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RESEARCH ARTICLE

SILICA IODIDE CATALYZED ULTRASOUND ASSISTED ONE-POT THREE-COMPONENT SYNTHESIS OF 3,4-DIHYDROPYRIMIDINE-2-(1*H*)-ONES/-THIONES

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Abstract

Aim and objective: A single-pot three-component reaction for a competent preparation of biologically active 3,4-dihydropyrimidineones/-thiones using Silica Iodide (SiO_2-I) as a reliable and reusable heterogeneous catalyst is developed.
Methods: The reaction proceeds *via* condensation of araldehydes, urea/thiourea, ethyl acetoacetate in ethanol under ultrasonic condition to afford the target molecules in best yields. The reaction proceeds in 30 min and SiO_2-I has shown high proficiency in performing this single-pot Biginelli reaction.
Results: The use of catalytic SiO_2–I (0.1 g) accelerated the reaction and gave the product in excellent yield. Maximum yield of the product was found to be 96% in ethanol
Conclusion: Study concludes the used method has shown many advantages, mild condition, short duration, simple isolation and best yields of products.
Keywords: Araldehydes, 3,4-dihydropyrimidine-2-(1*H*)-ones/-thiones, ethyl acetoacetate, silica iodide, ultrasonication, urea/ thiourea.

INTRODUCTION

Ultrasonication is recognized as a substantial mode for the sustainable synthetic organic processes[1-3] and provides several advantageous like tumbling time, minimization of waste, very high yields of the product by enhancing the rate and yield of the desired products in micro surroundings[4-5]. The viability of single-pot multicomponent reactions (MCRs) under ultrasonication using the heterogeneous silica iodide (SiO_2-I) as a catalyst has shown considerable progress in their efficiency from implementation and environmental points of view[6,7]. One of the significant, vital and biologically essential heterocyclic scaffolds is pyrimidine, and many natural products possess this motif. Molecules which are having pyrimidine skeleton exhibit unique therapeutic properties, and play essential role in biochemical reactions[8]. Pyrimidines have occupied a characteristic place in organic and medicinal chemistry and in designing pharmaceutical products since decades[9]. They exhibit a wide-range of bio activity such as: calcium channel blocking property, as antifungals, antimalarials, antibacterials, antihypertensive, anti-inflammatory agents, and inhibit fatty acid transportation, α1a- and neuropeptide Y antagonists and work as mitotic kinesin inhibitors[10-14]. Marine alkaloids such as: A and B-batzelladines, ptilocaulin and saxitoxin, due to the presence of dihydro-pyrimidine (DHPM) moiety in them are known for inhibiting the binding of HIV gp-120 to CD4 cells in AIDS chemotherapy[15]. 4-Aryl-5-isopropoxy-carbonyl-6-methyl-3,4-dihydropyrimidin - ones exhibit anti-microbical activity[16].

In 1893, Biginelli synthesized 3,4-dihydropyrimidine-2(1*H*)-ones *via* an acid catalysed single-pot three-component reaction of an α, β-ketoester, aldehyde and urea[17]. The reported protocol has drawbacks such as: prolonged reaction duration, low yield of products and tolerance of different functional groups throughout the reaction; which led to the growth of single-pot multi-component approaches towards getting the DHPMs and a number of reactions have been reported towards this condensation with a variety of catalysts such as: Lewis acids[18], Brønsted acids[19], polymer supported materials[20], ion-exchange resin[21], PTCs[19], ionic liquids[20], Brønsted bases[22], solid phase catalysts[23] and heterogeneous reagents[24], under microwave irradiation[25], ultrasonication[26], using other green synthetic

approaches[27], under solvent-less condition[28], grindstone technique[29], nano ZnO embedded in SBA-15[30] and dendrimer attached nano phosphotungstic acid particles immobilized on nano silica[31]. Many of these protocols involve harsh conditions, tedious work-up, and require long time, use of expensive reagents, non-recoverability of catalysts, strong acidic or basic conditions, environmental contamination, undesirable yields and non-tolerance of certain moieties. Hence, the progress of devising mild and eco-friendly methods which can overcome these drawbacks are of great significance towards the preparation of DHPMs. The ultrasonication method offers copious advantages like: better yield of the target molecules, superior reaction rates, works under mild and energy efficient reaction conditions, and minimization of waste takes place when compared with conventional methods.

MATERIALS AND METHODS

Commercially available reagents were used for the reactions. Liquid aldehydes were purified by distillation. Silica gel plates (Merck 60 F250) were used for following the reactions under the UV lamp. Agilent make Cary 630 FT-IR spectrophotometer for IR spectra; Varian Mercury instrument working at 400 MHz for ^{1}H NMR in $CDCl_3$ and Bruker AMX instrument (100 MHz) for ^{13}C NMR spectra in DMSO-d_6; Agilent Technologies (1200 series) instrument for LC-MS were used for characterization. SIDILU, Indian make sonic bath was used for sonic reactions (35 kHz at 25°C). SiO_2-I was prepared and characterized by K. B. Ramesh and M. A. Pasha[32].

Experimental procedure for the preparation of 4a–4m

1 mmol each of araldehyde, urea/thiourea, ethyl acetoacetate, SiO_2-I (0.1 g) and ethanol (5 mL) were taken in a 50 mL conical flask and sonicated for 30 min, filtered and the residue was washed with ethanol (5 mL×2). The product present in the filtrate and washings, was recovered by distillation and recrystallized from hot aq. ethanol. The structures were established by spectral analysis, from their melting points or by the comparison on TLC with the standard samples.

Spectral Data

4-(3′-Methoxyphenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4a):

IR (ATR, υ cm^{-1}): 3237, 3100, 2982, 1700, 1647, 1038;
^{1}H NMR: δ (ppm) = 9.13 (s, 1H, NH), 7.67 (s, 1H, NH), 6.76–7.24 (m, 4H, Ar-H), 5.10 (d, *J* = 2.4 Hz, 1H, CH), 3.95–4.00 (q, *J* = 7.2 Hz, 2H, CH_2), 3.70 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.07–1.11 (t, *J* = 7.2 Hz, 3H, CH_3);
^{13}C NMR: δ (ppm) = 14.5, 18.2, 53.7, 55.5, 59.6, 106.0, 111.1, 112.1, 119.5, 127.8, 148.4, 152.6, 158.9, 160.8, 167.1;
Mass (m/e): $[M+H]^+$ 291.1

4-(3′,4′-Dimethoxyphenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4b):

IR (ATR, υ cm^{-1}): 3247, 3107, 2955, 1706, 1680, 1024;
^{1}H NMR: δ (ppm) = 9.09 (s, 1H, NH), 7.62 (s, 1H, NH), 6.85–6.88 (d, *J* = 8.4 Hz, 1H,Ar-H), 6.823 (s, 1H, Ar-H), 6.75–6.77 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.07 (d, *J* = 2.8 Hz, 1H,CH), 3.95–4.00 (q, *J* = 6.8 Hz, 2H, CH_2), 3.69 (s, 6H, 2 × OCH_3), 2.23 (s, 3H, CH_3), 1.07–1.16 (t, *J* = 6.8 Hz, 3H, CH_3);
^{13}C NMR: δ (ppm) = 14.5, 18.0, 55.9, 59.0, 60.1, 106.0, 111.6, 118.2, 118.3, 136.6, 148.2, 148.3, 149.2, 152.6, 168.5;
Mass (m/e): $[M+H]^+$ 321.1

4-(3′-Nitrophenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4c):

IR (ATR, υ cm^{-1}): 3226, 3105, 2964, 1685, 1636, 1523;
^{1}HNMR: δ (ppm) = 9.32 (s, 1H, NH), 8.10–8.12 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 7.85 (s, 1H, NH), 7.61–7.68 (m, 2H, Ar-H), 5.28 (d, *J* = 2.4 Hz, 1H, CH), 3.96–4.01 (q, *J* = 6.8 Hz, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.06–1.09 (t, *J* = 6.8 Hz, 3H, CH_3);
^{13}C NMR: δ (ppm) = 14.2, 17.0, 54.1, 58.0, 59.3, 108.0, 122.6, 123.5, 128.0, 130.5, 145.3, 148.8, 148.9, 150.0, 164.2;
Mass (m/e): $[M+H]^+$ 306.1

4-(4′-Chlorophenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4d):

IR (KBr, υ cm^{-1}): 3329, 1670, 1580, 1540, 1498, 1432, 1335, 1303, 1234, 1199, 1138, 1084, 1025, 928, 877, 752, 690;
^{1}H NMR: δ (ppm) = 9.32 (s, 1H, NH), 8.19 (d, *J* = 8.7 Hz, 2H), 7.86 (s, 1H, NH), 7.45 (d, *J* = 8.7 Hz, 2H), 5.22 (s, 1H), 3.93 (q, *J* = 7.3 Hz, 2H), 2.22 (s, 3H), 1.05 (t, *J* = 6.9 Hz, 3H);
^{13}CNMR: δ (ppm) = 14.6, 18.4, 54.2, 59.2, 59.9, 98.2, 123.8, 124.4, 127.8, 128.2, 147.2, 152.3, 152.5, 158.2, 165.5.

4-(4′-Methylphenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4e)[33]:

IR (KBr, υ cm^{-1}): 3220, 3100, 1720 (sh), 1700;
^{1}H NMR: δ (ppm) = 9.19 (s, 1H, NH), 7.70 (s, 1H, NH), 7.12 (s, 4H), 5.11 (d, *J* = 3.0 Hz, 1H), 4.00 (q, *J* = 7.5 Hz, 2H), 2.28, 2.30 (2 s, 6H, 2 × CH_3), 1.12 (t, *J* = 7.5 Hz, 3H).

4-(2′-Nitrophenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4g)[33]:

IR (KBr, υ cm^{-1}): 3230, 3120, 1730, 1710, 1650;
^{1}H NMR: δ (ppm) = 9.37 (br s, 1H), 8.23 (d, *J* = 10.0 Hz, 2H), 7.91 (br s, 1H), 7.51 (d, *J* = 10 Hz, 2 H), 5.29 (d, *J* = 3.0 Hz, 1H), 4.00 (q, *J* = 7.5 Hz, 2H), 2.29 (s, 3H), 1.11 (t, *J* = 7.5 Hz, 3H).

4-(2′-Chlorophenyl)-6-methyl-2-oxo-3,4-dihydro(1*H*)-pyrimidine-5-ethyl carboxylate (4h)[33]:

IR (KBr, υ cm^{-1}): 3240, 3100, 1710, 1650;
^{1}H NMR: δ (ppm) = 9.39 (br s, 1H), 7.49–7.98 (m, 5H), 5.81 (d, *J* = 3.0 Hz, 1H), 3.88 (q, *J* = 7.5 Hz, 2H), 2.30 (s, 1H), 0.94 (t, *J* = 7.5 Hz, 3H).

4-(2′,3′-Dichlorophenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4i)[33]:

IR (KBr, υ cm^{-1}): 3360, 3220, 3100, 1690, 1640;
^{1}H NMR: δ (ppm) = 9.30 (br s, 1H, NH), 7.72 (br s, 1H, NH), 7.22–7.46 (m, 4H), 5.67 (d, *J* = 2.5 Hz, 1H), 3.91 (q, *J* = 7.5Hz, 2H), 2.32 (s, 3H), 1.08 (t, *J* = 7.5 Hz, 3H).

4-(2′-Trifluoromethylphenyl)-6-methyl-2-oxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4j)[33]:

IR (KBr, υ cm^{-1}): 3360, 3100, 1700, 1690, 1640;

^{1}H NMR: δ (ppm) = 9.32 (br s, 1H, NH), 7.80 (br s, 1H, NH), 7.50–7.61 (m, 1H), 7.25–7.43 (m, 2H), 5.69 (br s, 1H), 3.89 (q, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 0.97 (t, *J* = 7.5 Hz, 3H).

4-Phenyl-6-methyl-2-thioxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4k)[34]:

IR (KBr, υ cm^{-1}): 3243, 1711, 1627;

^{1}HNMR: δ (ppm) = 10.30 (s, 1H, NH), 9.63 (s, 1H, NH), 7.28 (m, 5H, Ar-H), 5.18 (s, 1H, CH), 4.00 (q, *J* = 7.0 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.10 (t, *J* = 7.06 Hz, 3H, CH_3).

^{13}CNMR: δ (ppm) = 12.2, 15.5, 52.2, 57.8, 99.2, 124.7, 125.8, 126.6, 143.1, 163.4, 172.6;

Mass (m/e): $[M+H]^+$ 277.1

4-(4′-Chlorophenyl)-6-methyl-2-thioxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4l)[34]:

IR (KBr, υ cm^{-1}): 3242, 1705, 1638;

^{1}HNMR: δ (ppm) = 10.58 (s, 1H, NH), 9.75 (s, 1H, NH), 7.45 (d, *J* = 0.8 Hz, 2H, Ar-H), 7.28 (d, *J* = 8.6 Hz, 2H, Ar-H), 5.16 (s, 1H, CH), 4.02 (q, *J* = 7.1 Hz, 2H, CH_2), 2.27 (s, 3H, CH_3), 1.12 (t, *J* = 7.1 Hz, 3H, CH_3); Mass (m/e): $[M+H]^+$ 311.06

4-(3′-Nitrophenyl)-6-methyl-2-thioxo-3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylate (4m)[34]

IR (KBr, υ cm^{-1}): 3170, 1715, 1661, 1593, 1540;

^{1}HNMR: δ (ppm) = 10.56 (s, 1H, NH), 9.80 (s, 1H, NH), 8.08 (s, 1H, Ar-H), 7.65–7.73 (m, 2H, Ar-H), 5.36 (s, 1H, CH), 4.04 (q, *J* = 7.6 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.11 (t, *J* = 7.5 Hz, 3H, CH_3);

Mass (m/e): $[M+H]^+$ 322.08

RESULTS AND DISCUSSION

In order to determine the generality of use of SiO_2-I[32] assisted ultrasonic single-pot three-component reaction, the influence of reaction medium, temperature, catalyst, amount of the catalyst required and the energy efficiency were examined for enhancing the rate and yield of the products by taking 1 mmol each of 3-methoxybenzaldehyde, urea and ethyl acetoacetate as model substrates.

Effect of catalyst

Various catalysts were subjected for screening under different conditions (at 28°C, reflux temperature and ultrasonication) to authenticate the right selection and the results are shown in the Table 1. To study the activity of catalyst, the present reaction was first studied without catalyst to get 20% product (entry 1). The yield of the product hardly enhanced with catalystic NaI, SiO_2, TiO_2, $CeCl_3$, $ZnCl_2$, K_2CO_3 and ZnO (entries 2–8). The use of catalytic SiO_2–I (0.1 g) accelerated the reaction and gave the product in excellent yield (96%, entry 10) in 30 min. Hence, SiO_2–I was therefore, selected under ultrasonication for further studies.

Table 1: Effect of various catalysts on the preparation of 4a under ultrasonic condition.

Entry	Catalyst	Time (min)	Yield (%)
1	No catalyst	90	20
2	NaI[a]	90	27
3	SiO_2[a]	90	24
4	TiO_2[a]	90	48
5	$CeCl_3$[a]	90	59
6	$ZnCl_2$[a]	90	62
7	K_2CO_3[a]	90	76
8	Nano ZnO[a]	90	87
9	SiO_2-I[b]	90	96
10	SiO_2-I[b]	30	96

[a]10 mol% catalyst in EtOH (5 mL); [b]0.1 g in EtOH (5 mL)

Solvent effect

Evaluation of different solvents was taken up and the results are presented in Table 2. To demonstrate the effect of the solvent, the reaction of 1 mmol each of 3-methoxybenzaldehyde, urea and ethyl acetoacetate was first studied under solvent-less condition to get 35% product under ultrasonic condition (entry 1), In nonpolar solvents the yield was very low (entries 2,3), and in polar solvents like 1,4-dioxane, DMSO, DMF and THF, the yields were moderate (entries 4–7); the most promising enhancement was seen when protic solvents such as: MeOH, H_2O and ethanol were used, and the yields were excellent (entries 8−10); and among these three solvents, acceleration of the rate of the reaction (30 min) and yield of the product (96%, entry 10), was found in ethanol.

Catalyst feed ratio

A study on the effect of catalyst-load on the progress of this successful reaction under ultrasonic condition was then taken up; the results are encapsulated in Table 3. From above results, it is evident that, SiO_2-I may activate the carbonyl group of the araldehyde and facilitate the attack of urea/thiourea (2) to form an acyl imine.

Table 2: Solvent effect on the SiO_2-I catalyzed synthesis of 4a.

Entry		Reaction Condition[c]					
		28 °C		Reflux		Ultrasound	
	Solvent[a]	Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	No solvent	300	15	300	24	30	30
2	*n*-Hexane	300	18	300	42	30	46
3	CH_3CN	300	22	300	38	30	45
4	1,4-dioxane	300	30	300	47	30	50
5	DMSO	300	25	300	30	30	35
6	DMF	300	20	300	26	30	30
7	THF	300	20	300	28	30	30
8	H_2O	300	35	300	60	30	70
9	MeOH	300	40	300	60	30	70
10	Ethanol	300	50	300	80	30	95

[a]5 mL; [b]Isolated yield; [c]3-methoxybenzaldehyde (1 mmol), urea (1 mmol), ethyl acetoacetate (1 mmol) and SiO_2-I (0.1 g).

The reaction was studied with 0.05, 0.06, 0.07, 0.08, 0.09 and 0.10 g of SiO_2–I; with the increase in the catalyst from 0.05 g to 0.1 g the yield got enhanced gradually from 57% with 0.05 g to 96% when 0.1 g of the catalyst (entry 6) was used. Further increase in the amount of SiO_2–I did not show much variation (entry 7). Total 0.1 g of SiO_2–I as catalyst in ethanol as a medium under ultrasonic condition was thus, used to prepare a variety of 3,4-dihydro-(1*H*)-pyrimidine-5-ethyl carboxylates from different substituted araldehydes, urea/thiourea and ethyl acetoacetate (Table 4). As can be seen, SiO_2–I worked as a best catalyst irrespective of nature of functional groups present in the nucleus of the araldehydes, and the reactions went to completion within 30 min. and afforded differentially substituted dihydropyrimidinones/-thiones in high yields.

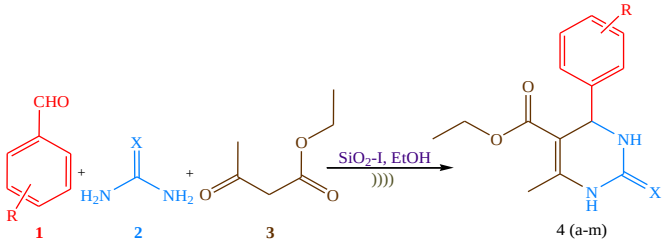
Table 3: Study of catalyst-load on the synthesis of 4a in ethanol.

Entry	Catalyst loading (g)	Yield[a] (%)
1	0.05	57
2	0.06	62
3	0.07	67
4	0.08	75
5	0.09	84
6	0.10	96
7	0.15	96

[a] Isolated yield.

The active methylene present in ethyl acetoacetate (3) may then attack the intermediate imine to produce ureide. This on subsequent cyclization may lead to the corresponding 2, 3-dihydropyrimidinones/-thiones.

Table 4: SiO_2–I catalysed synthesis of 4a–4m.



X= O, S

Entry	Aldehyde	X	Product[a]	Time (min)	Yield[b] (%)	M.P (ºC)
1	3-$CH_3OC_6H_4CHO$	O	4a	30	96	205−207
2	3,4-$CH_3OC_6H_3CHO$	O	4b	30	94	178−180
3	3-$NO_2C_6H_4CHO$	O	4c	30	92	225−227
4	4-ClC_6H_4CHO	O	4d	30	96	212−214
5	4-$CH_3C_6H_4CHO$	O	4e	30	95	210−212
6	4-$NO_2C_6H_3CHO$	O	4f	30	94	208−210
7	2-$NO_2C_6H_3CHO$	O	4g	30	93	218−220
8	2-ClC_6H_4CHO	O	4h	30	94	215−217
9	2,3-ClC_6H_3CHO	O	4i	30	93	244−246
10	2-$CF_3C_6H_4CHO$	O	4j	30	94	202−204
11	C_6H_5CHO	S	4k	30	92	207−208
12	4-ClC_6H_4CHO	S	4l	30	89	192−194
13	3-$NO_2C_6H_4CHO$	S	4m	30	86	206−207

[a]Compared on TLC with the standard samples and characterized by spectral analysis; [b]Isolated yield.

CONCLUSION

In conclusion, a versatile, SiO_2-I catalysed, energy efficient, single-pot three-component, green protocol for the synthesis of dihydropyrimidinones/-thiones in ethanol under ultrasonic condition is developed. Such a method has several advantages including: mild condition, short duration, simple isolation and best yields of products.

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AUTHOR'S CONTRIBUTION

Khanum A: preparation and characterization of the dihydropyrimidin-thiones. **Khan R:** preparation of the dihydropyrimidinones, getting the spectra, characterization of products and drafting of the manuscript. **Mangalavathi:** purification, getting the spectra and characterization of dihydropyrimidinones. **Pasha MA:** compilation of data, preparation and editing of the manuscript, supervision. The final manuscript was read and approved by all authors.

DATA AVAILABILITY

The data supporting the findings of this study are not currently available in a public repository but can be made available upon request to the corresponding author.

CONFLICT OF INTEREST

There is no conflict of interest between the authors for publishing this research work.

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