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ORIGINAL ARTICLE

Biological Activity and Efficient Synthesis of 3, 4-Dihydropyrimidin-2-(1*H*)-one/thione Derivatives

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KEYWORDS

Antimicrobial Activities
Silica Supported Calcium Chloride (SiO_2-$CaCl_2$)
3, 4-Dihydropyrimidin-2-(1*H*)-one/thione
One-pot
Solvent-free conditions

ABSTRACT: The present study aimed to use a method for the synthesis of some 3, 4-dihydropyrimidin-2-(1H) - ones/thiones. The study tried to answer the question whether this reaction can be performed without solvent and with new catalyst or not. To find answer to the question, we described a novel protocol for the efficient synthesis of 3, 4-dihydropyrimidin-2-(1H)-one derivatives using aromatic aldehyde, ethylacetoacetate, and urea/thiourea under solvent-free conditions by using SiO_2-$CaCl_2$ as a catalyst. Using this catalyst has some advantages; it's high yields, usable in mild conditions, available, reusable, ecofriendly, cost effective and environmentally friendly. The structural features of the synthesized compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR. The compounds were screened for antimicrobial activity. The results showed these compounds react against all the tested bacteria. We have demonstrated a novel method for the synthesis of substituted dihydropyrimidinones catalyzed by SiO_2-$CaCl_2$ under solvent-free conditions.

INTRODUCTION

Multicomponent reactions (MCRs) have manifested as a powerful tool for the rapid introduction of molecular diversity. The design and development of MCRs for the generation of heterocycles receives growing interest. The multi-component condensation reactions were an important tool in the organic synthesis as they possess ability of building up the in pharmaceutical molecules. Pharmacies are trying to develop green chemistry reactions. Multicomponents reaction as a powerful tool for the rapid introduction of molecular diversity is evident and developed for the generation of heterocycles receives growing interest [1-5]. Biginelli reaction is one of the most important multi-component reactions for the synthesis of dihydropyrimidinones/thiones. 3,4-dihydropyrimidin-2 (1H) ones / thiones (DHPMs) reported that the activity of many drugs as anti-viral, anti-bacterial, as Multi-drug resistance reversal and anti-

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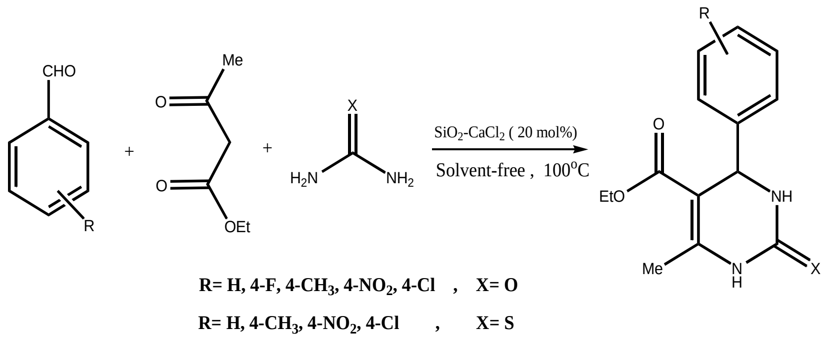
hypertensive effects as calcium channel modulators [6-11].

Biginelli reaction was low yield (20-50) the product [12]. Thus, in recent years several methods to improve the use of $Al(NO_3)_3 \cdot 9H_2O$ [13], $ZrCl_4$ [14], silica sulfuric acid [15], $CuCl_2 \cdot 2H_2O$ [16], $RuCl_3$ [17], Glutamic acid [18], bismuth(III) nitrate[19] different sources have been reported. However, some of these methods are expensive and harmful to the environment; stoichiometrically the amount of catalyst, low yields, incompatibility with other functional groups including product isolation methods is difficult. Therefore, there is still a need for a simple and efficient method for the synthesis of a pot dihydropyrimidinone and thiones under mild conditions. In recent years, green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous chemical materials. A part of our current studies was on the development of new routes in heterocyclic synthesis [18].

Herein, we wanted to use the SiO_2-$CaCl_2$ as a catalyst in a pot, three-component Biginelli reaction in solvent-free conditions between benzaldehyde, ethylacetoacetate and urea or thiourea production costs DHPMs (Figure 1).



R= H, 4-F, 4-CH_3, 4-NO_2, 4-Cl , X= O

R= H, 4-CH_3, 4-NO_2, 4-Cl , X= S

Figure 1. Synthesis of 3, 4-dihydropyrimidinones/thiones derivatives.

MATERIALS AND METHODS

All chemicals were obtained from Merck or Fluka. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Silica gel SILG/UV 254 plates were used for TLC. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^1H NMR and ^{13}C NMR spectra were determined on Bruker 400 DRX AVANCE instrument at 400 and 100 MHz, respectively.

Preparation of the catalyst

Silica gel (15 g, 100–200 mesh) was added to a magnetically stirred solution of $CaCl_2.2H_2O$ (1.35 g, 10 mmol) in distilled water (50 ml) at 40 °C over a 25 min period. The mixture was stirred for a further 40 min allowing for the calcium dichloride to adsorb onto the surface of the silica gel. The water was removed to give a powder which was dried in an oven at 110 °C for 2–3 h.

General procedure for the preparation of 3, 4-dihydropyrimidinones/thiones (5a–i)

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea/thiourea (1.25 mmol) and SiO_2-$CaCl_2$ (20 mol %) was heated with stirring for 30 min in 100°C. After cooling, the reaction mixture was poured into crushed ice with stirring. The crude product was filtered, washed with cold water, dried and recrystallized from 95% ethanol to give pure products (**5a–i**) (85–96). All compounds were fully characterized by M. p., IR, and ^1H NMR and ^{13}C NMR spectroscopy. The structures of all synthesized compounds (**5a–i**) have been depicted in Figure 1.

Spectra Data

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

White crystals, m.p. 203–204 °C. IR (KBr, cm^{-1}): 3267, 1731, and 1642. ^{1}H NMR (CDCl$_3$, δ ppm): 1.11 (t, 3H, *J*= 7.5 Hz, OCH$_2$CH$_3$), 2.25 (s, 3H, CH$_3$), 3.95 (q, 2H, *J*= 7.5 Hz, OCH$_2$), 5.11 (d, 1H, *J*= 2.2 -CH), 7.28 (m, 5H, Ar-H), 7.85 (s, 1H, NH), 9.2 (s, 1H, NH). ^{13}C NMR (CDCl$_3$, δ ppm): 15.18, 20.00, 55.25, 59.95, 103.45, 112.22, 117.24, 127.33, 127.67, 129.23, 133.42, 151.33, 157.38, 166.47.

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

White crystals, m.p. 182–184 °C. IR (KBr, cm^{-1}): 3249, 1745 and 1648. ^{1}H NMR (CDCl$_3$, δ ppm): 1.18 (t, 3H, J = 7.15 Hz, OCH$_2$ CH$_3$), 2.13 (s, 3H, CH$_3$), 4.18 (q, 2H, *J*= 7.11 Hz, OCH$_2$ CH$_3$), 6.15 (d, 1H, *J*= 2.20, -CH), 7.56 (s, 1H, NH), 7.79 (d, 2H, *J*= 8.1, Ar-H), 7.95 (d, 2H, *J*= 8.1, Ar-H), 9.25 (s, 1H, NH). ^{13}C NMR (CDCl$_3$, δ ppm): 17.46, 17.76, 58.48, 62.79, 105.92, 126.78, 135.66, 148.08, 156.37, 158.67, 159.65, 165.33.

5–(Ethoxycarbonyl)–4–(4–methylphenyl)–6–methyl–3, 4–dihydropyrimidin–2(1H)–one (5c):

White crystals, m.p. 216–217 °C. IR (KBr, cm^{-1}): 3244, 1720, 1630 and 1535. ^{1}H NMR (CDCl$_3$, δ ppm): 1.17 (t, 3H, J = 7.00 Hz, OCH$_2$ CH$_3$), 2.12 (s, 3H, CH$_3$), 2.38 (s, 3H, CH$_3$), 4.38 (q, 2H, *J*= 7.00 Hz, OCH$_2$ CH$_3$), 5.84 (d, 1H, *J*= 2.22 -CH), 7.31 (d, 2H, *J*= 8.33, Ar-H), 7.53 (d, 2H, *J* = 8.33, Ar-H), 7.56 (s, 1H, NH), 8.72 (s, 1H, NH). ^{13}C NMR (CDCl$_3$, δ ppm): 14.87, 18.15, 56.25, 58.49, 60.78, 100.32, 118.65, 128.86, 138.28, 146.84, 161.35, 163.47, 183.34.

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

White crystals m.p. 206–207 °C. IR (KBr, cm^{-1}): 3287, 1746, 1635, 1577 and 1345. ^{1}H NMR (CDCl$_3$, δ ppm): 1.21 (t, 3H, J = 7.12 Hz, OCH$_2$ CH$_3$), 2.33 (s, 3H, CH$_3$), 4.32 (q, 2H, *J*= 7.12 Hz, O CH$_2$ CH$_3$), 5.61 (d, 1H, *J* = 2.11, -CH), 7.21-7.53 (m, 4H, Ar-H), 7.88 (s, 1H, NH), 9.42 (s, 1H, NH). ^{13}C NMR (CDCl$_3$, δ ppm): 14.36, 19.78, 59.46, 61.61, 105.77, 126.41, 128.32, 129.51, 133.48, 136.34, 145.67, 162.44, 165.24, 178.11.

5–(Ethoxycarbonyl)–4–(4-chlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one (5e):

White crystals, m.p. 213–214 °C. IR (KBr, cm^{-1}): 3451, 3340, 1731, 1711, 1558 and 1276. ^{1}H NMR (CDCl$_3$, δ ppm): 1.03 (t, *J* =6.95 Hz, 3H, CH$_3$), 2.12 (s, 3H,CH$_3$), 4.18 (q, *J*= 6.95, 4.28 Hz , 2H, CH$_2$O), 5.20 (s, 1H, CH), 6.92–7.28 (m, 4H, Ar-H), 8.43 (s, 1H, NH), 9.23 (s, 1H, NH). ^{13}C NMR (CDCl$_3$, δ ppm): 15.13, 58.62, 61.67, 104.27, 123.15, 128.31, 128.72, 132.12, 132.78, 144.56, 160.11, 164.47, 176.36.

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

Yellow crystals, m.p. 209–211 °C. IR (KBr, cm^{-1}): 3235, 1715, 1645, 1585 and 1525. ^{1}H NMR (CDCl$_3$, δ ppm): 1.12 (t, 3H, J = 7.25 Hz, OCH$_2$ CH$_3$), 2.31 (s, 3H, CH$_3$), 4.18 (q, 2H, *J*= 7.25 Hz, OCH$_2$), 5.23 (d, 1H, *J*= 2.15 -CH), 7.38 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.11 (s, 1H, NH). ^{13}C NMR (CDCl$_3$, δ ppm): 14.66, 18.67, 56.87, 60.76, 100.25, 112.75, 118.39, 125.08, 128.22, 130.14, 133.61, 153.86, 163.42, 181.48.

5–(Ethoxycarbonyl)–4–(4–methylphenyl)–6–methyl–3, 4–dihydropyrimidin–2(1H)–thione (5g):

Yellow crystals, m.p. 192–194 °C. IR (KBr, cm^{-1}): 3236, 1724 and 1575. ^{1}H NMR (CDCl$_3$, δ ppm): 1.13 (t, 3H, *J*= 7.25 Hz, OCH$_2$ CH$_3$), 2.31 (s, 3H, CH$_3$), 2.56 (s, 3H, CH$_3$), 4.36 (q, 2H, *J*= 7.25 Hz, OCH$_2$ CH$_3$), 5.64 (d, 1H, *J*= 2.50 -CH), 7.12 (d, 2H, *J*= 9.10, Ar-H), 7.27 (d, 2H, *J*= 9.10, Ar-H), 7.76 (s, 1H, NH), 8.83 (s, 1H, NH). ^{13}C NMR (CDCl$_3$, δ ppm): 14.65, 17.38, 56.54, 57.43, 61.67, 100.11, 115.46, 128.89, 137.36, 148.12, 158.46, 160.37, 164.65.

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

Yellow crystals, m.p. 206–208 °C. IR (KBr, cm^{-1}): 3252, 1735, 1577, 1525 and 1333. ^1H NMR ($CDCl_3$, δ ppm): 1.16 (t, 3H, J 7.15 Hz, OCH_2 CH_3), 2.17 (s, 3H, CH_3), 3.87 (q, 2H, J= 7.15 Hz, OCH_2 CH_3), 6.48 (d, 1H, J= 2.38, -CH), 7.75 (d, 2H, J= 8.33, Ar-H), 7.79 (d, 2H, J= 8.33, Ar-H), 8.65 (s, 1H, NH), 9.31 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ ppm): 18.25, 19.55, 58.21, 61.27, 101.68, 122.36, 135.86, 137.56, 154.43, 156.57, 159.23, 165.08.

5–(Ethoxycarbonyl)–4–(4–chlorophenyl)–6–methyl–3, 4–dihydropyrimidin–2(1H)–thione (5i):

Yellow crystals, m.p. 191–195°C. IR (KBr, cm^{-1}): 3235, 1725 and 1622. ^1H NMR ($CDCl_3$, δ ppm): 1.08 (t, 3H, J= 7.09 Hz, OCH_2 CH_3), 2.46 (s, 3H, CH_3), 4.15 (q, 2H, J= 7.09 Hz, OCH_2 CH_3), 5.88 (d, 1H, J= 2.27, -CH), 7.23 (d, 2H, J= 9.22, Ar-H), 7.45 (s, 1H, NH), 7.98 (d, 2H, J= 9.22, Ar-H), 8.34 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, δ ppm): 14.52, 18.34, 56.67, 60.57, 105.27, 115.34, 133.57, 143.61, 155.11, 156.12, 159.34, 167.23.

Antimicrobial activity

The compounds **5a-i** were screened by disc diffusion method [21-22], for their antimicrobial activity *Escherichia coli* and *Staphylococcus aureus* and fungi, *Aspergillus niger* and *Helminthosporium oryzae* by comparing with standard bactericide Penicillin and standard fungicide Griseofulvin at three different concentrations (100, 50, 25 ppm). The tubes were incubated aerobically at 37ºC for 18-24h. The experiments were run in triplicates and the average results are included in Table 2.

RESULTS AND DISCUSSION

Nowadays, SiO_2-$CaCl_2$ is often used as a Lewis acid catalyst in the synthesis of organic compounds. The advantages of this catalyst include easy separation, environmentally friendly, reusable, clean, and economical. SiO_2-$CaCl_2$ can be used as a catalyst in the synthesis of organic compounds like SiO_2-$BaCl_2$ [20]. Dihydropyrimidines are associated with wide range of biological activities. We are interested to develop a simple method and cheap for the synthesis of Biginelli reaction DHPMs. Our own study of one pot three components Biginelli condensation using SiO_2-$CaCl_2$ as a catalyst (Figure1), the reaction with benzaldehyde, ethylacetoacetate and urea to afford the product DHPMs as a model reaction (**5a**) has begun. 4-Dihydropyrimidin-2-(1*H*) -one/thione derivatives of aldehydes, 1,3-dicarbonyl compounds with SiO_2-$CaCl_2$ have been synthesized with high yields (Table 1).

Table 1. SiO_2-$CaCl_2$ catalyzed synthesis of 3, 4-dihydropyrimidinones/thiones derivatives.

Entry	Compound	Substitution	X	M.p. (ºC)	Yield (%)
1	5a	H	O	203–204	94
2	5b	4-F	O	182-184	85
3	5c	4–Methyl	O	216–217	96
4	5d	4-Nitro	O	206–207	87
5	5e	4-Cl	O	213–214	90
6	5f	H	S	209–211	87
7	5g	4–Methyl	S	192–194	91
8	5h	4-Nitro	S	206–208	86
9	5i	4-Cl	S	191–195	88

Reaction conditions: 1 mmol aldehyde, 1 mmol ethyl acetoacetate, 1.25 mmol urea/thiourea and SiO_2-$CaCl_2$ (20 mol%) was heated with stirring for 30 min.

The catalyst was easily recovered by simple filtration after dilution of the reaction mixture with ethyl acetate and was reused after being vacuum dried. SiO_2-$CaCl_2$ was reused for four runs without significant loss of activity (Run 1: 92%; Run 2: 89%; Run 3: 87%; Run 4: 85%). The mechanism of formation of dihydropyrimidines using SiO_2-$CaCl_2$ as a catalyst is shown in Figure 2.

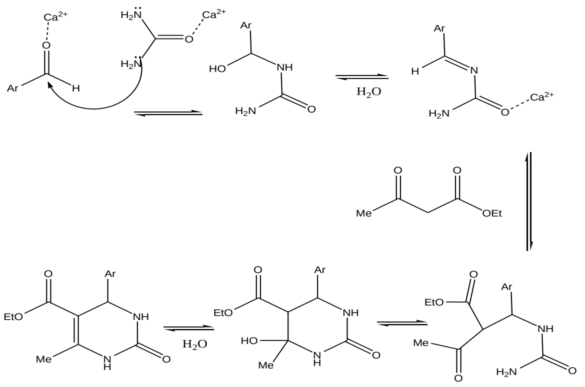


Figure 2. Mechanism of the synthesis of 3, 4-Dihydropyrimidin-2-(*1H*)-one catalyzed by SiO_2-$CaCl_2$

Using of heterogeneous solid catalysts has received great attention for organic synthesis in different areas. Heterogeneous solid are advantageous because they can be easily recovered from the reaction mixture by simple filtration and can be reused. In this research calcium ions are adsorbed on the sio$_2$ surface and as Lewis acid acts better in condition. Adsorption efficiency causes increases reactivity and high yields.

All the titled compounds (**a-i**) were screened for their antimicrobial activity, in this sequence first screened for the anti-bacterial activity against the growth of *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram –ve) at different concentrations (100, 50, 25 ppm) by disk diffusion method. All the compounds were good active against both the bacteria when compared to the reference compound Penicillin. Then they subjected for the antimicrobial activity evaluation against the growth of *Aspergillus Niger* and *Helminthosporium oryzae* at various concentrations (100, 50, 25 ppm) with Griseofulvin as the standard reference compound. The results of Zone of inhibition of title compounds were presented in Table 2. Majority of the title compounds showed good antifungal activity against both the fungi, especially **a**, **c** and **i** compounds. Due to the introduction of 5–(Ethoxycarbonyl)– 4–phenyl–6–methyl–3,4–dihydropyrimidin–2(1H)–one (**5a**) results activity in the range of 25, 50 and 100 μ g/ml against all the tested organisms and showed increase in activity against 100 μ g/ml the tested organisms.

Due to the introduction of 5–(Ethoxycarbonyl)–4–(4–methylphenyl)–6–methyl–3, 4–dihydropyrimidin–2(1H)–one (**5c**) with have methyl group at the *para* position of the aryl at C-4 position and oxygen atom on dihydropyrimidine ring showed increase in activity against 100 μ g/ml the tested organisms.

Due to the introduction of 5–(Ethoxycarbonyl)–4–(4–chlorophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**5i**) with have chloro group at the *para* position of the aryl at C-4 position and sulfur atom on dihydropyrimidine ring showed increase in activity against 100 μ g/ml the tested organisms.These observations may promote a development of our research in this field. Further development of this group of compounds may lead to compounds with better pharmacological profile than standard drugs and serve as templates for the construction of better drugs to combat bacterial and microbial infection.

Table 2. Biological Activity of the compounds **a-i** (µg/ mL)

Compound	**Zone of inhibition (%)**											
	Antibacterial activity						**Antimicrobial activity**					
	Escherichia coli			***Staphylococcus aureus***			***Aspergillus niger***			***Helminthosporium oryzae***		
	100	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**
5a	23	11	8	23	11	6	21	14	6	20	11	6
5b	21	10	6	20	10	6	21	10	7	19	11	5
5c	23	13	7	23	12	8	20	12	7	20	10	5
5d	22	10	6	21	10	5	19	11	6	16	9	6
5e	22	11	5	22	10	5	20	11	4	15	9	5
5f	21	10	6	22	11	6	20	12	5	14	10	5
5g	21	11	7	21	12	5	20	12	6	19	10	7
5h	22	10	5	22	12	6	19	9	5	18	11	6
5i	24	14	8	23	12	7	21	14	8	20	15	8
Penicillin Griseofulvin	20	12	8	20	12	8	20	10	5	20	10	5

CONCLUSION

We have demonstrated a novel method for the synthesis of substituted dihydropyrimidinones catalyzed by SiO_2-$CaCl_2$ under solvent-free conditions. DHPMs were obtained in moderate to high overall yields. This method has some advantages; its high yields, available, one-pot, experimentally simple under solvent-free conditions and easy to separate with reuse of the catalyst. The majority of the compounds (**a-i**) exhibited significant activity against selective bacteria and fungi and the zone of inhibition of these title compounds was almost comparable to that of the standard drugs. Thus some of compounds with comparable antimicrobial potency to the presently used commercial bactericides have been discovered.

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