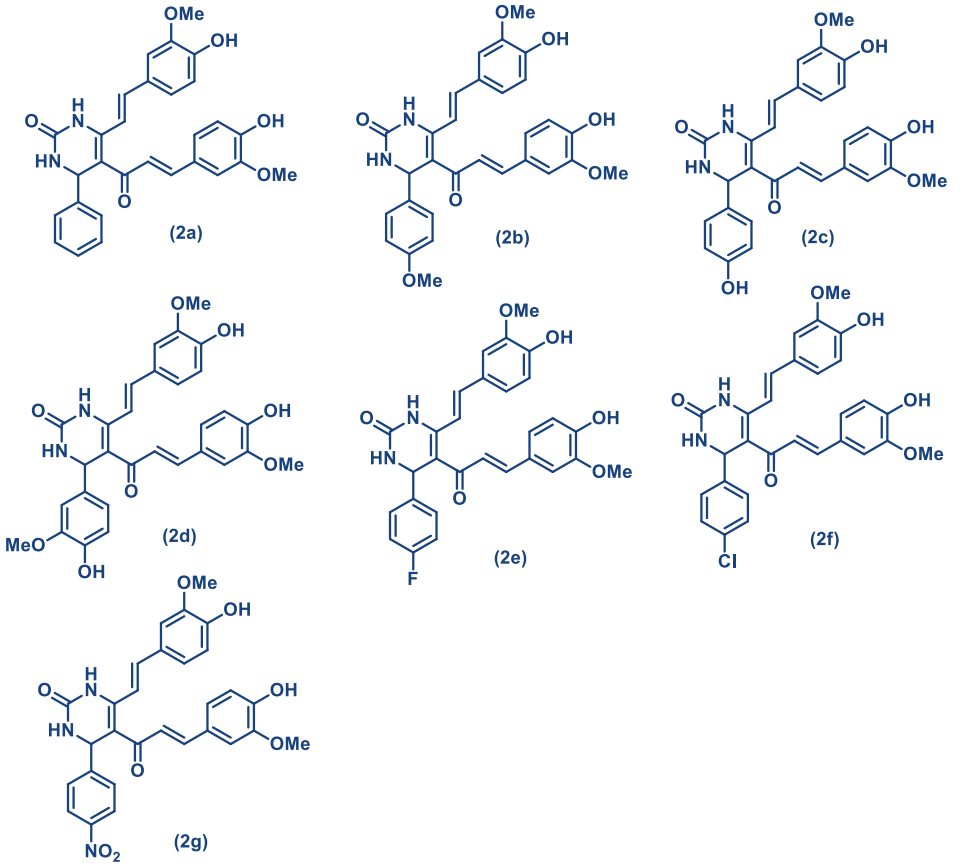

Figure 2: Derivatization of curcumin-DHP.

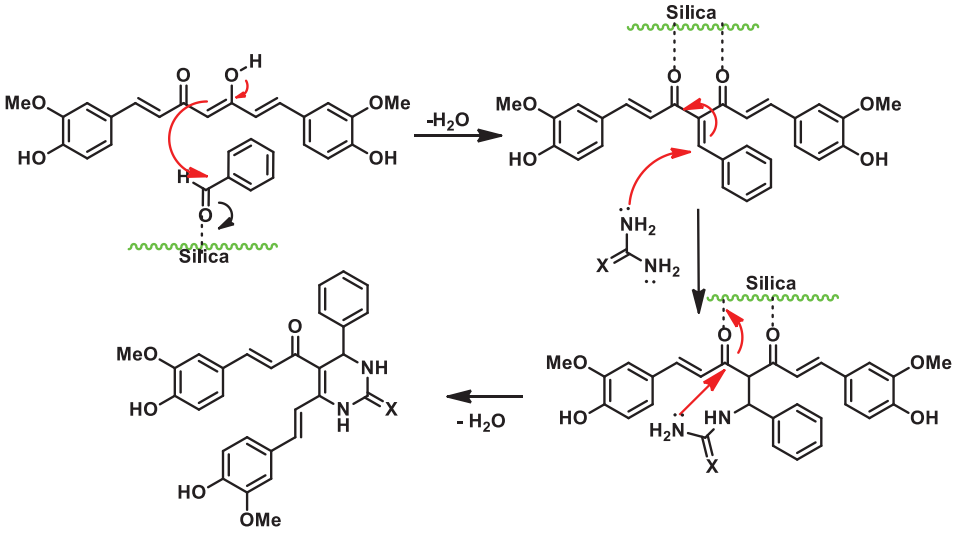

Figure 3: Hypothetical pathway showing transformation of curcumin to curcumin-DHP.

Scheme 1: Synthesis of 3,4-dihydropyrimidine curcumin analogs using silica chloride and PEG as catalyst: Solvent.

Table 1: Optimization of reaction condition with respect to amount of catalyst and MWI power using model reaction strategy.

Entry	SiO_2-Cl in mol%	MWI Power (Watt)	Time (in Min.)	Yield[a] (%)
1	No catalyst	600 W	30	Starting recover[b]
2	5	600 W	10	49%
3	10	600 W	10	84%
4	15	600 W	10	86%
5	20	600 W	10	89%
6	25	600 W	10	62%
7	10	400 W	10	53%
8	10	800 W	10	21%

[a]Isolated yield, [b]TLC check. MWI: Microwave irradiation

Table 2: Derivatization of curcumin-DHPM with respect to time and yield of reaction.

Entry	Product No.	Time in min.	Yield[a] %	M.P. (Lit.) in °C
1	**(2a)**	10	84	98 (98–100)
2	**(2b)**	10	93	184 (180–182)
3	**(2c)**	12	88	127 (129–131)
4	**(2d)**	12	90	100 (100–103)
5	**(2e)**	10	90	109 (110–112)
6	**(2f)**	10	89	204 (198–200)
7	**(2g)**	14	76	161 (162–164)

Reaction condition: Curcumin (2 mmol), benzaldehyde (2 mmol) in PEG-400, [a]Isolated yield. DHPM: Dihydropyrimidinones

Reaction performed at acidic *p*H has electron deficient environment and electron-donating substituent shown good productivity due to electron-donating capacity whereas electron-withdrawing groups like $–NO_2$ turns electronic availability situation even worst, hence productivity reduced drastically.

4. CONCLUSION

Describe methodology for the synthesis of 3,4-dihydropyrimidine curcumin analogs has productive with respect to yield. Describe catalyst easily obtained in step from cheaper starting material. Heterogonous catalyst could be significant advantage of present methodology. Easy workup procedure gives advantage to obtained pure product without applying tedious column chromatography. Green profile of reaction, readily available starting materials is another significant advantage of this method.

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***Bibliographical Sketch**

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