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One-pot synthesis of fused 3,4-dihydropyrimidin-2(1*H*)-ones and thiones using a novel ionic liquid as an efficient and reusable catalyst: improved protocol conditions for the Biginelli-like scaffolds

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Abstract

A novel ionic liquid with multi-SO_3H groups has been found to be an efficient acid catalyst for the one-pot three-component synthesis of fused 3,4-dihydropyrimidin-2(1*H*)-ones and thiones under solvent free conditions. Good yields, short reaction times, straight forward workup, reusability of the catalyst and green conditions are the most obvious advantages of this methodology.

Keywords: fused 3,4-dihydropyrimidin-2(1*H*)-ones; novel ionic liquid with multi-SO_3H groups; one-pot synthesis; solvent free conditions; thiones.

Introduction

3,4-Dihydropyrimidin-2(1*H*)-one derivatives have received considerable interest from the pharmaceutical industry due to their wide range of interesting biological and therapeutic properties such as calcium channel blockers, antihypertensive agents, α_{1a}-antagonists and neuropeptide Y(NPY) antagonists (Atwal et al., 1991). They are also known to possess antiallergic, antibacterial, antifungal, antitumor, anti-inflammatory, antiviral and anticancer activities (Kamaljit et al., 2011). The first synthetic method for the preparation of 3,4-dihydropyrimidine-2(1*H*)-ones (DHPMs) was reported by Biginelli. It involves a one-pot, three-component condensation of β-dicarbonyl compounds, aldehydes and urea or thiourea in ethanol under strongly acidic conditions. This reaction often requires harsh conditions, long reaction times and affords low yields in the case of substituted aromatic and aliphatic aldehydes (Atwal et al., 1989).

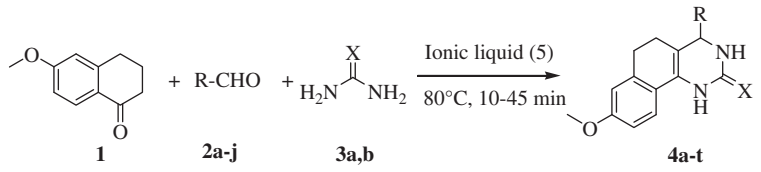
In view of the pharmaceutical importance of these compounds, many improved methods have been developed such as microwave irradiation (Bimal et al., 2007), ultrasound irradiation (Ji-Tai et al., 2003), the use of Lewis and protic acid promoters such as lanthanide triflate (Ma et al., 2000), KSF montmorillonite (Haixia et al., 2000), $SnCl_2 \cdot 2H_2O$ (Dennis et al., 2004), PPh_3 (Debache et al., 2008), $Mn(OAc)_3 \cdot 2H_2O$ (Kumar et al., 2001), Na_2SeO_4 (Rahim et al., 2009), silica sulfuric acid (Salehi et al., 2003), polyphosphate ester (Fabio and Kappe, 2001), indion-130 (Akshay et al., 2009) and HCOOH (Cheng and Qi, 2007). Peng and Deng (2001) have reported the synthesis of Biginelli-like scaffolds using expensive ionic liquids. Many of these reported methods suffer from drawbacks such as low yield, long reaction time, tedious workup, harsh reaction conditions and use of a large quantity of expensive reagents. To avoid these limitations, we have developed an efficient and environment-friendly one-pot synthesis of fused 3,4-dihydropyrimidin-2(1*H*)-ones and thiones under solvent free conditions using an inexpensive novel ionic liquid.

Results and discussion

In continuation of our interest on Lewis acid applications for the Biginelli reaction (Naveen Kumar et al., 2005), herein we report a simple, mild, efficient and eco-friendly procedure for the synthesis of fused 3,4-dihydropyrimidin-2(1*H*)-ones **4a–j** and thiones **4k–t** by one-pot three-component condensation of 6-methoxy-1-tetralone (**1**), aromatic aldehydes **2a–j** and urea (**3a**) or thiourea (**3b**) under solvent free conditions using Brønsted acidic ionic liquid (4-sulfobutyl)-tris(4-sulfophenyl)phosphonium hydrogen sulfate (**5**) with excellent yields (Scheme 1). This ionic liquid is inexpensive and can be easily prepared in the laboratory from the readily available starting materials (Scheme 2) (Bao et al., 2010).

First, an experiment was conducted using 6-methoxy-1-tetralone, benzaldehyde and urea as a model reaction. In the absence of ionic liquid **5**, the yield of the desired product **4a** was very low, and many side products were observed. Obviously, the ionic liquid **5** is an important component of the reaction.

The reactions conducted in the presence of the novel ionic liquid **5** and various acid catalysts (cellulose sulfuric acid, silica sulfuric acid, sulfuric acid and hydrochloric acid) under solvent free conditions at 80°C were examined (Table 1). It was found that the use of ionic liquid (**5**) provides a shorter reaction time and higher yield. The effects of temperature and amount of catalyst **5** on the reaction time and yield of the product were also examined (Table 2). The best results were obtained using 0.05 g (7.14 mol%, 0.0678 mmol) of **5** at 80°C (entry 6).



2a: R = C_6H_5
2b: R = 2-Cl-C_6H_4
2c: R = 4-Cl-C_6H_4
2d:R = 4-OCH_3-C_6H_4
2e: R = 3,4-$(OCH_3)_2$-C_6H_3
2f: R = 4-CH_3-C_6H_4
2g: R = 4-OH-C_6H_4
2h: R = 3-NO_2-C_6H_4
2i: R = 4-$N(CH_3)_2$-C_6H_4
2j: R = 4-OH-3-OCH_3-C_6H_3
3a:X = O
3b:X = S

4a: R = C_6H_5, X = O;
4b: R = 2-Cl-C_6H_4, X = O;
4c: R = 4-Cl-C_6H_4, X = O;
4d: R = 4-OCH_3-C_6H_4, X = O;
4e: R = 3,4-$(OCH_3)_2$-C_6H_3, X = O;
4f: R = 4-CH_3-C_6H_4, X = O;
4g: R = 4-OH-C_6H_4, X = O;
4h: R = 3-NO_2-C_6H_4, X = O;
4i: R = 4-$N(CH_3)_2$-C_6H_4, X = O;
4j: R = 4-OH-3-OCH_3-C_6H_3, X = O
4k: R = C_6H_5, X = S;
4l: R = 2-Cl-C_6H_4, X = S;
4m: R = 4-Cl-C_6H_4, X = S;
4n: R = 4-OCH_3-C_6H_4, X = S;
4o: R = 3,4-$(OCH_3)_2$-C_6H_3, X = S;
4p: R = 4-CH_3-C_6H_4, X = S;
4q: R = 4-OH-C_6H_4, X = S;
4r: R = 3-NO_2-C_6H_4, X = S;
4s: R = 4-$N(CH_3)_2$-C_6H_4, X = S;
4t: R = 4-OH-3-OCH_3-C_6H_3, X = S.

Scheme 1 Synthesis of fused 3,4-dihydropyrimidin-2(1*H*)-ones and thiones.

These conditions were used to synthesize various fused-ring 3,4-dihydropyrimidin-2(1*H*)-ones **4a–j** and thiones **4k–t** with excellent yields. After completion of the reaction, as indicated by thin layer chromatography (TLC), the catalyst **5** was recovered, washed with acetone dried and reused for subsequent reactions without significant loss in activity. For example, the reaction of 6-methoxy-1-tetralone, benzaldehyde and urea gave the corresponding 3,4-dihydropyrimidin-2(1*H*)-one **4a** in 96%, 95%, 95%, 93% and 92% yields over five cycles.

Conclusion

In conclusion, a novel ionic liquid (**5**) was shown to be an efficient catalyst for the synthesis of fused 3,4-dihydropyrimidin-2(1*H*)-ones and thiones under solvent free conditions. The protocol offers several advantages such as catalyst reusability, high yield of product, short reaction time, simple work-up procedure and easy isolation. We believe this methodology is superior to existing methodologies for the synthesis of fused 3,4-dihydropyrimidin-2(1*H*)-ones and thiones.

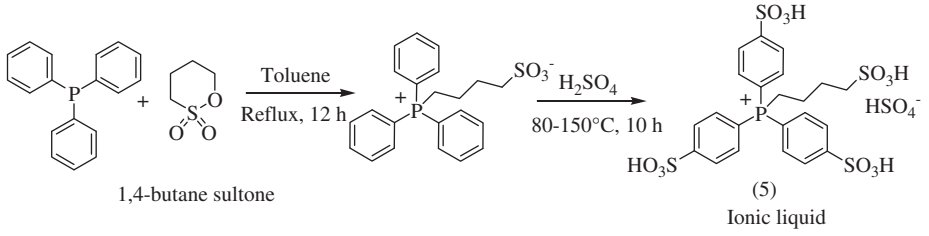
Experimental section

Melting points were determined in open capillaries and are uncorrected. The progress of the reaction was monitored by TLC and visualized with UV light and iodine vapors. IR spectra were recorded on Thermo Nicolet Nexus 670 spectrometer using KBr pellets. The C, H and N analysis of the compounds were done on a Carlo Erba modal EA1108; ^{1}H NMR and ^{13}C NMR spectra were obtained at 300 MHz and 75 MHz, respectively, on a Brucker spectrometer using TMS as an internal standard. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

General procedure for the synthesis of 4a–t

Ionic liquid **5** (0.05 g, 7.14 mol%, 0.068 mmol) was added to a mixture of 6-methoxy-1-tetralone (1 mmol), aromatic aldehyde (1 mmol) and urea or thiourea (1.2 mmol). The mixture was heated at 80°C for a period of time indicated below. After completion of the reaction as indicated by TLC, 5 mL of water was added and the mixture was stirred at room temperature for an additional 5 min. The precipitated product was filtered, washed with water, dried and crystallized from ethanol. The recovered catalyst **5** was washed with acetone dried and reused for subsequent reactions.

3,4,5,6-Tetrahydro-8-methoxy-4-phenylbenzo[*h*]quinazolin-2(1*H*)-one (4a) This compound was obtained from **1**, **2a** and **3a** as a pale yellow solid within 20 min; yield 0.29 g (95%); mp 255–258°C; IR: 3332, 3232, 3120, 2955, 2834, 1681, 1235 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 1H), 2.08 (m, 1H), 2.71 (m, 2H), 3.80 (s, 3H), 5.07 (s, 1H), 6.50 (s, 1H), 6.77 (m, 2H), 7.11 (d, *J*=6.3 Hz, 2H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): 158.8, 153.2, 145.1, 137.5, 128.6, 127.8, 127.4, 127.1, 122.5, 121.4, 113.6, 110.9, 105.0, 58.4, 55.1, 28.0, 23.5; MS: *m/z* 306 (M^+). Anal. calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.21; H, 6.13; N, 9.32.



Scheme 2 Synthesis of (4-sulfobutyl)-tris(4-sulfophenyl)phosphonium hydrogen sulfate (**5**).

Table 1 Effect of catalysts on the yield of 3,4,5,6-tetrahydro-8-methoxy-4-phenylbenzo[*h*]quinazolin-2(1*H*)-one (**4a**).

Entry	Catalyst	Time	Yield[a] (%)
1	Ionic liquid **5**	20 min	96
2	Cellulose sulfuric acid	3 h	88
3	Silica sulfuric acid	3 h	85
4	Sulfuric acid	4 h	54
5	Hydrochloric acid	4 h	42

[a]Isolated yield.

4-(2-Chlorophenyl)-3,4,5,6-tetrahydro-8-methoxybenzo[*h*]quinazolin-2(1*H*)-one (4b) This compound was obtained from **1**, **2b** and **3a** as a white solid within 20 min; yield 0.31 g (91%); mp 297–299°C; IR: 3392, 3235, 3110, 2954, 2825, 1673, 1217, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.98 (m, 1H), 2.20 (m, 1H), 2.77 (m, 2H), 3.82 (s, 3H), 5.02 (s, 1H), 6.49 (d, *J* = 6.3 Hz, 2H), 6.78 (m, 2H), 7.11 (d, *J* = 6.9 Hz, 2H), 7.43 (m, 2H) 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$): 158.6, 153.0, 144.7, 137.4, 132.4, 128.7, 128.5, 127.8, 127.6, 126.7, 122.6, 121.5, 113.8, 110.9, 104.8, 55.0, 50.3, 27.9, 23.7; MS: *m/z* 341 (M^++1). Anal. calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.67; H, 5.26; N, 8.41.

4-(4-Chlorophenyl)-3,4,5,6-tetrahydro-8-methoxybenzo[*h*]quinazolin-2(1*H*)-one (4c) This compound was obtained from **1**, **2c** and **3a** as a white solid within 10 min; yield 0.33 g (97%); mp 260–263°C; IR: 3365, 3220, 3115, 2941, 2828, 1692, 1247, 713 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.73 (m, 1H), 2.09 (m, 1H), 2.60 (m, 2H), 3.73 (s, 3H), 4.92 (s, 1H), 6.75 (s, 2H), 7.24 (s, 1H), 7.33 (d, *J* = 6.3 Hz, 2H), 7.42 (d, *J* = 6.3 Hz, 2H), 7.50 (d, *J* = 6.9 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR (DMSO-d_6): 158.7, 153.1, 143.2, 137.4, 131.9, 128.7, 128.5, 127.7, 122.5, 121.5, 113.7, 110.8, 104.9, 58.3, 55.0, 27.9, 23.3; MS: *m/z* 341 (M^++1). Anal. calcd for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.62; H, 5.27; N, 8.39.

3,4,5,6-Tetrahydro-8-methoxy-4-(4-methoxyphenyl)benzo[*h*]quinazolin-2(1*H*)-one (4d) This compound was obtained from **1**, **2d** and **3a** as a yellow solid within 45 min; yield 0.31 g (92%); mp 199–201°C; IR: 3372, 3251, 3112, 2941, 2825, 1675, 1235, 1192 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.74 (m, 1H), 2.06 (m, 1H), 2.71 (m, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 5.05 (s, 1H), 6.76 (m, 5H), 7.15 (d, *J* = 6.3 Hz, 2H), 7.67 (s, 1H), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$): 158.9, 158.3, 153.1, 138.4, 137.4, 128.1, 127.7, 122.3, 121.9, 114.1, 113.9, 111.6, 105.3, 58.6, 55.4, 55.2, 27.2, 23.8; MS: *m/z* 336 (M^+). Anal. calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.19; H, 6.13; N, 8.37.

Table 2 The effects of the amount of ionic liquid **5** and temperature on the yield of 3,4,5,6-tetrahydro-8-methoxy-4-phenylbenzo[*h*]quinazolin-2(1*H*)-one (**4a**).

Entry	Amount of catalyst (g/mol%)	Temp. (°C)	Time	Yield[a] (%)
1	–	23	12 h	–
2	–	80	6 h	Trace
3	0.04/5.7	23	6 h	Trace
4	0.04/5.7	80	1 h	88
5	0.04/5.7	120	30 min	88
6	**0.05/7.14**	**80**	**20 min**	**96**
7	0.05/7.14	120	20 min	95
8	0.06/8.57	80	20 min	96
9	0.06/8.57	120	20 min	95

[a]Isolated yield. Bold indicates the optimization conditions of the reaction.

3,4,5,6-Tetrahydro-8-methoxy-4-(3,4-dimethoxyphenyl)benzo[*h*]quinazolin-2(1*H*)-one (4e) This compound was obtained from **1**, **2e** and **3a** as a white solid within 45 min; yield 0.34 g (93%); mp 148–150°C; IR: 3365, 3228, 3117, 2941, 2820, 1698, 1220, 1185 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72 (m, 1H), 2.08 (m, 1H), 2.68 (m, 2H), 3.75 (s, 3H), 3.88 (s, 6H), 4.98 (s, 1H), 6.78 (m, 5H), 7.16 (d, *J* = 6.3 Hz, 1H), 7.68 (s, 1H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$): 159.6, 154.5, 149.6, 147.4, 138.4, 138.4, 127.9, 124.1, 121.5, 120.4, 115.1, 114.7, 112.1, 111.1, 105.7, 59.5, 55.3, 54.9, 27.1, 23.6; MS: *m/z* 366 (M^+). Anal. calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.71; H, 6.24; N, 7.44.

3,4,5,6-Tetrahydro-8-methoxy-4-*p*-tolylbenzo[*h*]quinazolin-2(1*H*)-one (4f) This compound was obtained from **1**, **2f** and **3a** as a yellow solid within 15 min; yield 0.28 g (87%); mp 258–260°C; IR: 3390, 3218, 3125, 2915, 2834, 1670, 1212 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.94 (m, 1H), 2.08 (m, 1H), 2.42 (s, 3H), 2.69 (m, 2H), 3.80 (s, 3H), 5.02 (s, 1H), 6.64 (m, 4H), 7.10 (d, *J* = 6.6 Hz, 2H), 7.35 (m, 2H) 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$): 159.9, 154.2, 142.1, 137.4, 136.0, 128.9, 127.7, 127.0, 122.5, 121.6, 113.7, 111.8, 104.8, 58.3, 55.1, 27.7, 24.5 23.7; MS: *m/z* 321(M^++1). Anal. calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.57; H, 6.51; N, 8.87.

3,4,5,6-Tetrahydro-4-(4-hydroxyphenyl)-8-methoxybenzo[*h*]quinazoline-2(1*H*)-one (4g) This compound was obtained from **1**, **2g** and **3a** as a pale yellow solid within 20 min; yield 0.29 g (90%); mp 275–277°C; IR: 3425, 3370, 3236, 3115, 2920, 2814, 1654, 1230 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.92 (m, 1H), 2.07 (m, 1H), 2.65 (m, 1H), 2.75 (m, 1H), 3.81 (s, 3H), 4.96 (s, 1H), 6.72 (m, 4H), 7.16 (d, *J* = 6.3 Hz, 2H), 7.33 (d, *J* = 6.6 Hz, 1H), 8.03 (s, 1H), 8.30 (s, 1H), 8.93 (s, 1H); ^{13}C NMR ($CDCl_3$): 158.7, 156.1, 153.1, 137.7, 137.4, 128.7, 127.5, 122.6, 121.5, 115.7, 114.2, 110.9, 104.5, 58.7, 55.5, 27.9, 23.5; MS: *m/z* 322 (M^+). Anal. calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.91; H, 5.77; N, 8.35.

3,4,5,6-Tetrahydro-8-methoxy-4-(3-nitrophenyl)benzo[*h*]quinazolin-2(1*H*)-one (4h) This compound was obtained from **1**, **2h** and **3a** as a yellow solid within 25 min; yield 0.32 g (91%); mp 254–256°C; IR: 3404, 3334, 3242, 3107, 2927, 1670, 1517, 1269 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.75 (m, 1H), 2.15 (m, 1H), 2.61 (m, 2H), 3.74 (s, 3H), 5.13 (s, 1H), 6.77 (s, 2H), 7.37 (s, 1H), 7.53 (d, *J* = 6.9 Hz, 1H), 7.69 (d, *J* = 6.3 Hz, 1H), 7.79 (d, *J* = 6.3 Hz, 1H), 8.15 (m, 2H), 8.60 (s, 1H); ^{13}C NMR (DMSO-d_6): 159.1, 155.2, 148.2, 146.0, 138.3, 133.2, 129.5, 127.9, 124.5, 122.3, 121.7, 118.7, 113.4, 110.8, 105.9, 57.3, 54.9, 28.0, 23.4; MS: *m/z* 352 (M^++1). Anal. calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.74; H, 4.91; N, 12.08.

4-(4-(Dimethylamino)phenyl)-3,4,5,6-tetrahydro-8-methoxybenzo[*h*]quinazolin-2(1*H*)-one (4i) This compound was obtained from **1**, **2i** and **3a** as a brown solid within 40 min; yield 0.31 g (89%); mp 298–300°C; IR: 3395, 3222, 3152, 2912, 2839, 1682, 1222, 1153 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.91 (m, 1H), 2.07 (m, 1H), 2.71 (m, 2H), 3.07 (s, 6H), 3.87 (s, 3H), 5.03 (s, 1H), 6.84 (m, 5H), 7.37 (d, *J* = 6.3 Hz, 2H), 7.47 (s, 1H); 8.76 (s, 1H); ^{13}C NMR ($CDCl_3$): 159.7, 153.5, 147.2, 137.4, 134.6, 128.0, 127.8, 123.5, 122.5, 114.1, 113.7, 111.8, 106.9, 58.6, 55.3, 42.4, 29.1, 23.7; MS: *m/z* 350 (M+1). Anal. calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.47; H, 6,46; N, 12.17.

3,4,5,6-Tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-8-methoxybenzo[*h*]quinazolin-2(1*H*)-one (4j) This compound was obtained from **1**, **2j** and **3a** as a pale yellow solid within 30 min; yield 0.32 g (91%); mp 271–273°C; IR: 3417, 3386, 3219, 3124, 2946, 2810, 1698, 1247, 1167 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80 (m, 1H), 2.14 (m, 1H), 2.58 (m, 1H), 2.69 (m, 1H), 3.76 (s, 3H), 3.80 (s, 3H), 4.95 (s, 1H), 7.01 (m, 6H), 8.00 (s, 1H), 8.31 (s, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$): 158.8, 155.1, 151.2, 143.3, 138.7, 137.4, 127.7, 122.4, 121.5, 120.8, 116.7, 113.7, 112.5, 110.8, 104.9, 58.6, 56.4, 55.3, 27.9, 24.1; MS: *m/z* 352 (M^+). Anal. calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.33; H, 5.64; N, 8.07.

3,4,5,6-Tetrahydro-8-methoxy-4-phenylbenzo[*h*]quinazoline-2(1*H*)-thione (4k) This compound was obtained from **1**, **2a** and **3b** as a white solid within 25 min; yield 0.30 g (93%); mp 272–274°C; IR: 3379, 3161, 2968, 1672, 1564, 1197, 1136 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.81 (m, 1H), 2.10 (m, 1H), 2.65 (m, 2H), 3.76 (s, 3H), 5.01 (s, 1H), 6.67 (m, 4H), 7.10 (d, *J* = 6.3 Hz, 2H), 7.36 (m, 3H), 9.02 (s, 1H); ^{13}C NMR ($CDCl_3$): 174.3, 159.0, 143.8, 137.5, 128.7, 127.2, 126.9, 126.8, 123.0, 120.5, 113.9, 110.9, 107.8, 57.8, 55.2, 27.6, 23.5; MS: *m/z* 322 (M^+). Anal. calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found: C, 70.54; H, 5.81; N, 8.87.

4-(2-Chlorophenyl)-3,4,5,6-tetrahydro-8-methoxybenzo[*h*]quinazoline-2(1*H*)-thione (4l) This compound was obtained from **1**, **2b** and **3b** as a white solid within 25 min; yield 0.33 g (93%); mp 270–272°C; IR: 3196, 2928, 2845, 1675, 1180, 1085, 732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80 (m, 1H), 2.16 (m, 1H), 2.66 (m, 2H), 3.81 (s, 3H), 4.96 (s, 1H), 6.74 (m, 4H), 7.13 (d, *J* = 6.3 Hz, 2H), 7.44 (m, 2H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$): 174.1, 158.7, 142.0, 138.2, 132.5, 128.7, 128.5, 128.3, 126.8, 126.7, 123.5, 120.7, 113.9, 110.8, 108.1, 56.1, 55.0, 27.5, 23.7; MS: *m/z* 356 (M^+). Anal. calcd for $C_{19}H_{17}ClN_2OS$: C, 63.95; H, 4.80; N, 7.85. Found: C, 63.57; H, 4.93; N, 7.99.

4-(4-Chlorophenyl)-3,4,5,6-tetrahydro-8-methoxybenzo[*h*]quinazoline-2(1*H*)-thione (4m) This compound was obtained from **1**, **2c** and **3b** as a yellow solid within 10 min; yield 0.34 g (95%); mp 240–243°C; IR: 3198, 2928, 2830, 1677, 1187, 1087, 741 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.81 (m, 1H), 2.15 (m, 1H), 2.60 (m, 2H), 3.74 (s, 3H), 4.95 (s, 1H), 6.76 (s, 2H), 7.32 (d, *J* = 6.3 Hz, 2H), 7.45 (d, *J* = 6.3 Hz, 2H), 7.63 (d, *J* = 6.9 Hz, 1H), 9.05 (s, 1H), 9.71 (s, 1H); ^{13}C NMR (DMSO-d_6): 174.2, 158.9, 141.9, 137.5, 132.4, 128.8, 128.6, 126.7, 123.1, 120.4, 113.9, 110.8, 107.9, 57.7, 55.1, 27.6, 23.4; MS: *m/z* 357 (M^++1). Anal. calcd for $C_{19}H_{17}ClN_2OS$: C, 63.95; H, 4.80; N, 7.85. Found: C, 63.71; H, 4.67; N, 7.92.

3,4,5,6-Tetrahydro-8-methoxy-4-(4-methoxyphenyl)benzo[*h*]quinazoline-2(1*H*)-thione (4n) This compound was obtained from **1**, **2d** and **3b** as a yellow solid within 30 min; yield 0.32 g (91%); mp 234–237°C [Literature (El-Baih et al., 2005) mp 236–237°C]; IR: 3192, 2920, 2824, 1671, 1173, 1124, 1082 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.91 (m, 1H), 2.06 (m, 1H), 2.71 (m, 2H), 3.80 (s, 6H), 5.03 (s, 1H), 6.56 (s, 1H), 6.77 (m, 2H), 6.88 (d, *J* = 6.3 Hz, 2H), 7.14 (d, *J* = 6.3 Hz, 1H), 7.25 (d, *J* = 6.6 Hz, 2H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$): 174.2, 159.9, 159.7, 137.8, 133.5, 128.7, 125.6, 120.5, 120.2, 114.8, 114.4, 111.0, 108.0, 60.2, 55.3, 28.2, 23.5; MS: *m/z* 352 (M^+). Anal. calcd for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95. Found: C, 67.82; H, 5.86; N, 8.14.

3,4,5,6-Tetrahydro-8-methoxy-4-(3,4-dimethoxyphenyl)benzo[*h*]quinazoline-2(1*H*)-thione (4o) This compound was obtained from **1**, **2e** and **3b** as a white solid within 40 min; yield 0.36 g (94%); mp 253–255°C; IR: 3190, 2922, 2831, 1682, 1192, 1133, 1084 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.93 (m, 1H), 2.06 (m, 1H), 2.72 (m, 2H), 3.81 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.04 (s, 1H), 6.80 (m, 6H), 7.16 (d, *J* = 6.6 Hz, 1H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$): 174.2, 158.8, 149.7, 147.9, 137.5, 137.1, 126.5, 123.0, 120.5, 120.3, 115.2, 113.7, 112.2, 110.8, 107.9, 58.0, 55.2, 54.2, 27.7, 23.5; MS: *m/z* 382 (M^+). Anal. calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32. Found: C, 65.73; H, 5.91; N, 7.09.

3,4,5,6-Tetrahydro-8-methoxy-4-*p*-tolylbenzo[*h*]quinazoline-2(1*H*)-thione (4p) This compound was obtained from **1**, **2f** and **3b** as a pale yellow solid within 35 min; yield 0.29 g (86%); mp 248–251°C; IR: 3197, 2983, 2931, 1674, 1188, 1136 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.93 (m, 1H), 2.07 (m, 1H), 2.41 (s, 3H), 2.70 (m, 2H), 3.81 (s, 3H), 5.03 (s, 1H), 6.67 (m, 3H), 7.12 (d, *J* = 6.6 Hz, 2H), 7.37 (m, 3H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$): 174.7, 159.3, 140.8, 138.1, 136.5, 129.0, 127.1, 126.9, 124.1, 121.4, 114.2, 111.2, 108.3, 58.2, 55.3, 27.9, 25.3, 23.7; MS: *m/z* 336 (M^+). Anal. calcd for $C_{20}H_{20}N_2OS$: C, 71.40; H, 5.99; N, 8.33. Found: C, 71.16; H, 6.32; N, 8.52.

3,4,5,6-Tetrahydro-4-(4-hydroxyphenyl)-8-methoxybenzo[*h*]quinazoline-2(1*H*)-thione (4q) This compound was obtained from **1**, **2g** and **3b** as a pale yellow solid within 30 min; yield 0.32 g (95%); mp 268–270°C; IR: 3412, 3173, 2925, 2812, 1656, 1167, 1055 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 1.94 (m, 1H), 2.06 (m, 1H), 2.69 (m, 2H), 3.80 (s, 3H), 4.92 (s, 1H), 6.77 (m, 4H), 7.15 (d, *J* = 6.3 Hz, 2H), 7.32 (d, *J* = 6.3 Hz, 1H), 8.01 (s, 1H), 8.31 (s, 1H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 174.2, 158.8, 156.6, 137.8, 136.4, 128.6, 126.5, 123.3, 120.4, 115.8, 114.0, 110.8, 108.2, 57.8, 55.3, 27.6, 23.6; MS: *m/z* 339 (M+1). Anal. calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.21; H, 5.48; N, 8.64.

3,4,5,6-Tetrahydro-8-methoxy-4-(3-nitrophenyl)benzo[*h*]quinazoline-2(1*H*)-thione (4r) This compound was obtained from **1**, **2h** and **3b** as a yellow solid within 20 min; yield 0.33 g (90%); mp 244–246°C; IR: 3186, 2972, 2935, 1674, 1566, 1195, 1018 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.90 (m, 1H), 2.14 (m, 1H), 2.64 (m, 2H), 3.80 (s, 3H), 4.99 (s, 1H), 7.09 (m, 4H), 7.74 (m, 2H), 8.13 (d, *J* = 6.3 Hz, 2H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$): 175.0, 159.2, 148.3, 144.7, 139.1, 133.3, 129.6, 127.4, 124.1, 122.4, 120.9, 119.2, 114.5, 111.8, 108.5, 56.7, 55.6, 27.7, 24.2; MS: *m/z* 368 (M^++1). Anal. calcd for $C_{19}H_{17}N_3O_3S$: C, 62.11; H, 4.66; N, 11.44. Found: C, 61.87; H, 4.75; N, 11.63.

4-(4-(Dimethylamino)phenyl)-3,4,5,6-tetrahydro-8-methoxybenzo[*h*]quinazoline-2(1*H*)-thione (4s) This compound was obtained from **1**, **2i** and **3b** as a yellow solid within 30 min; yield 0.33 g (90%); mp 274–276°C; IR: 3387, 3190, 2918, 2845, 1669, 1178, 1123, 1087 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.94 (m, 1H), 2.15 (m, 1H), 2.65 (m, 2H), 3.07 (s, 6H), 3.87 (s, 3H), 4.96 (s, 1H), 6.81 (m, 4H), 7.21 (m, 2H), 7.37 (d, *J* = 6.3 Hz, 2H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$): 174.2, 158.9, 147.7, 137.5, 133.3, 128.1, 126.7, 123.1, 120.4, 114.2, 113.9, 110.8, 107.9, 57.7, 55.1, 42.2, 27.6, 23.4; MS: *m/z* 365 (M^+). Anal. calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 69.39; H, 6.02; N, 11.68.

3,4,5,6-Tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-8-methoxybenzo[*h*]quinazoline-2(1*H*)-thione (4t) This compound was obtained from **1**, **2j** and **3b** as a pale yellow solid within 35 min; yield 0.32 g (87%); mp 264–266°C; IR: 3422, 3179, 2924, 2846, 1698, 1187, 1145, 1087 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.93 (m, 1H),

2.14 (m, 1H), 2.65 (m, 2H), 3.75 (s, 3H), 3.81 (s, 3H), 4.98 (s, 1H), 7.11 (m, 6H), 8.06 (s, 1H), 8.33 (s, 1H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$): 174.8, 158.9, 151.3, 143.8, 137.7, 137.4, 127.1, 123.4, 120.9, 121.4, 116.8, 113.8, 112.6, 110.9, 108.7, 58.0, 55.4, 54.2, 28.1, 24.3; MS: *m/z* 368 (M^+). Anal. calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.51; H, 5.33; N, 7.86.

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References

Akshay, M. P.; Mahesh, M. S.; Chirag, V. B.; Naval, K.; Jyoti, S.; Yogesh, T. N. An efficient, environment friendly and recyclable heterogeneous catalyst for the Biginelli condensation. *Lett. Org. Chem.* **2009**, *6*, 619–623.

Atwal, K. S.; Rovnyak, G. C.; O Reilly, B. C.; Schwartz, J. Synthesis of selectively functionalized 2-hetero-1,4 dihydropyrimidines. *J. Org. Chem.* **1989**, *54*, 5898–5907.

Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O Reilly, B. C. Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6 -methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. *J. Med. Chem.* **1991**, *34*, 806–811.

Bao, S.; Chen, L.; Ji, Y.; Yang, J. Efficient procedure for oxathioacetalization using the novel ionic liquid. *Chin. J. Chem.* **2010**, *28*, 2119–2122.

Bimal, K. B.; Anupama, T. R.; Arup, D.; Chhanda, M. Microwave-induced bismuth nitrate – catalyzed synthesis of dihydropyrimidones via Biginelli condensation under solventless conditions. *Tetrahedron Lett*. **2007**, *48*, 7392–7394.

Cheng, J.; Qi, D. Y. An efficient and solvent-free one-pot synthesis of dihydropyrimidinones under microwave irradiation. *Chin. Chem. Lett.* **2007**, *18*, 647–650.

Debache, A.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. A one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones catalyzed by triphenylphosphine as Lewis base. *Tetrahedron Lett.* **2008**, *49*, 6119–6121.

Dennis, R.; Fabrício, A. L.; Victor, S. S. D. S.; Karen, F. S. C.; Marcelo, G. M. D.; Marla, N. G. Multicomponent Biginelli's synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones promoted by $SnCl_2{\cdot}2H_2O$. *J. Braz. Chem. Soc.* **2004**, *15*, 165–169.

El-Baih, F. E. M.; Al-Rasheed, H. H.; Al-Hazimi, H. M. Synthesis of some pyridine and pyrimidine derivatives via Michael-addition. *J. Saudi Chem. Soc.* **2005**, *9*, 575–596.

Fabio, S. F.; Kappe, C. O. The Biginelli dihydropyrimidone synthesis using polyphosphate ester as a mild and efficient cyclocondensation/dehydration reagent. *Arkivoc* **2001**, *(ii)*, 122–134.

Haixia, L.; Jinchang, D.; Xianten, C.; Ziyi, Z. An efficient synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones catalyzed by KSF montmorillonite. *Molecules* **2000**, *5*, 1240–1243.

Ji-Tai, L.; Jun-Fen, H.; Jin-Hui, Y.; Tong-Shuang, L. An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation. *Ultrason. Sonochem.* **2003**, *10*, 119–122.

Kamaljit, S.; Kawaljit, S.; Baojie, W.; Scott, F.; Kelly, C.; Jan, B. Facile transformation of Biginelli pyrimidin-2(1*H*)-ones to pyrimidines. In vitro evaluation as inhibitors of Mycobacterium tuberculosis and modulators of cytostatic activity. *Eur. J. Med. Chem.* **2011**, *46*, 2290–2294.

Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. $Mn(OAc)_3{\cdot}2H_2O$ mediated three-component, one-pot, condensation reaction: an efficient synthesis of 4-aryl-substituted 3,4-dihydropyrimidin-2-ones. *Tetrahedron Lett.* **2001**, *42*, 7873–7875.

Ma, Y.; Qian, C.; Wang, L.; Yang, M. Lanthanide triflate catalyzed Biginelli reaction. One-pot synthesis of dihydropyrimidinones under solvent-free conditions. *J. Org. Chem.* **2000**, *65*, 3864–3868.

Naveen Kumar, V.; Someshwar, P.; Narsimha Reddy, P.; Thirupathi Reddy, Y.; Rajitha, B. Copper dipyridine dichloride as a mild and efficient catalyst for a one-pot condensation Biginelli reaction. *J. Heterocycl. Chem.* **2005**, *42*, 1–3.

Peng, J. J.; Deng, Y. Q. Ionic liquids catalyzed Biginelli reaction under solvent-free conditions. *Tetrahedron Lett*. **2001**, *42*, 5917–5919.

Rahim, H.; Maryam, H.; Majid, M. H.; Bita, B. Efficient sodium selenate-catalyzed synthesis of 3,4-dihydro-2(1*H*)-pyrimidinones and thiones under solvent-free conditions. *Bull. Chem. Soc. Ethiop.* **2009**, *23*, 141–144.

Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. *Tetrahedron Lett.* **2003**, *44*, 2889–2891.

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