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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

3,4-Hydropyrimidin-2-(1*H*)one derivatives: solid silica-based sulfonic acid catalyzed microwave-assisted synthesis and their biological evaluation as antihypertensive and calcium channel blocking agents

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Abstract Microwave assisted simple, efficient procedure for one-pot Biginelli condensation reaction of aldehydes, β-ketoesters, and urea or thiourea in solvent-free condition employing solid silica-based sulfonic acid as a novel, heterogeneous reusable catalyst is described. Compared to the classical Biginelli reaction conditions, the present method has the advantages of good yields, short reaction times, and experimental simplicity. The newly synthesized compounds have been screened to in vitro antihypertensive and calcium channel blocking activity done by IC_{50} measurement method with nifedipine as standard.

Keywords Solid silica-based sulfonic acid · 3,4-Dihydropyrimidin-2-(1*H*)ones · Microwave irradiation · Antihypertensive and calcium channel blocking activity · IC_{50} · Nifedipine

Introduction

In recent years, there has been an increasing interest in developing greener processes (Anastas and Kirchhoff, 2002). In this context, heterogeneous catalysis (Deepak *et al*., 2006; Vassylyev *et al*., 2005) is emerging as an alternative to homogeneous processes, since catalysts can be recovered after the reaction and reused several times to achieve very high turn-over numbers. One strategy to transform a homogeneous into heterogeneous process is to anchor the active site onto a large surface solid carrier provided that the anchoring methodology maintains the intrinsic activity and selectivity of the catalytic center (Mark *et al*., 2005). Among various solid supports, silica is usually preferred, since it displays many advantageous properties—excellent stability (chemical and thermal), high surface area, good accessibility, and organic groups can be robustly anchored to the surface, to provide catalytic centers (Mark *et al*., 2005; Overman *et al*., 1995).

In recent years, attention has turned toward solid acid catalysts for catalyzing organic reactions (James, 2002). Recently, silica functionalized sulfonic acid as heterogeneous solid acid catalyst has been used to carry out variety of reactions (Van Rhijn *et al*., 1998).

Nowadays, there has been renewed interest in the three component cyclocondensation of ethyl acetoacetate with aromatic aldehydes and urea (or thiourea) discovered by Biginelli in 1893 (Kappe, 2000a). 3,4-Dihydropyrimidinones and their sulfur analogs have been reported to possess diverse pharmacological properties such as antiviral, antibacterial, and antihypertensive, as well as efficiency as calcium channel modulators, and α-**1a**-antagonists (Kappe, 2000b). The batzelladine alkaloids containing the dihydropyrimidine unit are particularly notable, as they recently were found to be potent HIV gp-120-CD4 inhibitors (Overman *et al*., 1995). Therefore, the preparation of this heterocyclic core unit is under active investigation (Zhang *et al*., 2006). However, many of these reported methods suffer from drawbacks such as low yield of products, harsh

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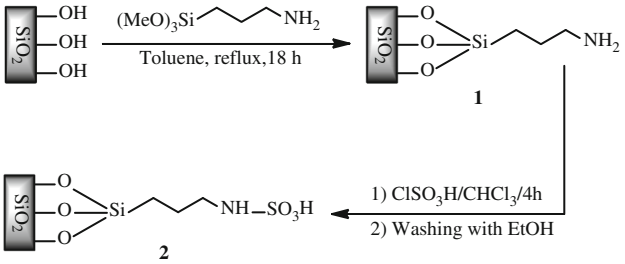


Scheme 1 Preparation of solid silica-based sulfonic acid

Table 1 Yields of the reaction in different conditions

Amount of catalyst (% mol)	Reaction time (min)/temperature (°C)	Yields (%)
0	7/90	67
1	7/90	74
2	7/90	82
3	7/90	95
4	7/90	95
5	7/90	94

reaction conditions, cumbersome experimental procedures, use of moisture sensitive, toxic, and costly catalysts. Therefore, there is a need to develop new catalysts which are easily available or prepared, cost effective, recoverable, reusable, and environment friendly. Moreover, the work-up procedure should be simpler.

Keeping in view the importance of Biginelli compounds and heterogeneous catalysis, we wish to report a mild and efficient method for one-pot synthesis of 3,4-dihydropyrimidinones/thiones in the presence of catalytic amount of solid silica-based sulfonic acid onto silica gel under heterogeneous conditions. The preparation procedure for catalyst **2** is outlined in Scheme 1 with slight modification than the already reported method (Biswanath *et al*., 2006).

Experimental

General

Silica gel (K100, 0.063–0.200 mm) was purchased from Merck (Germany) and 3-aminopropyltrimethoxy silane from Aldrich Chemical Company. All melting points were determined on a perfit melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on Brucker DRX-400 (400 MHz) spectrometer in DMSO-d_6 using tetramethylsilane as an internal standard, and IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer using KBr disks. Mass spectral data were recorded on Jeol JMS D-300 mass spectrometer at 70 eV. All yields refer to the isolated yields.

Catalyst preparation

Solid silica-based sulfonic acid (**2**)

To a mixture of 3-aminopropylsilica **1** (5 g) in chloroform (20 mL), chlorosulfonic acid (1 g, 0.6 mL) was added dropwise at 0 °C over 2 h. After addition was complete, the mixture was stirred for 2 h until HCl gas evolution stopped. Then, the mixture was filtered and washed with ethanol (30 mL) and dried at room temperature to obtain silica solid-based sulfonic acid (**2**) as a cream powder (5.13 g). Sulfur content of the samples determined by conventional elemental analysis was 9.29 %.

General procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones **1(a–n)** using solid silica-based sulfonic acid as catalyst

The mixture of ethyl acetoacetate (2.5 mmol), aldehyde (2.5 mmol), urea or thiourea (2.5 mmol), and solid silica-based sulfonic acid (3 mol% of SO_3H) was subjected to microwave irradiation in solvent-free condition for appropriate time (Table 1) in 900 W microwave oven for 6–7 min (successive irradiation of 30–40 s with cooling intervals of time as the temperature being 90 °C). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc (10 mL) and then solid silica-based sulfonic acid was separated by simple filtration due to its heterogeneous nature. The product was obtained after removal of the EtOAc under reduced pressure followed by treatment with water and crystallization from EtOH.

General procedure for the synthesis of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-ones **2(a–f)**

The mixture of cyclic ketone (1.0 mmol), aldehyde (1.0 mmol), urea (1.5 mmol), and solid silica-based sulfonic acid (3 mol% of SO_3H) was subjected to microwave irradiation in solvent-free condition for appropriate time (Table 1) in 900 W microwave oven for 7 min (successive irradiation of 30–40 s with cooling intervals of time as the temperature being 80 °C). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with EtOAc (10 mL) and then solid silica-based sulfonic acid was separated by simple filtration due to its heterogeneous nature. The product was obtained after removal of the EtOAc under reduced pressure followed by treatment with water and crystallization from EtOH.

*Ethyl-6-methyl-4-(3-methylfuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a**)*

Mp 217–219 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 1.12–1.13 (t, 3H, $J = 7.13$ Hz, CH_3), 1.82 (s, 3H, CH_3), 2.17 (s, 3H, furanic CH_3), 8.87–3.92 (q, 2H, $J = 7.17$ Hz, CH_2), 4.7 (d, 1H, $J = 2.14$ Hz, CH), 6.1 (d, 1H, $J = 2.21$ Hz, furanic H), 6.2 (d, 1H, $J = 2.19$ Hz, furanic H), 8.1 (s, 1H, NH), 8.9 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 13.8 (CH_3–CH_2), 16.3 (CH_3), 18.9 (CH_3-HetAr), 54.4 (C–NH), 65.3 (OCH_2), 106.7, 119.7, 109.8, 123.1 (C–HetAr), 145.2 (C=C–CO), 153.4 (C=C–NH), 165.1, 168.9 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3231 (NH stretch), 3125 (aromatic CH stretch), 2934 (aliphatic C–H stretch), 1726 (C=O stretch), 1623 (C=C stretch), 1472 (C=C bend), 1443 (O–CH_2–CH_3 bend), 1165 (C–NH bend), 1010 (CH_3–C–H bend), 903 (furan C–C bend), 692 (furan C–H bend); ESI–MS 265 (M+H); $C_{13}H_{16}N_2O_4$ (264.11): Calcd. C, 59.08; H, 6.10; N, 10.60; O, 24.22; Found. C, 59.10; H, 6.12; N, 10.56; O, 24.18.

*Ethyl-6-methyl-4-(5-methylfuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1b**)*

Mp 229–301 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H : 1.05–1.06 (t, 3H, $J = 7.09$ Hz, CH_3), 1.94 (s, 3H, CH_3), 2.20 (s, 3H, furanic CH_3), 3.94–4.01 (q, $J = 7.11$ Hz, 2H, CH_2), 4.9 (d, 1H, $J = 2.14$ Hz, CH), 6.3 (d, 1H, $J = 2.24$ Hz, furanic H), 6.4 (d, 1H, $J = 2.04$ Hz, furanic H), 8.3 (s, 1H, NH), 9.1 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 13.4 (CH_3–CH_2), 15.9 (CH_3), 18.3 (CH_3-HetAr), 53.5 (C–NH), 64.7 (OCH_2), 107.7, 110.6, 118.7, 122.5 (C-HetAr), 143.3 (C=C–CO), 152.7 (C=C–NH), 163.2, 167.2 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3220 (NH stretch), 3150 (aromatic C–H stretch), 2958 (aliphatic C–H stretch), 1748 (C=O stretch), 1611 (C=C stretch), 1452 (O–CH_2–CH_3), 1170 (C–NH), 1005 (CH_3–C–H), 907 (furan C–C), 699 (furan C–H); ESI–MS 265 (M+H); $C_{13}H_{16}N_2O_4$ (264.23): Calcd. C, 59.08; H, 6.10; N, 10.60; O, 24.22; Found. C, 59.12; H, 6.07; N, 10.52; O, 24.24.

*Ethyl-6-methyl-4-(3-thiophene-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1c**)*

Mp 217–219 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H : 0.93 (t, 3H, $J = 7.29$ Hz, CH_3), 2.3 (s, 3H, thiophenic CH_3), 2.82 (s, 3H, CH_3), 3.6–3.7 (q, 2H, $J = 7.26$ Hz, CH_2), 5.3 (d, 1H, $J = 2.21$ Hz, 2H), 7.1–7.3 (m, 2H, thiophenic H), 8.6 (s, 1H, NH), 9.0 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 14.1 (CH_3–CH_2), 15.2 (CH_3), 21.4 (CH_3-HetAr), 55.6 (C–NH), 68.8 (OCH_2), 108.8, 116.7, 123.6, 128.8 (C-HetAr), 144.4 (C=C–CO), 153.8 (C=C–NH), 164.3, 174.7 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3318 (NH stretch), 3116 (aromatic C–H stretch), 3012 (aliphatic C–H stretch), 1659 (C=O stretch), 1583 (C=C stretch), 1497 (C=C bend), 1423 (O–CH_2–CH_3 bend), 1136 (C–NH bend), 1023 (CH_3–C–H bend), 934 (thiophenic C–C bend), 679 (thiophinic C–H bend); ESI–MS 265 (M+H); $C_{13}H_{16}N_2O_3S$ (280.09): Calcd. C, 55.70; H, 5.75; N, 9.99; O, 17.12; S, 11.44; Found. C, 55.69; H, 5.74; N, 9.97; O, 17.16; S, 11.47.

*Ethyl-6-methyl-4-(5-thiophene-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1d**)*

Mp 223–225 °C; ^{1}H-NMR (400 MHz, DMSO-d_6d_6) δ_H : 0.81 (t, 3H, $J = 7.37$ Hz, CH_3), 2.1 (s, 3H, thiophenic CH_3), 2.87 (s, 3H, CH_3), 3.7–3.8 (q, 2H, $J = 7.33$ Hz, CH_2), 5.1 (d, 1H, $J = 2.25$ Hz, 2H), 7.2–7.3 (m, 2H, thiophenic H), 8.7 (s, 1H, NH), 8.9 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 13.5 (CH_3–CH_2), 15.9 (CH_3), 22.5 (CH_3-HetAr), 53.5 (C–NH), 67.7 (OCH_2), 107.7, 115.6, 122.5, 127.7 (C-HetAr), 143.3 (C=C–CO), 152.7 (C=C–NH), 163.2, 173.6 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3323, 3244 (NH stretch), 3124 (aromatic C–H stretch), 3028 (aliphatic C–H stretch), 1671 (C=O stretch), 1601 (C=C stretch), 1509 (C=C bend), 1450 (O–CH_2–CH_3 bend), 1170 (C–NH bend), 1011 (CH_3–C–H bend), 954 (thiophenic C–C bend), 698 (thiophinic C–H bend); ESI–MS 265 (M+H); $C_{13}H_{16}N_2O_3S$ (280.09): Calcd. C, 55.70; H, 5.75; N, 9.99; O, 17.12; S, 11.44; Found. C, 55.67; H, 5.72; N, 9.94; O, 17.15; S, 11.41.

*Ethyl-6-methyl-4-(1-methyl-1H-pyrrol-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1e**)*

Mp 194–196 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H : 1.06–1.11 (t, 3H, $J = 7.21$ Hz, CH_3), 2.24 (s, 3H, CH_3), 3.9–4.0 (q, 2H, $J = 7.29$ Hz, CH_2), 5.1 (d, 1H, $J = 2.12$ Hz, CH), 7.2–7.3 (m, 3H, pyrrolic H), 8.7 (s, 1H, NH), 9.1 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 14.4 (CH_3–CH_2), 25.5 (CH_3), 36.1 (CH_3-HetAr), 53.7 (C–NH), 67.2 (OCH_2), 102.8 (C=C–CO), 107.2, 109.4, 126.2. 127.1 (C-HetAr), 157.9 (C=C–NH), 163.3, 168.8 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3564, 3488 (NH stretch), 3082 (aromatic C–H stretch), 3025 (aliphatic C–H stretch), 1745 (C=O stretch), 1610 (C=C stretch), 1513 (C=C bend), 1450 (O–CH_2–CH_3 bend), 1166 (C–NH bend), 1110 (CH_3–C–H bend), 906 (pyrrolic C–C bend), 696 (pyrrolic C–H bend); ESI–MS 264 (M+H); $C_{13}H_{17}N_3O_3$ (263.32): Calcd. C, 59.30; H, 6.51; N, 15.96; O, 18.23; Found. C, 59.28; H, 6.47; N, 15.93; O, 18.26.

*Ethyl-4-(furan-2-yl)-6-metyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1f**)*

Mp 211–213 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H : 1.15–1.19 (t, 3H, $J = 7.32$ Hz, CH_3), 1.98 (s, 3H, CH_3),

3.88 (q, 2H, $J = 7.19$ Hz, CH_2), 5.12–5.13 (d, 1H, $J = 2.07$ Hz, CH), 6.40–6.50 (m, 2H, furanic H), 7.42 (d, $J = 2.23$ Hz, furanic H), 9.30 (s, 1H, NH), 10.02 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 13.9 (CH_3–CH_2), 16.9 (CH_3), 47.6 (C–NH), 59.4 (OCH_2), 98.17 (C=C–CO), 106.0, 110.3, 122.1, 142.4 (C-HetAr), 154.5 (C=C–NH), 162.8, 164.6 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3247, 3365 (NH stretch), 3181 (aromatic C–H stretch), 3042 (aliphatic C–H stretch), 1740 (C=O stretch), 1601 (C=C stretch), 1509 (C=C bend), 1451 (O–CH_2–CH_3 bend), 1172 (C–NH bend), 1002 (CH_3–C–H bend), 905 (furanic C–C bend), 697 (furanic C–H bend); ESI–MS 251 (M+H); $C_{12}H_{14}N_2O_4$ (250.57): Calcd. C, 57.59; H, 5.64; N, 11.19; O, 25.57; Found. C, 57.56; H, 5.62; N, 11.23; O, 25.60.

*Ethyl-4-(thiophen-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1g**)*

Mp 200–202 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H : 0.9 (t, 3H, $J = 7.18$ Hz, CH_3), 2.22 (s, 3H, CH_3), 3.9–4.0 (q, 2H, $J = 7.23$ Hz, CH_2), 5.1 (d, 1H, $J = 2.07$ Hz, CH), 6.9–7.3 (m, 3H, thiophenic H), 9.4 (s, 1H, NH), 9.6 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 15.7 (CH_3–CH_2), 23.9 (CH_3), 55.6 (C–NH), 67.4 (OCH_2), 107.0 (C=C–CO), 122.3, 126.5. 131.8, 142.4 (C-HetAr), 154.5 (C=C–NH), 164.6, 174.8 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3278, 3385 (NH stretch), 3210 (aromatic C–H stretch), 3029 (aliphatic C–H stretch), 1739 (C=O stretch), 1609 (C=C stretch), 1510 (C=C bend), 1450 (O–CH_2–CH_3 bend), 1171(C–NH bend), 1010 (CH_3–C–H bend), 905 (thiophenic C–C bend), 697 (thiophenic C–H bend); ESI–MS 267 (M+H); $C_{12}H_{14}N_2O_3S$ (266.24): Calcd. C, 54.12; H, 5.30; N, 10.52; O, 18.02; S, 12.04; Found. C, 54.16; H, 5.27; N, 10.55; O, 18.05; S, 12.01.

*Etyhyl-4-(1H-pyrrol-2-yl)-6-metyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1h**)*

Mp 182–184 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H : 0.9–1.0 (t, 3H, $J = 7.10$ Hz, CH_3), 2.81 (s, 3H, CH_3), 3.6 (q, 2H, $J = 7.16$ Hz, CH_2), 4.8 (d, 1H, $J = 2.14$ Hz, pyrrolic H), 5.2 (d, 1H, $J = 2.07$ Hz, CH_2), 7.2–7.3 (m, 3H, pyrrolic H), 8.8 (s, 1H, NH), 9.1 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 15.9 (CH_3–CH_2), 24.2 (CH_3), 57.6 (C–NH), 68.1 (OCH_2), 107.7 (C=C–CO), 110.6, 113.7, 122.5. 134.7 (C-HetAr), 158.2 (C=C–NH), 165.2, 170.7 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3298, 3231 (NH stretch), 3068 (aromatic C–H stretch), 2988 (aliphatic C–H stretch), 1716 (C=O stretch), 1610 (C=C stretch), 1511 (C=C bend), 1452 (O–CH_2–CH_3 bend), 1171 (C–NH bend), 1011 (CH_3–C–H bend), 884 (pyrrolic C–C bend), 697 (pyrrolic C–H bend); ESI–MS 250 (M+H); $C_{12}H_{15}N_3O_3$ (249.62): Calcd. C, 57.82; H, 6.07; N, 16.86; O, 19.26; Found. C, 57.80; H, 6.05; N, 16.83; O, 19.25.

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

Mp 212–214 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 1.11 (t, 3H, $J = 7.04$ Hz, OCH_2CH_3), 2.32 (s, 3H, CH_3), 4.03 (q, 2H, $J = 7.12$ Hz, OCH_2CH_3), 5.78 (d, 1H, $J = 2.28$ Hz, –CH), 7.51 (d, 2H, $J = 9.18$ Hz, Ar–H), 7.69 (s, 1H, NH), 8.16 (d, 2H, $J = 9.16$ Hz, Ar–H), 9.05 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 14.22 (CH_3–CH_2), 18.71 (CH_3), 55.81 (C–NH), 60.15 (OCH_2), 101.60 (C=C–CO), 118.15, 125.3, 130.37, 138.34, 146.5, 152.26 (Ar–C), 153.41 (C=C–NH), 159.15, 165.85 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3235, 1740, 1631; ESI–MS 306 (M+H); $C_{14}H_{15}N_3O_5$ (305.10): Calcd. C, 55.08; H, 4.95; N, 13.76; O, 26.20; Found. C, 55.10; H, 4.93; N, 13.78; O, 26.22.

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

Mp 215–217 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 1.12 (t, 3H, $J = 7.14$ Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.91 (q, 2H, $J = 7.16$ Hz, OCH_2CH_3), 5.70 (d, 1H, $J = 2.28$ Hz, –CH), 7.21 (d, 2H, $J = 9.18$ Hz, Ar–H), 7.69 (s, 1H, NH), 7.94 (d, 2H, $J = 9.18$ Hz, Ar–H), 9.16 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 14.18 (CH_3–CH_2), 18.62 (CH_3), 55.72 (C–NH), 60.21 (OCH_2), 101.55 (C=C–CO), 118.17, 122.9, 126.6, 130.32, 142.29, 152.31 (Ar–C), 153.39 (C=C–NH), 159.17, 165.83 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3225, 1720, 1615; ESI–MS 295 (M+H); $C_{14}H_{15}ClN_2O_3$ (294.07): Calcd. C, 57.05; H, 5.13; Cl, 12.03; N, 9.50; O, 16.29; Found. C, 57.08; H, 5.15; N, 9.47; O, 16.31.

*5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**1k**)*

Mp 206–208 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 1.09 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.97 (q, 2H, $J = 7.1$ Hz, OCH_2), 5.05 (d, 1H, $J = 2.15$ Hz, –CH), 7.28 (m, 5H, Ar–H), 7.75 (s, 1H, NH), 9.20 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 14.11 (CH_3–CH_2), 17.94 (CH_3), 54.91 (C–NH), 60.05 (OCH_2), 100.95 (C=C–CO), 113.05, 125.15, 127.81, 129.05, 131.20, 147.9 (Ar–C), 150.16 (C=C–NH), 155.47, 163.81 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3240, 1722, 1638; ESI–MS 261 (M+H); $C_{14}H_{16}N_2O_3$ (260.11): Calcd. C, 64.60; H, 6.20; N, 10.76; O, 18.44; Found. C, 64.63; H, 6.18; N, 10.78; O, 18.45.

*5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (**1l**)*

Mp 208–210 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 1.11 (t, 3H, J = 7.21 Hz, OCH_2CH_3), 2.29 (s, 3H, CH_3), 4.12 (q, 2H, J = 7.24 Hz, OCH_2), 5.16 (d, 1H, J = 2.05 Hz, –CH), 7.51 (m, 5H, Ar–H), 7.81 (s, 1H, NH), 9.41 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 14.23 (CH_3–CH_2), 17.91 (CH_3), 54.85 (C–NH), 60.15 (OCH_2), 100.90 (C=C–CO), 112.84, 115.12, 125.15, 127.2, 129.64, 131.45 (Ar–C), 150.27 (C=C–NH), 162.63 (C=O), 180.25 (C=S); IR (ν_{max}; KBr, cm^{-1}): 3240, 1720, 1640, 1595, 1530; ESI–MS 277 (M+H); $C_{14}H_{16}N_2O_2S$ (276.09): Calcd. C, 60.85; H, 5.84; N, 10.14; O, 11.58; S, 11.60; Found. C, 60.83; H, 5.86; N, 10.16; O, 11.55; S, 11.62.

*5-(Ethoxycarbonyl)-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (**1m**)*

Mp 205–207 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 1.15 (t, 3H, J = 7.14 Hz, OCH_2CH_3), 2.27 (s, 3H, CH_3), 4.02 (q, 2H, J = 7.11 Hz, OCH_2CH_3), 5.81 (d, 1H, J = 2.06 Hz, –CH), 7.23–7.37 (m, 4H, Ar–H), 7.78 (s, 1H, NH), 9.34 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_c: 14.14 (CH_3–CH_2), 18.60 (CH_3), 55.64 (C–NH), 60.21 (OCH_2), 101.34 (C=C–CO), 126.25, 128.02, 129.32, 130.75, 135.65, 144.34 (Ar–C), 160.40 (C=C–NH), 165.64 (C=O), 182.65 (C=S); IR (ν_{max}; KBr, cm^{-1}): 3245, 1725, 1632, 1575, 1545; ESI–MS 322 (M+H); $C_{14}H_{15}N_3O_4S$ (321.07): Calcd. C, 52.33; H, 4.70; N, 13.08; O, 19.92; S, 9.98; Found. C, 52.30; H, 4.72; N, 13.10; O, 19.89; S, 9.95.

*5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (**1n**)*

Mp 153–155 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 1.17 (t, 3H, J = 7.11 Hz, OCH_2CH_3), 2.37 (s, 3H, CH_3), 4.12 (s, 3H, –OCH_3), 4.15 (q, 2H, J = 7.10 Hz, OCH_2CH_3), 5.44 (d, 1H, J = 2.15 Hz, –CH), 7.11 (d, 2H, J = 8.15 Hz, Ar–H), 7.37 (d, 2H, J = 8.11 Hz, Ar–H), 7.84 (s, 1H, NH), 9.43 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6d_6) δ_C: 14.32 (CH_3–CH_2), 18.05 (CH_3), 55.49 (C–NH), 60.45 (OCH_2), 101.84 (C=C–CO), 114.32, 124.6, 127.74, 137.25, 141.1, 147.15 (Ar–C), 159.45 (C=C–NH), 165.62 (C=O), 182.48 (C=S); IR (ν_{max}; KBr, cm^{-1}): 3240, 1725, 1635, 1574, 1540; ESI–MS 307 (M+H); $C_{15}H_{18}N_2O_3S$ (306.10): Calcd. C, 58.80; H, 5.92; N, 9.14; O, 15.67; S, 10.47; Found. C, 58.82; H, 5.90; N, 9.15; O, 15.65; S, 10.45.

*4-(5-Methylfuran-2-yl)-6-(thiophen-2-yl)-3,4-dihydropyrimidin-2-(1H)-one (**2a**)*

Mp 223–225 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 2.31 (s, 3H, furanic CH_3), 5.33–5.44 (dd, 2H, J = 6.08 Hz, alkylic H, aliphatic H), 6.19–6.31 (m, 2H, furanic H), 6.7 (a, 1H, NH), 6.9 (s, 1H, NH), 7.2 (m, 3H, furanic H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 15.9 (CH_3-HetAr), 53.5 (C–NH), 101.2 (C=C-olefin carbon), 105.7, 110.6, 150.6, 152.7 (C-furan ring), 122.5, 126.6, 132.3, 137.7 (C-thiophene ring), 142.2 (C=C–NH), 163.6 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3477, 3411 (NH stretch), 3159 (aromatic C–H stretch), 2970 (aliphatic C–H stretch), 1753 (C=O stretch), 1650 (C=C stretch), 1403 (C–N bend), 1137 (C–O–C bend); ESI–MS 261 (M+H); $C_{13}H_{12}N_2O_5S$ (260.43): Cacld. C, 59.98; H, 4.65; N, 10.76; O, 12.29; S, 12.32; Found. C, 59.96; H, 4.67; N, 10.75; O, 12.31; S, 12.35.

*4-(5-Methylthiophen-2-yl)-6-(thiophen-2-yl)-3,4-dihydropyrimidin-2-(1H)-one (**2b**)*

Mp 241–243 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 2.42 (s, 3H, thiphenic CH_3), 5.2 (d, 1H, J = 4.12 Hz, pyrimidine CH), 5.3 (d, 1H, J = 4.21 Hz, olefinic H), 6.5 (s, 1H, NH), 6.7 (s, 1H, NH), 7.21–7.48 (m, 5H, thiophenic H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 14.6 (CH_3-HetAr), 51.7 (C–NH), 105.3 (C=C-olefin carbon), 118.2, 127.1, 136.1, 143.9, 121.3, 132.7, 139.1(C-thiophene rings), 174.8 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3550, 3477 (NH stretch), 3140 (aromatic C–H stretch), 2924 (aliphatic C–H stretch), 1759 (C=O stretch), 1674 (C=C stretch), 1348 (C–C bend), 1186 (C–O–C bend); 1129 (C–S–C bend), ESI–MS 277 (M+H); $C_{13}H_{12}N_2OS$ (276.73): Cacld. C, 56.49; H, 4.38; N, 10.14; O, 5.79; S, 23.20; Found. C, 56.50; H, 4.35; N, 10.15; O, 5.80; S, 23.23.

*4-(5-Methyl-1H-pyrrol-2-yl)-6-(thiophen-2-yl)-3,4-dihydropyrimidin-2-(1H)-one (**2c**)*

Mp 227–229 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 2.31 (s, 3H, pyrrolic CH_3), 5.4 (d, 1H, J = 4.7 Hz, pyrimidine CH), 5.1 (d, 1H, J = 4.5 Hz, olefinic H), 6.8 (s, 1H, NH), 7.1 (s, 1H, NH), 7.34–7.45 (m, 5H, pyrrolic H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 15.7 (CH_3-HetAr), 52.8 (C–NH), 103.8 (C=C-olefin carbon), 119.3, 122.4, 128.2 (C-pyrrole ring), 133.8, 137.2, 140.2, 144.0 (C-thiophene ring), 175.9 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3577 (NH stretch), 3167 (aromatic C–H stretch), 3024 (aliphatic C–H stretch), 1763 (C=O stretch), 1658 (C=C stretch), 1361 (C–C bend), 1194 (C–O–C bend); 1143 (C–NH–C bend), ESI–MS 260 (M+H); $C_{13}H_{12}N_3OS$ (259.53): Cacld. C, 60.21; H, 5.05; N, 16.20; O, 6.17; S, 12.36; Found. C, 60.19; H, 5.02; N, 16.15; O, 6.15; S, 12.34.

*4,6-Diphenyl-3,4-dihydropyrimidin-2(1H)-one (**2d**)*

Mp 234–236 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 9.51 (s, 1H, NH), 9.21 (s, 1H, NH), 7.21–7.62 (m, 10H, Ar–H),

5.20 (d, 1H, $J = 4.1$ Hz, C=CH), 5.12 (d, 1H, $J = 4.1$ Hz, CH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 51.9 (C–NH), 96.8 (C=C-olefin carbon), 126.9, 126.4, 128.6, 128.7, 134.2, 136.6, 143.2, (AR–C), 150.2 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3312, 1685, 1598, 1449; ESI–MS 251 (M+H); $C_{16}H_{14}N_2O$; (250.30); Calcd. C, 76.78; H, 5.64; N, 11.19; O, 6.39. Found. C, 76.53; H, 5.34; N, 11.02; O, 6.13.

*4-(4-Chlorophenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2e**)*

Mp 264–266 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 9.42 (s, 1H, NH), 9.12 (s, 1H, NH), 7.19–7.78 (m, 9H, Ar–H), 5.60 (d, 1H, $J = 4.3$ Hz, C=CH), 5.01 (d, 1H, $J = 4.3$ Hz, CH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 52.7 (C–NH), 97.5 (C=C-olefin carbon), 126.4, 128.3, 141.3, 132.3, 128.6, 128.7, 134.2, 136.6 Ar–C), 150.2 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3319, 1683, 1569, 1463; ESI–MS 285 (M+H); $C_{16}H_{13}ClN_2O_3$; (284.74); Calcd. C, 67.49; H, 4.60; Cl, 12.45, N, 9.84, O, 5.62. Found. C, 67.18; H, 4.24; Cl, 12.21; N, 9.32, O, 5.41.

*4-(4-Methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2f**)*

Mp 257–259 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H: 9.23 (s, 1H, NH), 8.87 (s, 1H, NH), 7.18–7.56 (m, 9H, Ar–H), 5.85 (d, 1H, $J = 5.6$ Hz, C=CH), 5.26 (d, 1H, $J = 5.6$ Hz, CH), 3.69 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C: 51.9 (C–NH), 97.5 (C=C-olefin carbon), 114.1, 126.4, 127.9, 128.0, 128.7, 134.2, 135.5, 136.6, 150.2 (Ar–C), 158.6 (C=O); IR (ν_{max}; KBr, cm^{-1}): 3345, 1645, 1536, 1422; ESI–MS 281 (M+H); $C_{17}H_{16}N_2O_2$; (280.32); Calcd. C, 72.84; H, 5.75, N, 9.99; O, 11.42. Found. C, 72.53; H, 5.42; N, 9.73; O, 11.19.

Pharmacological evaluation

Pharmacological evaluation is a crucial thing to ensure the activity of the compounds. In this era, the prevalence of heart diseases has increased to a great extent. Antihypertensive agents are among the most commonly used to treat the variety of heart diseases. Literature review revealed that substituted dihydropyrimidine containing compounds show different biological activities. So, the newly synthesized compounds are also evaluated for their antihypertensive activity and calcium channel blocking activity.

Antihypertensive activity

Purpose and rationale

There are various in-vivo and in-vitro methods are available for evaluation of antihypertensive activity. Antihypertensive activity was performed by in-vitro method in which effect of test compounds on blood pressure is measured (Guan *et al*., 2007).

Procedure

Animals were procured from School of Life Sciences, University of Hyderabad, Hyderabad. All animals were kept in polyacrylic cages and maintained under standard housing conditions (room temperature 24–27 °C and humidity 60–65 % with 12:12 light: dark cycles). Food was provided in the form of dry pellets and water ad libitum. All experiments involving animals complies with the ethical standards of animal handling and approved by Institutional Animal Ethics Committee (Approval number LSCP/IAEC/06/01). Spontaneous hypertensive rats (SHRs) of 200 ± 20 g body weight were used. Rats were divided into 2 groups, each group had 9 animals.

Heparin at the dose of 2,000 IU/kg by I.V. route has been administered to rats of either sex. Rats of either sex have been anesthetized with pentothal sodium 80 mg/kg given by intraperitoneally. Blood pressure transducer was calibrated initially by using of mercury manometer. For each rat, the carotid artery was cannulated and attached to blood pressure transducer to record the initial arterial blood pressure which will be calibrated initially by using of mercury manometer. In the similar way on the opposite side, the jugular vein was cannulated to administer 0.3 ml heparinised saline for checking normal flow of fluid in the vein then the different doses of test samples were used to measure the effect on blood pressure by inhibition of adrenaline response (Hiroyuki *et al*., 2000).

Calcium antagonism in the isolated rat ileum

Purpose and rationale

Contraction of ileum was induced by adding potassium chloride & calcium chloride to the organ bath containing slightly modified Tyrode solution (NaCl = 8.0 g/l, KCl = 0.2 g/l, $CaCl_2$ = 0.18 g/l, NaH_2PO_4 = 0.1 g/l, $MgCl_2$ = 0.1 g/l, Glucose = 1.0 g/l, $NaHCO_3$ = 1.0 g/l). Test drugs with calcium channel blocking activity have a relaxing effect (Gilani *et al*. 2012).

Procedure

The adult (♂ or ♀) Wistar rats (200–310 g) were maintained in plastic cages (47 × 34 × 18 cm^3) with sawdust lining (renewed on alternate days), kept at 23–25 °C, 60 ± 4 % humidity, and 12/12 h light/dark cycles. The animals were provided with standard diet and tap water ad libitum. The

diet constituted of mixture of the following ingredients (g): flour (380), fiber (380), molasses (11.5), NaCl (5.8), vitamins mixture (2.5), potassium metabisulphate (1.2), vegetable oil (38), fish meal (170), and powdered milk (150). All experiments involving animals complies with the ethical standards of animal handling and approved by Institutional Animal Ethics Committee. Rats were divided into two groups each group had 9 animals.

The assembly was being set up and arrangement was made for experiment. The animal kept for overnight fasting was stunned by a sharp blow on the head and sacrificed by cutting neck blood vessels. The abdominal cavity was quickly opened and a piece of ileum was isolated. It was placed in a petridish containing tyroide solution maintained at 37 °C. The mesentery of ileum was removed and the interior contend was washed by blowing tyrode solution ($NaCl = 8.0$ g/l, $KCl = 0.2$ g/l, $CaCl_2 = 0.18$ g/l, $NaH_2PO_4 = 0.1$ g/l, $MgCl_2 = 0.1$ g/l, Glucose = 1.0 g/l, $NaHCO_3 = 1.0$ g/l) with help of pipette. The tissue was mounted in mammalian organ bath and connected to isotonic frontal writing lever. The tissue was allowed to stabilize for 30 min. The responses of acetylcholine were taken till the maximum effect was obtained. The normal tyrode solution was changed with tyrode containing test solution. The responses of acetylcholine were taken with same dose and continued till maximum effect obtained. The percentage of relaxation from the test-drug, precontracted level was calculated for each concentration of test compound. An IC_{50} was calculated by linear regression analysis:

$$y = 96.18x + 1.372$$

If y = 50 %, then $x = 0.5$ ml dose

$$\begin{aligned}\text{IC50 of nifedipine} &= \text{dose for 50 \% inhibition} \times \text{conc.} \\ &\div \text{bath capacity} = (0.5\ \text{ml}) \\ &\times (1{,}000\ \mu\text{g/ml}) \div 25\ \text{ml} \\ &= 20\ \mu\text{g/ml}\end{aligned}$$

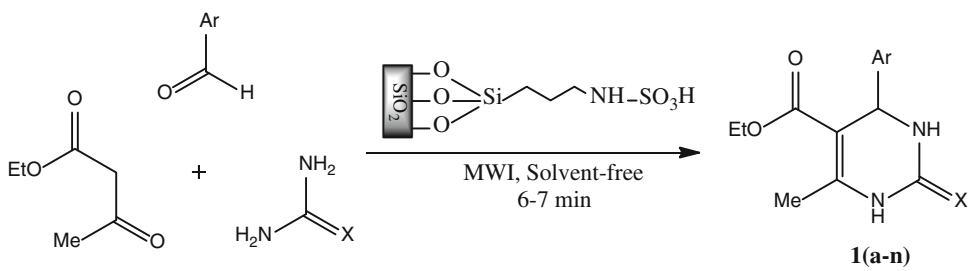
Results and discussion

It was showed that no desirable product could be detected when a mixture react in the absence of solid silica-based sulfonic acid, which indicated that the catalyst should be necessary. Then, the model reaction to synthesize **1k** by the reaction of ethyl acetoacetate, benzaldehyde, and urea was investigated with different amounts of solid silica-based sulfonic acid (0–5 mol%). Yields of the reaction in different conditions are shown in Table 1.

We found that most of the Lewis acids could promote the reaction, but the yields were not so high. In comparison with other catalysts, the use of 3 mol% of solid silica-based sulfonic acid could make the yield 95 % under the microwave power of 900 W and the irradiation time of 7 min. It could be seen that 3 mol% of solid silica-based sulfonic acid gave the best result of this reaction, although other factors could not yet be optimized.

Based on the above optimized results, i.e., 3 mol% amount of solid silica-based sulfonic acid as a catalyst, we further examined the effects of the microwave power and the irradiation time on the same model reaction to afford **1k**, as shown in Scheme 2. The results are listed in Table 2. It could be found that with the increase of the microwave power from 250 to 900 W, the yield of **1k** showed a linear increase from 48 % to 85 % when the irradiation time was 4 min. However, with the microwave power of 900 W, when we increased the microwave irradiation time, the yield of **1k** increased first, but a slight decrease was observed for more than 7 min. So, the optimized microwave power and the irradiation time were 900 W and 7 min, respectively.

The method can be used for wide range of reactants with different functional groups. We have synthesized some novel compounds containing methyl-substituted heteroaryl aldehydes (Table 3) and heteroaryl ester units (Table 4). All reactions proceeded expeditiously and delivered good yields with broad range of structurally diverse aryl and heteroaryl aldehydes used in this condensation. α, β-unsaturated aldehydes react selectively with aldehyde functional group, whereas acid sensitive heterocyclic aldehydes exclusively gave dihydropyrimidones in high yield. We found that electron donating or withdrawing group on aromatic aldehydes gave almost good to excellent yield. In all the cases, the pure product was isolated by simple filtration without use of any chromatography or cumbersome reaction workup.



1(a-n)

Scheme 2 Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones **1** (**a**–**n**)

Table 2 Effect of the microwave power and the irradiation time on the formation of **1k**

Entry	Time (min)	Power (W)	Yields (%)[a]
1	4	250	48
2	4	300	53
3	4	400	58
4	4	500	63
5	4	600	67
6	4	700	72
7	4	750	77
8	4	800	81
9	4	900	85
10	2	900	36
11	3	900	62
12	5	900	88
13	7	900	95
14	8	900	94
15	9	900	93

[a] Reaction conditions: benzaldehyde (2.5 mmol), ethyl acetoacetate (2.5 mmol), urea (2.5 mmol), solid silica-based sulfonic acid (3 mmol) in microwave irradiation of 900 W at 90 °C under solvent-free condition

Table 3 Solid-silica-based sulfonic acid catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones **1** (**a**–**n**)

Entry	Ar	X	Product[a]	Yield (%)[b]	M.p (°C)	
					Found	Reported[c]
1	3-CH_3–C_4H_2O	O	**1a**	93	217–219	–
2	5-CH_3–C_4H_2O	O	**1b**	92	229–301	–
3	3-CH_3–C_4H_2S	O	**1c**	91	217–219	–
4	5-CH_3–C_4H_2S	O	**1d**	90	223–225	–
5	1-CH_3–C_4H_3N	O	**1e**	87	194–196	–
6	C_4H_3O	O	**1f**	94	211–213	210–212
7	C_4H_3S	O	**1g**	93	200–202	202–203
8	C_4H_4N	O	**1h**	85	182–184	181–183
9	4-NO_2–C_6H_4	O	**1i**	92	212–214	211–213
10	4-Cl–C_6H_4	O	**1j**	89	215–217	213–215
11	C_6H_5	O	**1k**	95	206–208	205–207
12	C_6H_5	S	**1l**	89	208–210	209–211
13	3-NO_2–C_6H_4	S	**1m**	87	205–207	204–205
14	4-OCH_3–C_6H_4	S	**1n**	91	153–155	151–153

[a] Reaction conditions: aldehyde (2.5 mmol), ethyl acetoacetate (2.5 mmol), urea/thiourea (2.5 mmol), solid silica-based sulfonic acid (3 mmol) in microwave irradiation 990 W at 90 °C under solvent-free condition

[b] Isolated yields

[c] Products were characterized by comparison of their physical and spectroscopic data with those reported in the literature (Atul *et al.* 2009; Hitendra *et al.*, 2007)

This investigation has been extended to cyclic ketones like acetophenone and 2-acetyl thiophene (Scheme 3). The products formed **2**(**a**–**f**) are listed in Table 4.

With catalyst **2**, the proposed mechanism for the Biginelli reaction involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of the type **A** from aldehyde and urea component. Interception of the iminium ion **A** by ethyl acetoacetate produces an open chain ureide **B**, which subsequently cyclizes to dihydropyrimidinone **C** (Scheme 4).

The reusability of the catalyst was also investigated. For this purpose, the same model reaction to synthesize the compound **1k** was again studied under the optimized conditions. After completion of the reaction, the catalyst was filtered, washed with worm ethanol, dried at 100 °C under vacuum for 2 h, and reused for the same reaction process. As shown in Fig. 1, the catalyst could be reused for eight times with out reduction in the catalytic activity of the catalyst.

All the eight newly synthesized compounds **1**(**a**–**e**) and **2**(**a**–**c**) were screened for antihypertensive and calcium channel blocking activity. The results are summarized in Tables 5 and 7. Nifedipine was used as standard reference drug (Table 6) for screening of antihypertensive and

Table 4 Solid-silica-based sulfonic acid catalyzed synthesis of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-ones **2**(**a**–**f**)

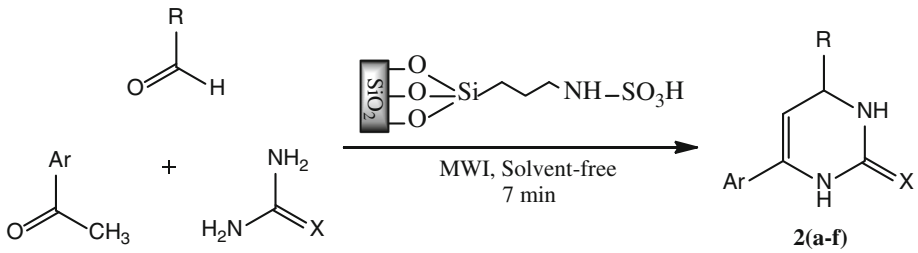
Entry	R	Ar	Products[a]	Yield[b] (%)	M.P (°C)	
					Found	Reported[c]
1	5-CH_3–C_4H_2O	C_4H_3S	**2a**	90	223–225	–
2	5-CH_3–C_4H_2S	C_4H_3S	**2b**	92	241–243	–
3	1-CH_3–C_4H_3N	C_4H_3S	**2c**	86	227–229	–
4	C_6H_5	C_6H_5	**2d**	91	234–236	233–235
5	4-(Cl)–C_6H_4	C_6H_5	**2e**	87	264–266	267–269
7	4-(CH_3O)–C_6H_4	C_6H_5	**2f**	89	257–259	259–261

[a] Reaction conditions: aldehyde (1 mmol), cyclic keto ester (1 mmol), urea/thiourea (1.5 mmol), solid silica-based sulfonic acid (3 mmol) in microwave irradiation of 900 W at 90 °C under solvent-free condition

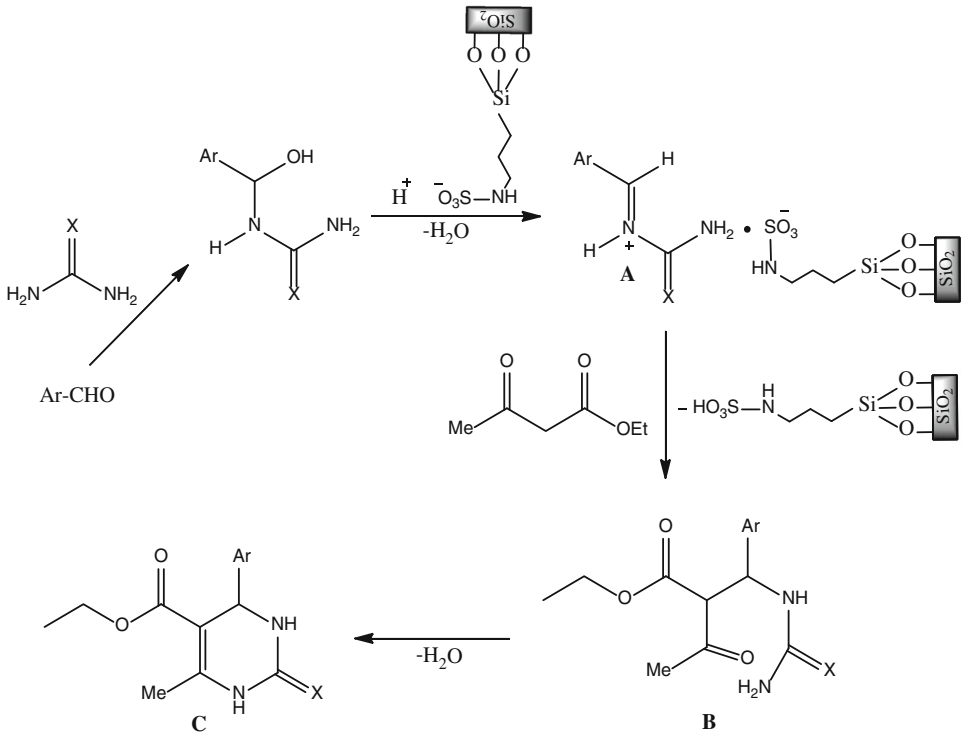
[b] Isolated yields

[c] Products were characterized by comparison of their physical and spectroscopic data with those reported in the literature (Anil *et al.*, 2007)

Scheme 3 Synthesis of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-ones **2**(**a**–**f**)



Scheme 4 Proposed mechanism for the formation of pyrimidine derivative



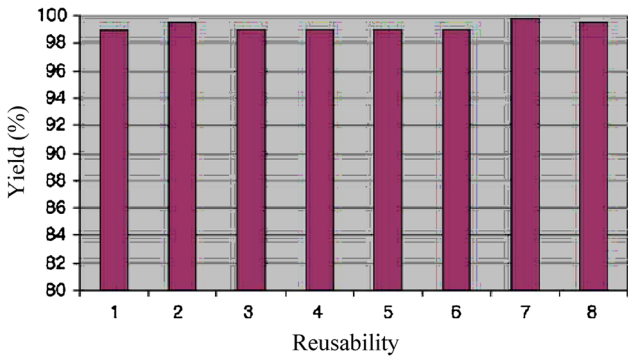
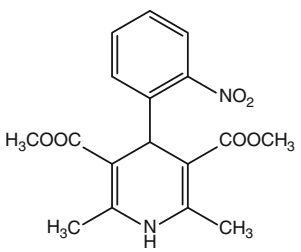
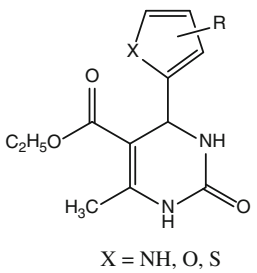


Fig. 1 Reusability of solid silica-based sulfonic acid

calcium channel blocking because nifedipine and test compounds both have similar bioisosteric nucleus. In the test samples (dihydropyrimidine ring) there are two nitrogen (N) atoms which are bioisosteric with (CH) and one methyl group (CH_3) which is bioisosteric with ketone (C=O) of nifedipine (dihydropyridine ring). The ester (–COO–) linkage of nifedipine is similar to the test compounds.



Nifedipine



Synthesized molecule

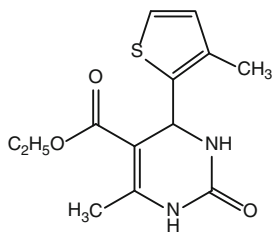
Compound **1c** was found to have better antihypertensive activity and compound **2a** found to have better calcium channel blocking activity.

Table 5 Screening of antihypertensive activity

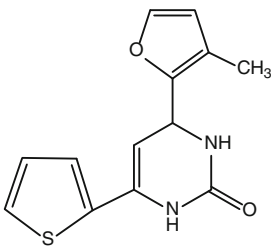
Compound	Dose (ml)	Control (mmHg) (H)	Test (mmHg) (h)	% inhibition in blood pressure
Nifedipine	0.3	29.17	20.00	31.44
	0.3	28.34	20.84	26.46
1a	0.3	29.17	24.17	17.14
	0.3	30.00	23.34	22.20
1b	0.3	27.50	21.67	21.20
	0.3	29.17	22.50	22.87
1c	0.3	29.17	20.00	31.44
	0.3	30.00	21.67	27.77
1d	0.3	29.17	25.00	14.30
	0.3	29.17	25.84	11.16
1e	0.3	29.17	24.17	17.14
	0.3	29.17	23.84	18.27
2a	0.3	28.34	22.50	20.61
	0.3	27.50	24.17	12.10
2b	0.3	28.34	22.50	20.61
	0.3	28.34	24.17	14.71
2c	0.3	28.34	25.00	11.79
	0.3	27.50	22.50	17.14

Table 6 Screening of Calcium channel blocking activity of Nifedipine

Compound	Dose (ml)	Control (cm) (H)	Test (cm) (h)	% inhibition	IC_{50} (μg/ml)
Nifedipine	0.1	3.4	3.0	11.76	20
	0.2	3.4	2.7	20.58	
	0.3	3.4	2.3	32.35	
	0.4	3.3	2.1	35.29	
	0.5	3.3	1.7	48.48	
	0.6	3.3	1.2	61.76	



1c



2a

Table 7 Screening of calcium channel blocking activity

Compound	Dose (ml)	Control (cm) (H)	Test (cm) (h)	% Inhibition	IC_{50} (μg/ml)
1a	0.1	3.3	3.0	9.09	
	0.3	3.3	2.3	30.30	22
	0.5	3.4	1.9	44.12	
1b	0.1	3.4	3.1	8.82	
	0.3	3.4	2.5	26.47	36.54
	0.5	3.3	2.4	27.72	
1c	0.1	3.3	3.1	6.06	
	0.3	3.3	2.4	27.27	21.06
	0.5	3.3	1.9	42.43	
1d	0.1	3.3	3.0	9.09	
	0.3	3.4	2.1	38.23	22
	0.5	3.3	2.0	41.18	
1e	0.1	3.4	3.0	11.76	
	0.3	3.4	2.8	17.65	21.10
	0.5	3.3	1.7	48.48	
2a	0.1	3.4	2.8	17.64	
	0.3	3.4	2.2	35.29	19.76
	0.5	3.4	1.7	50.00	
2b	0.1	3.4	2.5	26.47	
	0.3	3.3	2.3	30.30	28.99
	0.5	3.3	1.9	42.42	
2c	0.1	3.4	3.0	11.76	
	0.3	3.4	2.4	29.41	24.26
	0.5	3.4	2.0	41.18	

Conclusion

In summary we have developed a simple, efficient, and green protocol for the synthesis of dihydropyrimidinones using solid silica-based sulfonic acid catalyst under microwave irradiation in solvent-free conditions. The short reaction times, simple work-up in isolation of the products in high yields with high purity, mild reaction conditions, and recyclability of supported catalyst are features of this new procedure. The newly synthesized compounds **1**(**a–e**) and **2**(**a–c**) have been screened to antihypertensive and calcium channel blocking activity. Among them, compound **1c** was found to have better antihypertensive activity and compound **2a** found to have better calcium channel blocking activity. The remaining compounds revealed moderate to good antihypertensive and calcium channel blocking activity.

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