

MILD ACIDIC CHARCOAL CATALYZED SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1H)-ONE/-THIONE DERIVATIVES

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Abstract. A mild catalyst system with comparative reduction in amount of catalyst was demonstrated. The multicomponent synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones using acetic acid supported on activated charcoal as a mild acid catalyst in ethanol under both conventional as well as microwave irradiation conditions has been achieved. The obtained catalyst system is more efficient under microwave irradiation than under conventional conditions with shorter reaction times (3-9 min) and excellent yields (78-94 %).

Keywords: Biginelli reaction, acetic acid, acidic charcoal, microwave irradiation.

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Introduction

Polymer supported reagents have been utilized successfully for the synthesis of substituted 3,4-dihydropyrimidin-2(1H)-ones (or thiones) (DHPMs) [1]. Several polymers-based efficient catalysts were reported for the Biginelli advancements, such as biocatalysts [2], clays and minerals, alumina [3], silica [4], cyclodextrins, hetero-polyacids[5], hetero-polyanions, and organo-catalysts [6]. Organic polymers such as resins, calixarenes, cyclodextrins and polymeric carbon were found to be effective catalysts and catalyst support [6]. A polymeric form of carbon was employed as catalyst in the form of expandable graphite [7] and graphite [8] for synthesizing DHPMs. The use of polymeric carbon as a support for the LaCl₃ catalyst supported on graphite [9] under microwave conditions; sulphonated carbon materials prepared using concentrated sulphuric acid, at elevated temperature [10]; sulphuric acid immobilized on activated charcoal in *n*-hexane-acetonitrile under reflux conditions [11], were reported as catalytic conditions for the one-pot multicomponent Biginelli reaction, thereby providing heterogeneous protocol. However, the limitations such as the use of sulphuric acid as a catalyst and longer reaction times require the development of simpler and safer method.

Thus, the purpose of the study was to synthesize 3,4-dihydropyrimidin-2(1H)-one

and -thione derivatives by using charcoal supported acetic acid as the catalyst system. The optimized method employed in this study allows to overcome the use of hazardous strong acids, expensive catalysts and to employ a cheap and readily available catalyst system.

Experimental

Generalities

All starting reagents, including aromatic aldehydes, ethyl acetoacetate, urea, thiourea, acetic acid, charcoal, ethanol, ethyl acetate, petroleum ether *etc.*, were purchased from commercial sources Loba Chemie Pvt. Ltd., Merck Specialities Pvt. Ltd. and used without further purification. *Melting point values* were determined using the conventional method and are uncorrected. Reactions were monitored by *thin layer chromatography* on silica gel 60 F254 plates. A conventional household microwave oven operating at 800 W was used for irradiation. All the synthesized products are known compounds and were identified by comparing their melting points and spectra data with those reported in the literature.

Preparation of mild acidic charcoal

To a 50 mL round bottom flask fitted on a magnetic stirrer containing 10 mL ethanol was added 1 mL of glacial acetic acid and stirred to get a homogeneous solution. Further, to a homogenized solution of ethanolic acetic acid, 1 g

of activated charcoal was added in portions and stirred for 10 min to ensure uniform adsorption. Ethanol was then removed by rotary evaporator to get dry acetic acid adsorbed charcoal powder. The loading of acetic acid on charcoal was found 14–16 mmol/g (80–91%), determined titrimetrically using 0.01 N NaOH for a 0.1 g sample of mild acidic charcoal with phenolphthalein indicator.

The conventional method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones

A 50 mL round bottom flask containing the mixture of aldehyde (**1**) (10 mmol), ethyl acetoacetate (**2**) (10 mmol), urea/thiourea (**3**) (12 mmol) and 0.1 g mild acidic charcoal catalyst was refluxed with 10 mL ethanol for the appropriate time. The progress of the reaction was monitored by TLC using the ethyl acetate and *n*-hexane solvent system. After reaction completion, the warm reaction mixture was filtered on a filtration funnel to separate the charcoal residue. The charcoal residue was washed with ethanol (3×3 mL). The products were obtained from the filtrate after removal of ethanol by rotary evaporator. The recrystallization of crude products from ethanol afforded good to excellent yields of DHPMs and thiones [12].

Microwave irradiation method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones

To an Erlenmeyer flask containing a mixture of aldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea/thiourea (12 mmol) in 10 mL ethanol was added 0.1 g mild acidic charcoal catalyst subjected to microwave irradiation for the indicated period of time. The reaction mixture was irradiated with a time interval of 1 min and the reaction progress was monitored using TLC. After reaction completion, the work-up procedure was employed as described in the conventional method.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4a)

IR (KBr, cm^{-1}): 3480, 3247, 2980, 1728, 1705, 1646, 1466, 1222, 1090. ^1H NMR (400 MHz, δ , ppm) (DMSO- d_6): δ 9.17 (s, 1H), 7.75–7.69 (m, 1H), 7.37–7.27 (m, 2H), 7.24 (ddt, J = 6.9, 3.3, 1.5 Hz, 3H), 5.15 (d, J = 3.4 Hz, 1H), 3.99 (q, J = 7.0 Hz, 2H), 2.25 (s, 3H), 2.09 (s, 2H), 1.10 (t, J = 7.1 Hz, 3H). MS (m/z): 261 (M+1) [13].

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4b)

IR (KBr, cm^{-1}): 3520, 3362, 2991, 1737, 1705, 1652, 1566, 1250. ^1H NMR (400 MHz, δ , ppm) (DMSO- d_6): δ 9.33 (s, 1H), 9.08 (d,

J = 2.2 Hz, 2H), 7.62–7.56 (m, 2H), 7.07–6.99 (m, 3H), 6.83 (s, 1H), 6.73–6.65 (m, 3H), 5.05 (d, J = 3.3 Hz, 2H), 3.98 (q, J = 7.1 Hz, 3H), 2.23 (s, 5H), 2.09 (s, 1H), 1.10 (t, J = 7.1 Hz, 5H), 1.06 (s, 1H). [13].

5-(Ethoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4c)

IR (KBr, cm^{-1}): 3343, 3107, 2981, 1704, 1651, 1520, 1347, 1213. ^1H NMR (400 MHz, δ , ppm) (DMSO- d_6): δ 9.37 (s, 1H), 8.25–8.17 (m, 2H), 7.91 (dd, J = 3.5, 2.0 Hz, 1H), 7.54–7.47 (m, 2H), 5.27 (d, J = 3.3 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 2.26 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). [14].

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4d)

IR (KBr, cm^{-1}): 3479, 3413, 3246, 2928, 1724, 1705, 1651, 1513, 1224, 1220. ^1H NMR (400 MHz, δ , ppm) (DMSO- d_6): δ 9.13 (s, 1H), 8.25–8.17 (m, 2H), 7.91 (dd, J = 3.5, 2.0 Hz, 1H), 7.54–7.47 (m, 2H), 5.27 (d, J = 3.3 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 2.26 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). [14].

5-(Ethoxycarbonyl)-4-(*n*-propyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4e)

IR (KBr, cm^{-1}): 3237, 3015, 1735, 1712, 1666, 1599, 1287. ^1H NMR (400 MHz, δ , ppm) (CDCl_3): δ 8.04 (s, 1H), 5.85 (s, 1H), 4.33 (dt, J = 7.6, 3.5 Hz, 1H), 4.28–4.12 (m, 2H), 2.30 (s, 3H), 2.19 (s, 2H), 1.67–1.39 (m, 2H), 1.30 (t, J = 7.1 Hz, 4H), 0.93 (t, J = 7.1 Hz, 3H). [15].

5-Ethoxycarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4f)

IR (KBr, cm^{-1}): 3380, 3186, 2986, 1720, 1703, 1660, 1586, 1270. ^1H NMR (400 MHz, δ , ppm) (DMSO- d_6): δ 9.81 (s, 1H), 9.65 (s, 1H), 7.37–7.21 (m, 5H), 5.17 (d, J = 3.4 Hz, 1H), 4.00 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 1.10 (s, 3H). MS (m/z): 277 (M+1). [12].

5-Ethoxycarbonyl-6-methyl-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-thione (4g)

IR (KBr, cm^{-1}): 3487, 3290, 2857, 1750, 1698, 1634, 1534, 1232. ^1H NMR (400 MHz, δ , ppm) (DMSO- d_6): δ 1.07 (t, J = 7.6 Hz, 3H), 2.4 (s, 3H), 4.1 (q, J = 7.6 Hz, 2H), 5.68 (s, 1H), 6.91–7.15 (m, 4H), 7.72 (s, 1H), 9.65 (s, 1H), 9.95 (s, 1H). MS (m/z): 293 (M+1). [16].

5-(Ethoxycarbonyl)-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-thione (4h)

IR (KBr, cm^{-1}): 3410, 3269, 2897, 1755, 1631, 1575, 1365, 1268. ^1H NMR (400 MHz, δ , ppm) (CDCl_3): δ 7.52 (d, J = 8.7 Hz, 1H), 6.92–6.81 (m, 2H), 6.16 (q, J = 1.3 Hz, 1H), 4.14 (t, J = 5.9 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 2.42 (d, J = 1.2 Hz, 3H), 2.17–2.06 (m, 2H). [12].

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4i)

IR (KBr, cm^{-1}): 3463, 3192, 2889, 1737, 1708, 1653, 1573, 1243. ^1H NMR (400 MHz, δ , ppm) ($\text{DMSO}-d_6$): δ 9.9 (s, 1H), 9.60 (s, 1H), 7.13 (d, $J=8.7$ Hz, 2H), 6.89 (d, $J=8.7$ Hz, 2H), 5.11 (d, $J=3.4$ Hz, 1H), 4.01 (q, $J=7.1$ Hz, 2H), 3.72 (s, 3H), 2.28 (s, 3H), 1.11 (t, $J=7.0$ Hz, 3H). [12].

5-Ethoxycarbonyl-4-(n-propyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4j)

IR (KBr, cm^{-1}): 3337, 3019, 1745, 1705, 1651, 1520, 1320. ^1H NMR (400 MHz, δ , ppm) (CDCl_3): δ 8.41 (s, 1H), 7.94 (s, 1H), 4.37 (dt, $J=7.7, 3.7$ Hz, 1H), 4.28–4.09 (m, 2H), 2.32 (s, 3H), 2.18 (s, 1H), 1.69–1.55 (m, 1H), 1.55–1.43 (m, 1H), 1.46 (s, 1H), 1.47–1.30 (m, 1H), 1.30 (s, 1H), 1.28 (d, $J=7.1$ Hz, 2H), 0.92 (t, $J=7.0$ Hz, 3H). [17].

Results and discussion

Firstly, the heterogeneous mild acid catalyst system was developed by using glacial acetic acid and activated charcoal as solid support (1:1 v/w ratio) to achieve the synthesis of DHPMs and -thiones. Titrimetrically, the loading of acetic acid was determined to 80–91% per 0.1 g support. The model Biginelli reaction was performed using benzaldehyde, ethyl acetoacetate and urea (1:1:1.2) in ethanol with the different amounts of mild acidic charcoal catalyst. Both conventional

as well as microwave irradiation (800 W, 40%) methods were demonstrated to optimize the catalyst amount (Scheme 1).

The optimized catalytic conditions showed satisfactory results with respect to the yield and purity of the compounds under both reaction conditions with 0.1 g, as described in Table 1. No significant change in reaction time and in yield was observed with the catalyst amount higher than 0.1 g; therefore 0.1 g of mild acidic charcoal as a catalyst was employed for the synthesis of Biginelli derivatives. The microwave method was apparently more efficient than the conventional method with notably short reaction time and excellent yields of products (Table 1 and Table 2).

Table 1

Effect of catalyst amount on the conventional and on the microwave assisted model Biginelli reaction.

Entry	Catalyst, g	Conventional method		Microwave irradiation	
		Time, min	Yield, %	Time, min	Yield, %
1	0.025	120	79	12	83
2	0.050	90	83	9	88
3	0.075	60	88	7	91
4	0.100	40	90	3	94
5	0.125	40	88	3	94
6	0.150	40	88	3	93

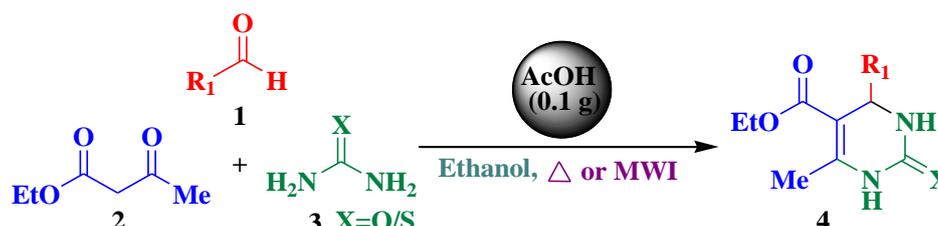
Optimization of acidic charcoal catalyst amount.

Table 2

Mild acidic charcoal catalyzed synthesis of dihydropyrimidin-2(1H)-ones and -thiones under conventional, as well as microwave irradiation conditions.

Entry	Product	R1	X	Conventional heating		Microwave irradiation		Melting point, °C	
				Time, min	Yield, %	Time, min	Yield, %	Observed	Reported
1	4a	C_6H_5-	O	40	90	3	94	200-202	200-202[12]
2	4b	4-OH-	O	40	76	4	84	228-230	228-230[12]
3	4c	4- NO_2-	O	35	88	3	92	208-210	210-212[16]
4	4d	4- OCH_3-	O	140	72	8	79	194-196	196-198[12]
5	4e	<i>n</i> -Propyl	O	90	92	4	94	180-182	180-182[15]
6	4f	C_6H_5-	S	120	88	5	92	204-206	205-207[12]
7	4g	2-OH-	S	120	76	6	84	206-208	206-208[16]
8	4h	4-Cl-	S	40	85	3	87	178-180	180-182[12]
9	4i	4- OCH_3-	S	140	74	9	78	154-156	154-156[12]
10	4j	<i>n</i> -Propyl	S	90	90	4	94	148-150	148-152[17]

Mild acidic charcoal employed as a catalyst for the synthesis of different Biginelli derivatives.



Scheme 1. Mild acidic charcoal catalyzed Biginelli reaction.

The mild acidic charcoal catalyst was then employed to synthesize DHPM and -thione derivatives using substituted aromatic aldehydes, ethyl acetoacetate and urea or thiourea. To verify the catalytic efficiency of mild acidic charcoal, DHPM and -thione derivatives were prepared under microwave irradiation and conventional refluxing conditions. Under both conditions the mild acid charcoal catalyst was found efficient, but under microwave conditions the efficiency was appreciably good (yielding 78–94% in comparison to conventional conditions (72–98% yielding) (Table 2).

The aldehydes bearing electron releasing and electron withdrawing groups were reacted successfully under both conventional and microwave conditions. The evaluation of mild acidic charcoal catalyst for Biginelli multicomponent cyclo-condensation proved to be

noteworthy. The use of acetic acid for the Biginelli reaction reported in the literature has been compared with the mild acidic charcoal catalyzed by microwave irradiation displayed in Table 3.

Some of the methods used acetic acid solvent in the presence of acid catalyst such as Lewis acids and protic acids. The mild acidic charcoal catalyst proved a short reaction time (3 min) and excellent yield (94%). Compared to conventional heating conditions, MWI conditions required shorter reaction times (Table 3). The comparison shown in Table 4 could be accounted for a summary of microwave assisted methods for the synthesis of DHPMs and -thiones. The variety of reported methods involved different amounts of catalyst and variations in reaction times, with varied ranges of DHPMs yields.

Table 3

Comparison of methods used acetic acid for the Biginelli reaction.

Entry	AcOH, mL	Solvent, mL	Catalyst	Activation mode	T, °C	Time, min	Yield, %	Ref.
1	0.1	THF (30)	CuCl/BF ₃ .OEt ₂	Heat	66	480	82	[18]
2	3	EtOH (1)	FeCl ₃	MWI	120	10	74	[19]
3	10	AcOH	H ₃ BO ₃	Heat	100	30	94	[20]
4	25	EtOH (10)	-	Heat	78	240	90	[21]
5	1	EtOH (50)	-	Heat	78	240	87	[22]
6	20	AcOH	HCl	Heat	100	480	93	[23]
7	20	AcOH	HCl	Heat	100	480	52*	[24]
8	20	AcOH	Meldrum's acid	Heat	118	600	41	[25]
9	1	EtOH (10)	AcOH-Charcoal	MWI	-	3	94	This work

*With 1,3-diphenyl-1,3-propanedione; AcOH: acetic acid; EtOH: ethanol; THF: tetrahydrofuran. Some methods which employed acetic acid are compared.

Table 4

Comparison of microwave assisted protocols for Biginelli reaction.

Entry	Catalyst used (amount)	Solvent, mL	Time, min	Yield, %	Ref.
1	FeCl ₃ /Si-MCM-41 (0.03 g/ 20 wt %)	-	3	89	[26]
2	Acidic Al ₂ O ₃ (20 g)	Methanol (30)	6	86	[27]
3	Acidic Al ₂ O ₃ or montmorillonite K ₁₀ clay (20 g)	EtOH (10)	8	75	[28]
4	I ₂ - Al ₂ O ₃ (neutral) (0.5 g)	-	1	90	[29]
5	ZrO ₂ -pillared clay (0.25 g)	-	5	94	[30]
6	PEG-SO ₃ H	-	6	91	[31]
7	Polystyrene sulphonic acid [PSSA] (20% solution)	Water	20	89	[32]
8	LaCl ₃ -graphite (1.5 g)	-	8	85	[9]
9	FeCl ₃ /Nanopore Silica (0.05 g)	-	15	75	[33]
10	Al ₂ O ₃ -SO ₃ H (0.5 g)	-	2	88	[28]
11	N-Bromosuccinamide (0.35g)	-	30	75	[34]
12	nanosized Ni _{0.45} Zn _{0.55} Fe ₂ O ₄ (0.03 g)	-	10	67	[35]
13	[PyPS] ₃ PW ₁₂ O ₄₀ (0.314 g)	-	5	95	[36]
14	3D printed α-Al ₂ O ₃ (0.350 g)	-	10	95	[37]
15	AcOH-Charcoal (0.1 g)	EtOH (10)	3	94	This work

Different catalyst systems under microwave irradiation conditions are compared.

Comparison of solid supported organic catalysts for Biginelli reaction.

Entry	Catalyst used (amount)	Reaction conditions	Time, min	Yield, %	Ref.
1	PsMImPF ₆ (0.1 g)	AcOH (40 mL), 100 °C	120	98	[38]
2	PANI-HBF ₄ .DHS (5 wt %)	EtOH, reflux	360	97	[39]
3	PANI-PTSA (5 wt %)	Methanol (10 mL), reflux	120	97	[40]
4	Ps-AlCl ₃ (1.28 g)	EtOH (10 mL), reflux	180	89	[41]
5	PS-AFDPAT (0.65 g)	EtOH (50 mL), reflux	300	90	[42]
6	PVSA (10 mol%)	EtOH or H ₂ O (5 mL),	60	88/94	[43]
7	PPF-SO ₃ H (0.25 g)	EtOH (15 mL), reflux	480	81	[44]
8	NSPVP (4 mol%)	Solvent free, 100 °C	6	90	[45]
9	PSBIL (50 mg)	EtOH (5 mL), 110 °C	1080	91	[46]
10	PANI-FeCl ₃ (0.2 g)	Acetonitrile, reflux	1440	83	[47]
11	H ₂ SO ₄ - Charcoal (133 % w/w)	<i>n</i> -Hexane- Acetonitrile, reflux	35	95	[11]
12	AcOH-Charcoal (0.1 g)	EtOH (10 mL), MWI	3	94	This work

Organic polymer supported catalysts for the Biginelli reaction are compared.

Few of the methods involved relatively more amount of catalyst (10–25 mL) and in some cases yields were good (82–93 %); with relatively more reaction time (240–480 min). The catalysts supported on clays, acidic alumina, nano-silica etc. and also, heteropolyacids and nanopolymers as catalysts were compared. In addition, the present charcoal supported acetic acid catalyst was also compared with the solid supported organic catalysts under different reaction conditions for the synthesis of Biginelli DHPMs and-thiones as per the Table 5.

The described solid supported organic catalysts in the Table 5 provided good yields comparable to the conventional reaction conditions with longer reaction times. The preparation methods for the solid or polymer supported organic catalyst, presented in Table 5, involve multiple steps and needs more expensive characterization methods. The functionalized polymers, resins as a catalyst were compared under both solvent and solvent-free conventional heating conditions. Concentrated sulphuric acid supported on charcoal support employed as a catalyst under conventional refluxing conditions was also compared. The reusability of recovered charcoal support for six cycles after activation and adsorption with acetic acid as per the procedure for preparation of mild acidic charcoal catalyst has also been demonstrated.

Conclusions

In conclusion, acetic acid adsorbed on activated charcoal as a mild catalyst was efficiently screened for the synthesis of Biginelli DHPMs and -thiones. The estimated adsorption of acetic acid on charcoal was observed as 80–91% per 0.1 g sample of charcoal. The amount of acetic acid as catalyst also reduced considerably

due to the large surface area provided by charcoal particles which also capably improved the yields. The increase in yields can also be supported by large surface area provided for reactants by charcoal particles.

The use of cheap, green, and easily available charcoal as solid support for acetic acid makes the method environment friendly. In the present article, a simple and convenient synthesis of known DHPMs and -thiones using mild acidic charcoal as catalyst was reported. In future, using the optimized protocol synthesis of novel DHPMs and -thiones will be planned.

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Supplementary information

Supplementary data are available free of charge at <http://cjm.asm.md> as PDF file.

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