I.A.U. Karaj Branch

Journal of Applied Chemical Research, 9, 1, 95-101 (2015)

Journal of Applied Chemical Research
www.jacr.kiau.ac.ir

SiO_2-$BaCl_2$ as a Highly Efficient and Reusable Heterogeneous Catalyst for the One-pot Synthesis of 3,4-dihydropyrimidin-2-(1H)- one/thione Derivatives Under Solvent-free Conditions

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(Received 14 Aug. 2014; Final version received 21 Oct. 2014)

Abstract

An efficient protocol for the synthesis of 3,4-dihydropyrimidin-2-(1H)-one/thione derivatives via multi-component coupling reaction of aromatic aldehydes, β-ketoester and urea or thiourea under solvent-free conditions using Silica Supported Barium Chloride as a catalyst is described. All prepared compounds with melting points, IR, ^{1}H NMRand ^{13}C NMR were identified. High yields, mild conditions, easy availability and reusability were some advantages of this catalyst.

Keywords: *3,4-Dihydropyrimidin-2-(1H)-ones/thiones, Multi-component reactions, Silica Supported Barium Chloride (*SiO_2-$BaCl_2$*), Solvent-free conditions.*

Introduction

The multi-component condensation reactions are an important tool in the organic synthesis as they possess ability of building up the pharmaceutical molecules. Pharmacies are trying to develop green chemistry reactions; Solvent-free synthesis of complex organic structures as drugs is the dream of every pharmacy. Multi-component reaction as a powerful tool for develops for the synthesis of heterocyclic compounds 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 and anti-hypertensive effects as calcium channel

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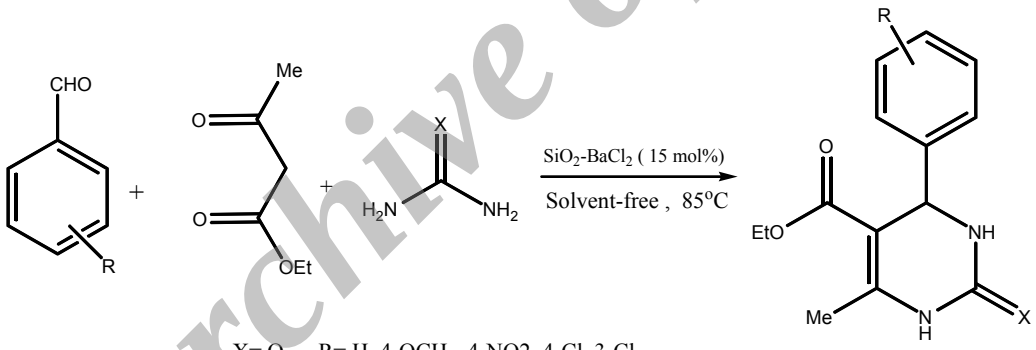
modulators [6-9]and as Multi-drug resistance reversal [10-11].

Biginelli reaction was low yield (20-50) the product [12]. Thus, in recent years several methods were stablished to improve the use of $Al(NO_3)_3.9H_2O$ [13] , zeolites [14], $BF_3.OEt_2$ [15], $SbCl_3$ [16] , Natural Catalyst [17], Glutamic acid [18] and different ways 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, eco-friendly industrial application and use of green and reusable catalyst has been studied. Thus, green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous chemical materials, as part of our current studies on the development of new routes in heterocyclic synthesis [18].

Herein, we want to use the SiO_2-$BaCl_2$ as a catalyst in a pot, three-component Biginelli reaction in solvent-free conditions between benzaldehyde, ethylacetoacetate and urea or thiourea production costs DHPMs (Scheme 1).



X= O , R= H, 4-OCH_3, 4-NO2, 4-Cl, 3-Cl

X= S, R= H, 3-NO2, 4-OCH_3, 2-NO2, 3-OCH_3

Scheme 1. synthesis of 3,4-dihydropyrimidinones/thiones derivatives.

Experimental

All chemicals were obtained from Merck or Fluka. Melting points were measured on an Electrothermal 9100 apparatus. 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.

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

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.25 mmol) and SiO_2-$BaCl_2$ (15 mol%) was heated with stirring for 45 min in 85◦C. After cooling, the reaction mixture was poured into

crushed ice with stirring. The crude product was filtered and washed with cold water, dry them, recrystallized from 95% ethanol to give pure products (**5a–j**) (82–94). All compounds were fully characterized by m.p., IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The structures of all synthesized compounds (**5a–j**) have been depicted in Scheme 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}): 3248, 1729, 1636. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.12 (t, 3H, *J*= 7.2 Hz, OCH_2CH_3), 2.28 (s, 3H, CH3), 3.90 (q, 2H, *J*= 7.2 Hz, OCH_2), 5.13 (d, 1H, *J*= 2.2 -CH), 7.26 (m, 5H, Ar-H), 7.71 (s, 1H, NH), 9.32 (s, ^{1}H, NH). ^{13}C NMR (100 MHz, $CDCl_3$,/ppm): 15.1, 19.0, 55.2, 59.9, 101.0, 112.2, 114.1, 126.3, 126.9, 128.4, 132.1, 149.1, 156.7, 164.1.

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

White crystals, m.p. 202–203 °C. IR (KBr, cm^{-1}): 3246, 1734, 1632. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.15 (t, 3H, *J*= 7.15 Hz, OCH_2 CH_3), 2.45 (s, 3H, CH_3), 3.94 (s, 3H, -O CH_3), 4.14 (q, 2H, *J*= 7.15 Hz, OCH_2 CH_3), 5.58 (d, 1H, *J*= 2.50 -CH), 7.08 (d, 2H, *J*= 9.10, Ar-H), 7.25 (d, 2H, *J*= 9.10, Ar-H), 7.74 (s, 1H, NH), 9.45(s, 1H, NH). ^{13}C NMR (100 MHz,$CDCl_3$,δ/ppm): 14.5, 18.2, 56.1, 56.4, 61.1, 100.2, 116.8, 129.3, 138.5, 147.9, 158.0, 159.5, 165.4.

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

White crystals, m.p. 212–214 °C. IR (KBr, cm^{-1}): 3260, 1740, 1635, 1580, 1545. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.15 (t, 3H, *J* = 7.12 Hz, OCH_2 CH_3), 2.33 (s, 3H, CH_3), 4.22 (q, 2H, *J*= 7.12 Hz, O CH_2 CH_3), 5.75 (d, 1H, *J* = 2.11, -CH), 7.24-7.46 (m, 4H, Ar-H), 7.88 (s, 1H, NH), 9.45 (s, 1H, NH). ^{13}C NMR (100 MHz,CDCl*J*,δ/ppm): 14.66, 19.12, 58.12, 60.68, 101.71, 127.45, 128.82, 129.55, 132.39, 135.28, 145.83, 161.02, 165.58, 180.29.

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

White crystals, m.p. 215–216 °C. IR (KBr, cm^{-1}): 3338, 3289, 2996, 1685, ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.14 (t, *J* =7.4 Hz, 3H, CH_3), 1.98 (s, 3 H, CH_3), 4.15 (q, *J*= 7.4, 4.55 Hz, 2H, CH_2O), 5.15 (s, 1H, CH), 6.8–7.38 (m, 4H, Ar-H): 7.22 (s, 1H, NH), 9.35 (s, 1H, NH). ^{13}C NMR (100 MHz,$CDCl_3$,δ/ppm): 18.37, 56.36, 60.44, 101.48, 123.21, 125.72, 126.52, 130.26, 130.83, 142.77, 159.61, 161.12, 175.87.

5–(Ethoxycarbonyl)–4–(3-chlorophenyl)–6–

*methyl–3,4–dihydropyrimidin–2(1H)–one (**5e**):*

White crystals, m.p. 192–193 °C. IR (KBr, cm^{-1}): 3235, 1725, 1630. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.11 (t, 3H, *J* = 7.16 Hz, OCH_2 CH_3), 2.30 (s, 3H, CH_3), 4.01 (q, 2H, J= 7.16 Hz, OCH_2 CH_3), 5.96 (d, 1H, *J*= 2.30, -CH), 7.22-7.55 (m, 4H, Ar-H), 7.66 (s, 1H, NH), 9.18 (s, 1H, NH). ^{13}C NMR (100 MHz,$CDCl_3$,δ/ppm): 14.65, 19.04, 56.33, 60.67, 100.89, 125.31, 128.35, 128.98, 129.83, 136.67, 143.64, 154.78, 159.57, 165.25.

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

Yellow crystals, m.p. 208–210 °C. IR (KBr, cm^{-1}): 3235, 1715, 1645, 1585, 1525. ^{1}H NMR (400 MHz,$CDCl_3$,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). 13C NMR (100 MHz,CDCl3,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–(3-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**5g**):*

Yellow crystals, m.p. 206–208°C. IR (KBr, cm^{-1}): 3251, 1722, 1631. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.14 (t, 3H, *J* 7.02 Hz, OCH_2 CH_3), 2.39 (s, 3H, CH_3), 4.16 (q, 2H, *J*= 7.02 Hz, OCH_2 CH_3), 6.09 (d, 1H, *J*= 2.33, -CH), 7.78 (d, 2H, *J*= 8.88, Ar-H), 7.89 (s, 1H, NH), 8.25 (d, 2H, *J*= 8.88, Ar-H), 9.12 (s, 1H, NH). ^{13}C NMR (100 MHz,$CDCl_3$,δ/ppm): 15.02, 19.11, 56.31, 60.75, 100.90, 120.18, 130.77, 139.55, 154.76, 155.79, 158.95, 166.44.

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

Yellow crystals, m.p. 156–158 °C. IR (KBr, cm^{-1}): 3433, 3295, 2967, 1709, 1613, 1300, 1291. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.22 (t, *J* =7.6 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.86 (s, 3H, Ar-OCH_3), 4.14 (q, *J*= 7.6, 4.1 Hz, 2H, CH_2O), 5.18 (s, 1H, CH), 6.8 (s, 1H, NH), 6.82–7.84 (m, 4H, Ar-H), 9.42 (s, 1H, NH). ^{13}C NMR (100 MHz,$CDCl_3$,δ/ppm): 15.43, 19.62, 56.35, 56.78, 61.44, 100.02, 112.73, 126.11, 135.56, 147.67, 161.48, 164.29, 179.37.

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

Yellow crystals, m.p. 190–192°C. IR (KBr, cm^{-1}): 3238, 1725, 1622, 1572, 1355, 1310. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.16 (t, 3H, *J*= 7.09 Hz, OCH_2 CH_3), 2.44 (s, 3H, CH_3), 4.12 (q, 2H, *J*= 7.09 Hz, OCH_2 CH_3), 5.79 (d, 1H, *J*= 2.27, -CH), 7.24 (d, 2H, *J*= 9.22, Ar-H), 7.79 (s, 1H, NH), 7.84 (d, 2H, *J*= 9.22, Ar-H), 9.20 (s, 1H, NH). ^{13}C NMR (100

MHz,$CDCl_3$,δ/ppm): 14.58, 18.72, 56.46, 61.32, 101.92, 119.77, 131.59, 143.57, 154.26, 155.67, 159.98, 165.65.

*5–(Ethoxycarbonyl)–4–(3–methoxyphenyl) –6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**5j**):*

Yellow crystals, m.p. 160–162°C. IR (KBr, cm^{-1}): 3238, 1725, 1618, 1570, 1566. ^{1}H NMR (400 MHz,$CDCl_3$,δ/ppm): 1.18 (t, 3H, *J* = 7.14 Hz, OCH_2 CH_3), 2.44 (s, 3H, CH_3), 4.23 (s, 3H, -O CH_3), 4.38 (q, 2H, *J*= 7.14 Hz, OCH_2 CH_3), 5.84 (d, 1H, *J*= 2.22 -CH), 7.31 (d, 2H, *J*= 8.33, Ar-H), 7.42 (d, 2H, *J* = 8.33, Ar-H), 7.56 (s, 1H, NH), 9.21 (s, 1H, NH). ^{13}C NMR (100 MHz,$CDCl_3$,δ/ppm): 14.87, 19.15, 56.25, 56.49, 60.78, 100.32, 115.65, 128.86, 138.28, 145.84, 160.35, 163.47, 181.66.

Results and Discussion

SiO_2-$BaCl_2$ can be used as a catalyst in the synthesis of organic compounds [19]. The features of this catalyst could be high demand, easy separation, environmentally, reusability, cleanness and affordability. Dihydropyrimidines shows a wide range of biological activities. We are interested to develop a simple method for the synthesis of Biginelli reaction DHPMs. Our own study of one pot three components Biginelli condensation using SiO_2-$BaCl_2$ as a catalyst (Scheme1), the reaction with benzaldehyde, ethylacetoacetate and urea to afford the product DHPMs as a model reaction (5a) has begun.

We were successful, 4-Dihydropyrimidin-2 (1H) -one/thione derivatives of aldehydes, 1,3-dicarbonyl compounds with SiO_2-$BaCl_2$ have been synthesized with high yields (Table 1).Using SiO_2-$BaCl_2$ as the catalyst, the increased yield of reaction dramatically and easily removed and reused.

Table 1. SiO_2-$BaCl_2$catalyzed synthesis of 3,4-dihydropyrimidinones/thiones derivatives.

Entry	Compound	Substitution	X	M.p. (°C)	Yield (%)
1	5a	H	O	203	93
2	5b	4–Methoxy	O	202	91
3	5c	4-Nitro	O	212	94
4	5d	4-Chloro	O	215	92
5	5e	3-Chloro	O	192	91
7	5f	H	S	208	88
8	5g	3-Nitro	S	206	87
9	5h	4–Methoxy	S	156	83
10	5i	2–Nitro	S	190	82
11	5j	3–Methoxy	S	160	87

Reaction conditions: 1 mmol aldehyde, 1 mmol ethyl acetoacetate, 1.25 mmol urea/thiourea and SiO_2-$BaCl_2$ (15 mol%) were refluxed with stirring for 45 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-$BaCl_2$ was reused for four runs without significant loss of activity (Run 1: 90%; Run 2: 88%; Run 3: 87%; Run 4: 84%).

In order to standardize the reaction conditions for the condensation reaction, it was decided to synthesize 3,4-dihydropyrimidin-2(1H)-one (5a) from benzaldehyde, urea or thiourea, and ethylacetoacetate using of SiO_2-$BaCl_2$, and compared to other reported methods we found that the reaction is fast. The results were compared to the reported methods, and according to Table 2 the present method was more efficient.

Table 2. SiO_2-$BaCl_2$ in comparison with some catalyst for synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one.

Entry	Conditions	Time (h:min)	Yield (%)	Reference
1	$Al(NO_3)_3 \cdot 9H_2O$/ SF, 80°C	0:15	98	[13]
2	Sulfated tungstate/ SF, 80°C	1:00	92	[13]
3	PPA-SiO_2/CH_3CN, reflux	1:00	88	[13]
4	$FeCl_3$ immobilized in Al-MCM 41/CH_3CN, reflux	4:00	85	[13]
5	[Hmim]HSO_4/solvent-free, 110°C	0:20	92	[13]
6	Alpha-zirconium sulfophenylphosphonate/SF, 80°C	18:0	89	[13]
7	1,3-Dichloro-5,5-dimethylhydantoin/CH_3CN, reflux	4:00	89	[13]
8	$Bi(NO_3)_3$/SF	1:30	92	[20]
9	SiO_2-$BaCl_2$/ SF, 85°C	0:45	93	In this research

Conclusion

In is concluded that SiO_2-$BaCl_2$ as a catalyst for the synthesis dihydropyrimidinones/thiones replaced under solvent-free conditions. The advantages of this method is that the method is reusable, one-pot, multi-component, with simple separation ,its reaction time is short, high yields, under solvent-free conditions with reused catalyst.

Acknowledgments

We gratefully acknowledge the financial support from the Research Council of Islamic Azad University, Tonekabon Branch.

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