An efficient one-pot synthesis of 3,4-dihydropyrimidin-2-(*1H*)-ones/thiones catalysed by 2-thienylboronic acid

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A simple efficient one-pot three-component condensation for synthesis of 3,4-dihydropyrimidin-2-(*1H*)-ones/thiones in good to excellent yields using 2-thienylboronic acid as a catalyst was described.

Keywords: three-component condensation, 2-thienylboronic acid, Biginelli reaction, 3,4-dihydropyrimidin-2-(*1H*)-ones/thiones

Recently, the synthesis of 3,4-dihydropyrimi-din-2(*1H*)-ones/thiones (DHPMs) has attracted interest of organic chemists. This interest can be attributed to 3,4-dihydropyrimidin-2(1*H*)-ones/thiones showing potent therapeutical and pharmacological properties, such as anti-inflammatory, antitumor, and antibacterial activity. Some have been successfully used as calcium channel blockers[1], antihypertensive agents[2], and a_{1a}-antagonists[3]. Several alkaloids containing the dihydropyrimidine core unit, exhibiting anticancer activity and antiviral activities, have been studied. The DHPM monastrol (**1**, Fig. 1) as a novel cell-permeable molecule can block normal bipolar spindle assembly in mammalian cells causing cell cycle arrest[4,5]. Thus the synthesis and investigation of dihydropyrimidines are of much current importance.

In the past, the Biginelli reaction had not attracted much attention. In 1978, Khanna first discovered the cardiovascular activity of Biginelli compounds arousing interest. This reaction suffers from long reaction times, acidic reaction conditions and low-yields of the products. A variety of catalysts have been reported to improve the efficiency of the Biginelli reaction, such as $NiCl_2{\cdot}6H_2O$,[7] *p*-TsOH,[8] $LaCl_3{\cdot}7H_2O$,[9] $Cu(OTf)_2$,[10] $FeCl_3$,[11] $ZrCl_4$,[12] $Bi(OTf)_3$,[13] [bmim][$FeCl_4$],[14] TCICA,[15] NH_2SO_3H,[16] CuI,[17] $CuCl_2{\cdot}H_2O$,[18] $BiCl_3$,[19] $Mn(OAc)_3{\cdot}2H_2O$,[20] $InBr_3$,[21] $BF_3{\cdot}OEt_2$,[22] $LiClO_4$,[23] YbOTf,[24] NH_4Cl,[25] $InCl_3$[26] or MTSA[27] and so on. Asymmetric syntheses using such as $CeCl_3/InCl_3$,[28] $Yb(OTf)_3$[29] attached to chiral ligands were recently reported. Other studies using microwave irradiation,[30] solid phase reagents,[31] and polymer-supported catalysts,[32] have been also reported.

Boronic acids are effective catalysts for the Biginelli reaction,[33,34] but to our knowledge, heterocyclic boronic acid, ferrocenic boronic acid or substituted phenylboronic acids have not been tested as catalysts in the Biginelli reaction. We now report our research on arylboronic acids as catalysts for the Biginelli reaction. We found that 2-thienylboronic acid as a simple efficient catalyst for the synthesis of 3,4-dihydropyrimidin-2-(*1H*)-ones/thiones, the yield was up to 97%. A variety of new dihydropyrimidines were synthesised using 2-thiophenylboric acid as a catalyst in 5 hours.

Results and discussion

We optimised the reaction conditions in terms of catalyst, solvent and reaction time. 4-Chloro-benzaldehyde was selected as the model substrate and acetonitrile which is less toxic, and is commonly used in Biginelli reaction, was chosen as solvent. The results are summarised in table 1. Initially, the combination of **4** (0.2 mol%), **5** (0.3 mol%), **6** (0.2 mol%) and phenylboronic acid(0.02 mol%) as catalyst were selected for study, and the desired **1a** was isolated in 54% yield (entry 1). Arylboronic acids with electron-donating group showed less improvement (entries 2 and 3), while having electron-withdrawing group exhibited good activity, furnishing **1a** in 74–95% yield (entries 4–6). The above results indicated that the structure of the acid was crucial for the present reaction. At the same time, we examined naphthalen-1-ylboronic acid (**2g)** and 1,1′-ferrocenediboronic acid (**2h)**, yet both were not as efficient as 3,4-difluorophenylboronic acid (entry 7 and 8). When we tested 2-thienylboronic acid (**2i)**, we were surprised that the yield rose to 97% (entry 9). Then the effects of the solvent on the reaction were studied and acetonitrile was found to be the best. Finally, we studied the reaction times and found the perfect reaction time was 5 hours (entry 9). On the basis of these investigations, the preferred reaction condition is ethyl acetoacetate:aldehydes:urea/thiourea:2-thienylboronic acid = 1:1:1.5:0.1 in CH_3CN (5 mL) 85 °C for 5 hours.

With the optimised conditions in hand, a variety of new dihydropyrimidines were synthesised in good to excellent yields, as show in Table 2. We found that aromatic aldehydes all gave higher yields than heteroaromatic aldehydes.

In conclusion, we have developed a simple and efficient method for a one-pot three-component synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones/thiones using 2-thienylboronic acid as the catalyst. This process may be useful in the pharmaceutical and biochemical fields.

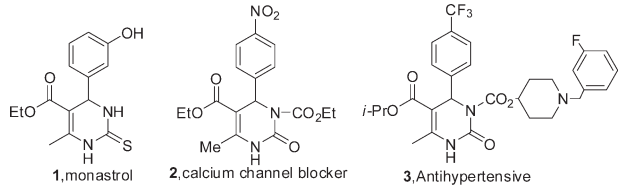

Fig. 1 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

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Experimental

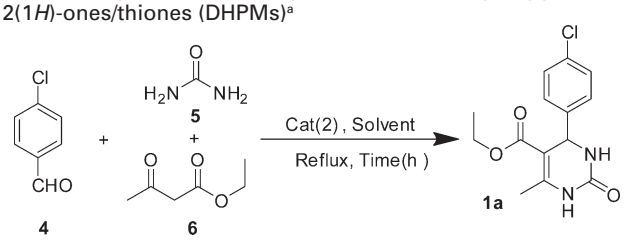
^{1}H spectra and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 MHz spectrometer and using *d*-DMSO (500 MHz for ^{1}H or 125 MHz for ^{13}C, respectively) as solvent. IR spectra (film) were recorded on a NEXUS FI/IR spectrometer. Melting points were taken on Büchi M-560. Mass spectra (MS) were carried out on Varian1200 and measured by the EI method. The reaction mixture was monitored by TLC on silica gel plates (60 F-254). Microanalyses were performed on a LECO CHNS-932 Elemental Analyser. All boronic acids were purchased from Fluka (Buchs, Switzerland) chemical company.

Synthesis of 3,4-dihydropyrimi din-2(1H)-ones/thiones (**1a**–**n**)*; general procedure*

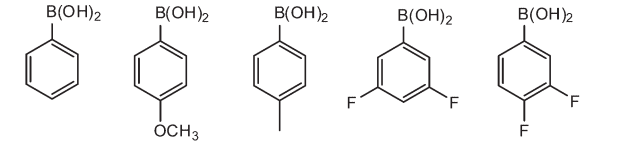
The mixture of ethyl acetoacetate (2 mmol), aromatic aldehyde (2 mmol), urea/thiourea (3 mmol), CH_3CN (5 mL) and 2-thienylboronic acid (0.1 mmol) was refluxed for 5 hours. The reaction mixture was monitored by TLC. After completion, the reaction mixture was poured into crushed ice, filtrated washed with 95% ethanol, dried, and recrystallised from 95% ethanol. The structures and yields of the products are given in Table 2.

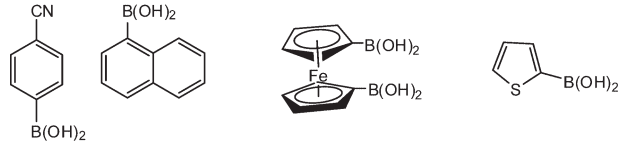
5-Ethoxycarbonyl-6-methyl-4(4-hydroxy-3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**1e**): Yellow solid; IR (film) 1697, 1643 cm^{-1}; ^{1}H NMR (500 MHz, d-DMSO) δ 1.09 (t, *J* = 7.0 Hz, 3H), 2.25 (s, 3H), 3.99 (m, 2H), 5.14 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.41 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.77 (d, *J* = 3.4 Hz, 1H), 9.27 (s, 1H), 10.97 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 165.1, 151.7, 151.3, 148.7, 136.2, 136.0, 133.3, 122.7, 119.4, 98.6, 59.3,

Table 1 Optimisation for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (DHPMs)[a]



Catalyst





Entry	Catalyst	Solvent	Time/h	Yield[b]/%
1	**2a**	CH_3CN	5	54
2	**2b**	CH_3CN	5	21
3	**2c**	CH_3CN	5	10
4	**2d**	CH_3CN	5	76
5	**2e**	CH_3CN	5	95
6	**2f**	CH_3CN	5	75
7	**2g**	CH_3CN	5	Trace
8[c]	**2h**	CH_3CN	5	Trace
9	**2i**	CH_3CN	5	97
10	**2i**	CH_2Cl_2	5	23
11	**2i**	MeOH	5	34
12	**2i**	EtOH	5	77
13	**2i**	Toluene	5	54
14	**2i**	CH_3CN	1	30
15	**2i**	CH_3CN	2.5	82
16	**2i**	CH_3CN	3	95

[a] Reaction conditions: **4** (0.2 mol%), **5** (0.3 mol%), **6** (0.2 mol%) catalyst (0.02 mol%), Solvent (5 mL), reflux. [b] Isolated yield. [c] Reaction conditions: **4** (0.2 mol%), **5** (0.3 mol%), **6** (0.2 mol%) catalyst (0.01 mol%), Solvent (5 mL), reflux.

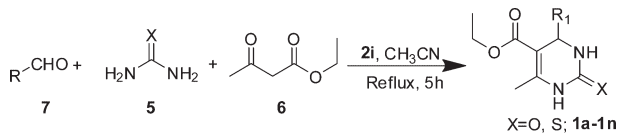
53.0, 17.8, 14.0; MS *m/z* 321 (M^+); Anal. Calcd for $C_{14}H_{15}N_3O_6$: C, 52.32; H, 4.72; N, 13.08. Found: C, 52.28; H, 4.64; N, 12.97%.

Ethyl-4-(4-hydroxy-3-nitrophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1f**): Yellow solid; IR (film) 1709, 1654 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.11 (t, *J* = 7.0 Hz, 3H), 2.30 (s, 3H), 4.02 (m, 2H), 5.16 (s, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.38 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 9.65 (d, *J* = 3.2 Hz, 1H), 10.40 (s, 1H) ^{13}C NMR (125 MHz, d-DMSO) δ 174.6, 165.3, 152.1, 145.9, 136.6, 135.1, 133.7, 123.4, 120.0, 100.6, 60.1, 53.4, 17.6, 14.4; MS *m/z* 337 (M^+); Anal. Calcd for $C_{14}H_{15}N_3O_5S$: C, 49.84; H, 4.49; N, 12.46. Found: C, 49.72; H, 4.31; N, 12.38%.

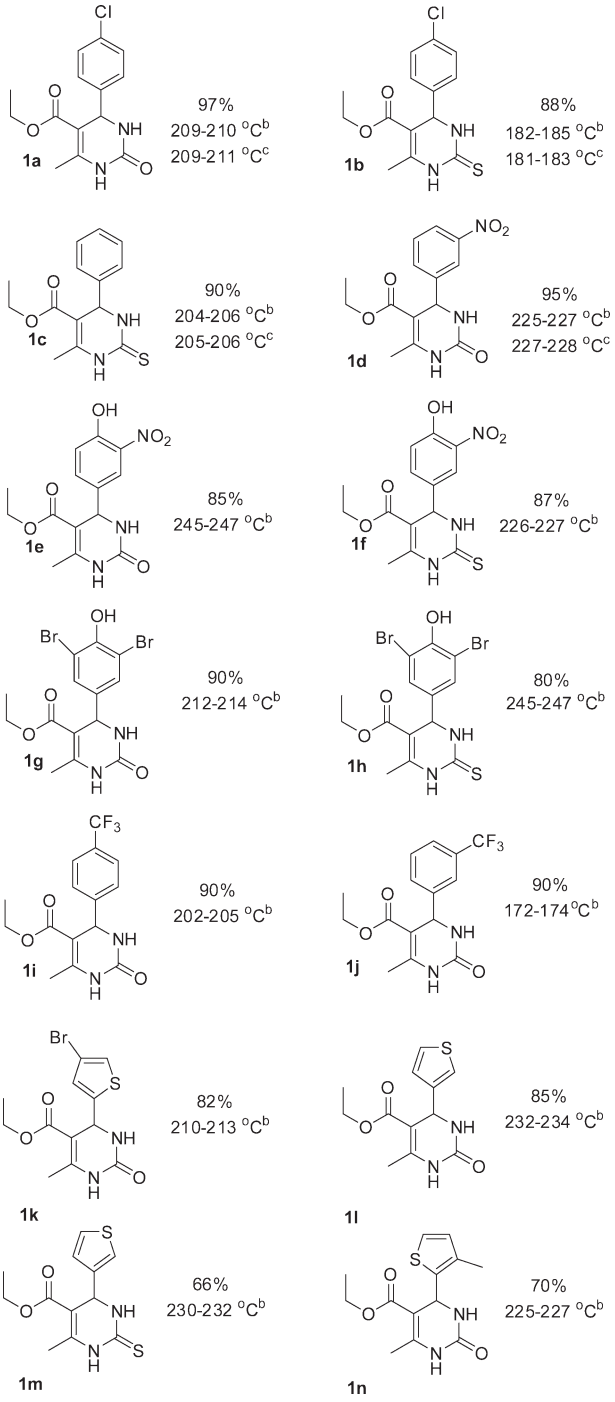
Ethyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1g**): White solid; IR (film) 3104, 1684 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.12 (t, *J* = 7.0 Hz, 3H), 2.26 (s, 3H), 4.01 (m, 2H), 5.08 (s, 1H), 7.33 (s, 2H), 7.74 (s, 1H), 9.26 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 165.6, 152.2, 150.3, 149.4, 139.6, 139.6, 130.5, 112.2, 99.0, 59.8, 53.2, 18.3, 18.2, 14.5; MS *m/z* 432 (M^+); Anal. Calcd for $C_{14}H_{14}Br_2N_2O_4$: C, 38.90; H, 3.27; N, 6.48. Found: C, 38.80; H, 3.18; N, 6.32%.

Ethyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimid ine-5-carboxylate (**1h**): White solid; IR (film) 3307, 1667 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.12 (t, *J* = 7.0 Hz, 3H), 2.30 (s, 1H), 4.03 (m, 2H), 5.11 (s, 1H), 7.32 (s, 1H), 9.62 (s, 1H), 10.40 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 174.7, 165.4, 150.7, 146.0, 138.2, 130.7, 112.3, 100.5, 60.2, 53.2, 53.1, 17.7, 17.6, 14.5; MS *m/z* 448 (M^+); Anal. Calcd for $C_{14}H_{14}Br_2N_2O_3S$: C, 37.51; H, 3.16; N, 6.25. Found: C, 37.40; H, 3.02; N, 6.10%.

Table 2 Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones via 2-thiophenylboric acid cascade process[a]



Products and yield



[a] Reaction conditions: **2i** (0.02 mol%), **5** (0.3 mol%), **6** (0.2 mol%), **7** (0.2 mol%), CH_3CN (5 mL), reflux, 5 h. [b] Melting point measured. [c] Melting point from ref.27.

Ethyl-6-methyl-2-oxo-4-(4-(trifluoromethyl) phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1i**): White solid; IR (film) 3120, 1707 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.09 (t, *J* = 7.0 Hz, 3H), 2.27 (s, 3H), 3.99 (q, *J* = 7.0, *J* = 7.0 Hz, 2H), 5.24 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 3.1 Hz, 2H), 9.30 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 165.6, 152.4, 149.7, 149.5, 128.6, 128.2, 127.6, 126.0, 125.9, 123.3, 99.0, 59.8, 54.1, 18.2, 14.5; MS *m/z* 328 (M^+); Anal. Calcd for $C_{15}H_{15}F_3N_2O_3$: C, 54.86; H, 4.62; N, 8.53. Found: C, 54.71; H, 4.46; N, 8.47%.

Ethyl-6-methyl-2-oxo-4-(3-(trifluoromethyl) phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1j**): White solid; IR (film) 2982, 1691 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.08 (t, *J* = 7.0 Hz, H), 2.27 (s, 3H), 3.99 (m, 2H), 5.26 (d, *J* = 2.7 Hz, 1H), 7.59 (m, 4H), 7.83 (d, *J* = 3.2 Hz, 1H), 9.31 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 165.6, 152.3, 149.5, 146.7, 130.8, 129.6, 128.9, 124.6, 120.6, 99.0, 59.7, 54.2, 18.2, 14.4; MS *m/z* 328 (M^+); Anal. Calcd for $C_{15}H_{15}F_3N_2O_2S$: C, 52.31; H, 4.40; N, 8.14. Found: C, 52.23; H, 4.23; N, 7.09%.

Ethyl-4-(4-bromothiophen-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1k**): White solid; IR (film) 3108, 1718 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.17 (t, *J* = 7.1 Hz, 3H), 2.23 (s, 3H), 4.08 (q, *J* = 7.0 Hz, 2H), 5.39 (s, 1H), 6.86 (s, 1H), 7.51 (s, 1H), 7.95 (d, *J* = 3.3 Hz, 1H), 9.39 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 165.3, 152.4, 151.0, 126.3, 122.9, 108.3, 99.3, 60.0, 18.1, 14.6; MS *m/z* 344 (M^+); Anal. Calcd for $C_{12}H_{13}BrN_2O_3S$: C, 41.86; H, 3.82; N, 8.14. Found: C, 41.75; H, 3.67; N, 7.08%.

Ethyl-6-methyl-2-oxo-4-(thiophen-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1l**): White solid; IR (film) 2980, 1649cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.15 (t, *J* = 7.0 Hz, 3H), 2.22 (s, 3H), 4.05 (q, *J* = 7.0 Hz, 2H), 5.21 (s, 1H), 6.98 (d, *J* = 4.9 Hz, 1H), 7.15 (s, 1H), 7.45 (m, 1H), 7.74 (d, *J* = 2.9 Hz, 1H), 9.17 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 165.8, 153.0, 148.8, 146.2, 127.1, 126.6, 121.2, 99.9, 59.7, 49.9, 18.1, 14.6; MS *m/z* 266 (M^+); Anal. Calcd for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.31; N, 10.52. Found: C, 54.06; H, 5.16; N, 10.43%.

Ethyl-6-methyl-4-(thiophen-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1m**): Yellow solid; IR (film) 2980, 1665 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.15 (t, *J* = 7.0 Hz, 3H), 2.27 (s, 3H), 4.07 (m, 2H), 5.24 (s, 1H), 6.97 (d, *J* = 5.0 Hz, 1H), 7.16 (d, *J* = 2.3 Hz, 1H), 7.49 (dd, *J* = 2.9, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 175.2, 165.5, 145.6, 144.8, 127.5, 126.5, 122.0, 101.3, 60.1, 50.0, 17.6, 14.6; MS *m/z* 282 (M^+); Anal. Calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.05; H, 5.01; N, 9.93. Found: C, 50.97; H, 4.96; N, 9.80%.

Ethyl-6-methyl-4-(3-methylthiophen-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1n**): Grey solid; IR (film) 2980, 1699 cm^{-1}; ^1H NMR (500 MHz, d-DMSO) δ 1.08 (t, *J* = 7.0 Hz, 3H), 2.21 (s, 3H), 2.24 (s, 3H), 3.96 (m, 2H), 5.45 (s, 1H), 6.75 (d, *J* = 5.0 Hz, 1H), 7.21 (d, *J* = 5.0 Hz, 1H), 7.76 (d, *J* = 2.4 Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (125 MHz, d-DMSO) δ 165.5, 152.1, 143.0, 133.3, 130.2, 126.1, 123.4, 100.5, 59.8, 48.0, 14.5, 18.1, 13.7; MS *m/z* 280 (M^+); Anal. Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.77; N, 10.00. Found: C, 55.66; H, 5.58; N, 9.92%.

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