Synthesis of 3,4-Dihydropyrimidin-2(*1H*)-ones Using $HClO_4$-SiO_2 as a Heterogeneous and Recyclable Catalyst

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A simple and efficient synthesis of 3,4-dihydropyrimidinones or thiones is described, using silica-supported perchloric acid ($HClO_4$-SiO_2) as a heterogeneous catalyst from an aldehyde, β-dicarbonyl compound, and urea or thiourea under solvent-free conditions. Compared to the classical Biginelli reactions, this method consistently has the advantage of high yields, short reaction time, easy separation, and tolerance towards various functional groups.

Key Words : Dihydropyrimidinones, Dihydropyrimidinthiones, $HClO_4$-SiO_2, Silica-supported catalyst

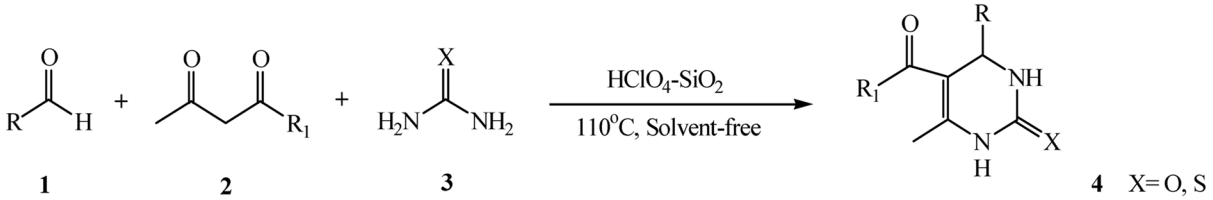
Introduction

3,4-Dihydropyrimidinones (DHPMs) and their sulfur analogs have attracted considerable interest because of their wide range of biological activities such as calcium channel blockers, antihypertensive, antiviral,[1] anti-carcinogenic,[2] anti-inflammatory,[3,4] antibacterial,[5] and alpha-1a-antagonists.[6,7] Additionally, their particular structure has been found in natural marine alkaloid batzalladines which are the first low molecular weight natural products reported in the literature to inhibit the binding of HIV gp-120-CD4 cell, so disclosing a new path towards the development of AIDS therapy.[8] Thus, the synthesis of these heterocyclic compounds is interesting for both organic synthesis and medicinal activity. Biginelli reaction for the synthesis of DHPMs has received renewed interest and several improved procedures have been reported. Some of them include an one-pot combination of boron trifluoride etherate/cuprous chloride,[9] a polyphosphate ester,[10] and an acidic clay montmorillonite KSF.[11] Recently, Lewis acids have also been used in order to improve the synthetic yields.[12-20] In addition, some other methods such as microwave-assisted,[21-23] solid-phase,[24] ultrasound,[25] and fluorous-phase[26] synthesis have been demonstrated to achieve the synthesis. However, in spite of their potential utility, most of these reported methods suffer from drawbacks such as harsh reaction conditions, cumbersome experimental procedures, and use of catalysts moisture sensitive, toxic, and expensive. Therefore, efficient chemical coupling of three or more components in a single operation by a catalytic process is valuable and the development of a new catalyst which is easily available, cost-effective and recoverable is an important goal of the modern organic synthesis.

Results and Discussion

Recently, $HClO_4$-SiO_2 has been found to be very efficient heterogeneous catalyst for β-keto enol ethers, enaminones, and enamino esters synthesis.[27,28] These results encouraged us to explore this catalyst for the synthesis of DHPMs. The catalyst can be easily prepared from the readily available ingredients, perchloric acid and silica gel.[29] A model study was conducted with benzaldehyde, ethyl acetoacetate, and urea to examine catalytic efficiency for DHPMs. The reaction was optimized under several temperature conditions (30, 50, 80, and 110 °C) with conversion yield and reactivity. The best result was achieved by undergoing the reaction at 110 °C under solvent-free conditions (Scheme 1). The condensation reaction did not occur in the absence of the catalyst even after prolonged reaction time.

Under the optimized reaction condition, similar condensation using various aldehydes, 1,3-dicarbonyl compounds, and urea or thiourea were investigated. Aromatic aldehydes having electron-donating as well as electron-withdrawing substituents underwent the conversion smoothly. All reactions were complete within 15-40 min. Electron-withdrawing groups were observed to accelerate the reaction compared to electron-donating groups. Previous Lewis acid



1 **2** **3** **4**

Scheme 1

Table 1. $HClO_4$-SiO_2 catalyzed one-pot synthesis of 3,4-dihydropyrimidinones or thiones under solvent-free conditions

Entry	R	R_1	X	Time (min)	Product	Yield (%)
1	C_6H_5	OEt	O	20	**4a**	98 (95)[a]
2	4-(CH_3O)-C_6H_4	OEt	O	30	**4b**	85 (81)[a]
3	2,4-$(Cl)_2$-C_6H_3	OEt	O	22	**4c**	88
4	C_6H_5CH=CH	OEt	O	30	**4d**	95
5	4-(OH)-C_6H_4	OEt	O	28	**4e**	92
6	4-(NO_2)-C_6H_4	OEt	O	20	**4f**	94
7	2-(Cl)-C_6H_4	OEt	O	18	**4g**	89
8	4-(Cl)-C_6H_4	OEt	O	20	**4h**	87
9	2,4,6-$(OCH_3)_3C_6H_2$	OEt	O	30	**4i**	95 (90)[a]
10	2-Thienyl	OEt	O	30	**4j**	96 (92)[a]
11	3-(NO_2)-C_6H_4	OEt	O	22	**4k**	92
12	4-(CH_3)-C_6H_4	OEt	O	18	**4l**	95
13	2-(Br)-C_6H_4	OEt	O	25	**4m**	92
14	2-(OH)-C_6H_4	OEt	O	35	**4n**	89
15	4-(F)-C_6H_4	OEt	O	32	**4o**	90
16	*n*-Bu	OEt	O	20	**4p**	88
17	C_6H_5	OMe	O	15	**4q**	99 (94)[a]
18	4-(CH_3O)-C_6H_4	OMe	O	35	**4r**	95 (91)[a]
19	2,4-$(Cl)_2$-C_6H_3	OMe	O	15	**4s**	88
20	4-(F)-C_6H_4	OMe	O	30	**4t**	86
21	4-(NO_2)-C_6H_4	OMe	O	20	**4u**	96
22	C_6H_5	CH_3	O	20	**4v**	98 (94)[a]
23	4-(CH_3O)-C_6H_4	CH_3	O	28	**4w**	89 (86)[a]
24	4-(NO_2)-C_6H_4	CH_3	O	20	**4x**	93
25	C_6H_5	OEt	S	40	**4y**	95
26	4-(CH_3O)-C_6H_4	OEt	S	40	**4z**	93

[a]Isolated yield (%) of the catalyst recycling reactions.

catalyzed condensation required several hours for the completion.[12-20] DHPMs were formed as a single product and isolated in high yields (Table 1). Acid-sensitive aldehyde such as cinnamaldehyde was adopted well without the formation of any side products, which normally underwent polymerization in the presence of protic acids (Table 1, entry 4). Aliphatic aldehydes were also undergone to afford the corresponding DHPMs in high yields (Table 1, entries 16). The results using acetylacetone and methyl acetoacetate were also tabled instead of ethyl acetoacetate (Table 1, entries 17-24). Thiourea was introduced to generate 3,4-dihydropyrimidin-2(1*H*)-thiones which were also of much interest with regard to biological activity.[7] Thio analog products of DHPMs (Table 1, entries 25-26) were successfully synthesized under the similar condition. Another meaningful aspect of the present procedure is tolerance towards various functional groups such as Cl, OH, NO_2, OMe, and heterocyclic moieties under the reaction conditions. Every substituent in aldehyde component has been accommodated and remained after the reaction. The heterogeneous catalyst could be easily isolated by filteration from the reaction mixture. $HClO_4$-SiO_2 was recovered and reused without further activation. Only slight reduction in the catalytic activity was found during consecutive use of the recovered catalyst, showing yield variation of less than 5% in the formation of DHPMs in the Table 1.

A plausible mechanism for the catalytic synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones or thiones is suggested on the basis of our own observations and the literature[30] and described in Scheme 2.

Summary

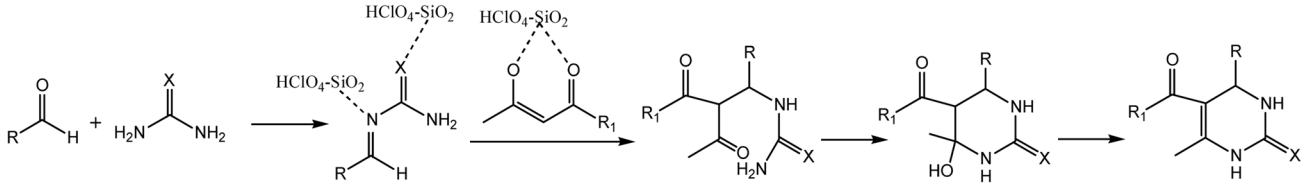
We have developed a simple and efficient procedure for the synthesis of dihydropyrimidinones or thiones, using $HClO_4$-SiO_2 as a heterogeneous catalyst. The present procedure describes useful improvement in the reaction condition for the Biginelli condensation. The mild reaction conditions, rapid conversion, high yields, simple experimental procedure, and catalyst reusability are notable advantages of the present method.

Experimental Section

General procedure for the synthesis of DHPMs: A mixture of an aldehyde (10.0 mmol), β-dicarbonyl compound (10.0 mmol) and urea or thiourea (12.0 mmol) and catalytic amount of $HClO_4$-SiO_2 (0.50 g) was stirred at 110 °C for 15 to 40 min. After complete disappearance of starting material as indicated by TLC, the resulting mixture was diluted with ethyl acetate (50 mL) and filtered. The catalyst was completely recovered from the residue. The filtrate was concentrated under vacuo and the product was purified by silica gel column chromatography using ethyl acetate and hexane as eluent to afford pure 3,4-dihydropyrimidin-2(1*H*)-ones in high yields. The spectral and analytical data of some of the representative compounds are given below.

Compound **4a**: IR (KBr) ν_{max} 3242, 1725, 1640, 1462, 1319, 1232, 1092, 780 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.73 (s, 1H), 7.28 (m, 5H), 5.15 (s, 1H), 3.99 (q, J = 7.1 Hz, 2H), 2.26 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); LCMS: *m*/*z* 260 $[M]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%. Found: C, 64.54; H, 6.24; N, 10.85%.

Compound **4b:** IR (KBr) ν_{max} 3241, 1702, 1647, 1460,



Scheme 2

1319, 1230, 1092, 782 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.19 (s, 1H), 7.69 (s, 1H), 7.16 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.07 (s, 1H), 3.99 (q, J = 7.1 Hz, 2H), 3.72 (s, 3H), 2.25 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H); LCMS: m/z 290 $[M]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.08; H, 6.20; N, 9.65%. Found: C, 61.66; H, 6.25; N, 9.56%.

Compound **4i:** IR (KBr) ν_{max} 3244, 2940, 1703, 1641, 1462, 1319, 1230, 1092, 780 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.17 (s, 1H), 7.68 (s, 1H), 6.62 (s, 2H), 5.50 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.70 (s, 3H), 2.99 (s, 6H), 2.38 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); LCMS: m/z 350 $[M]^+$. Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.28; N, 8.00%. Found: C, 58.24; H, 6.32; N, 8.15%.

Compound **4j:** IR (KBr) ν_{max} 3430, 3249, 2930, 1705, 1650, 1430, 1231, 1096, 791 cm^{-1}; ^{1}H-NMR: (200 MHz, DMSO-d_6): δ 9.22 (s, 1H), 7.71 (s, 1H), 6.89-6.96 (m, 3H), 5.51 (s, 1H), 4.18 (q, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H); LCMS: m/z 266 $[M]^+$. Anal. Calcd for $C_{12}H_{14}N_2O_3S$: C, 54.13; H, 5.26; N, 10.52; S, 12.03%. Found: C, 54.10; H, 5.30; N, 10.56; S, 12.08%.

Compound **4q:** IR (KBr) ν_{max} 3332, 1696, 1651, 1462, 1319, 1231, 1092, 781 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.23 (s, 1H), 7.75 (s, 1H), 7.34-7.21 (m, 5H), 5.15 (d, J = 2.8 Hz, 1H), 3.53 (s, 3H), 2.25 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); LCMS:m/z 246 $[M]^+$. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.71; N, 11.38%. Found: C, 63.56; H, 5.74; N, 11.29%.

Compound **4r:** IR (KBr) ν_{max} 3360, 1697, 1645, 1460, 1319, 1230, 1090, 780 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.20 (s, 1H), 7.68 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.08 (d, J = 2.8 Hz, 1H), 3.70 (s, 3H), 3.52 (s, 3H), 2.24 (s, 3H), LCMS: m/z 276 $[M]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.80; N, 10.15%. Found: C, 60.78; H, 5.87; N, 10.08%.

Compound **4v:** IR (KBr) ν_{max} 3257, 1699, 1670, 1466, 1316, 1228, 1092, 784 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.15 (s, 1H), 7.77 (s, 1H), 7.20-7.34 (m, 5H), 5.25 (d, J = 2.4 Hz, 1H), 2.25 (s, 3H), 2.06 (s, 3H); LCMS: m/z 230 $[M]^+$. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17%. Found: C, 67.86; H, 6.20; N, 12.12%.

Compound **4w:** IR (KBr) ν_{max} 3242, 1715, 1624, 1460, 1318, 1230, 1092, 784 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.16 (s, 1H), 7.78 (s, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.20 (d, J = 3.0 Hz, 1H), 3.70 (s, 3H), 2.29 (s, 3H); 2.06 (s, 3H); LCMS: m/z 260 $[M]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%. Found: C, 64.65; H, 6.28; N, 10.82%.

Compound **4y:** IR (KBr) ν_{max} 3252, 1651, 1598, 1561, 1230, 1092, 780 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 10.32 (s, 1H), 9.64 (s, 1H), 7.35-7.20 (m, 5H), 5.16 (d, J = 3.5 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 2.28 (s, 3H); 1.09 (t, J = 7.0 Hz, 3H); LCMS: m/z 276 $[M]^+$. Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; S, 11.60% Found: C, 60.80; H, 5.90; N, 10.20; S, 11.65%.

Compound **4z:** IR (KBr) ν_{max} 3250, 1651, 1598, 1564, 1238, 1090, 780 cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d_6): δ 10.29 (s, 1H), 9.58 (s, 1H), 7.14-6.88 (m, 4H), 5.10 (s, 1H), 3.99 (q, J = 7.0 Hz, 2H), 3.71 (s, 3H), 2.27 (s, 3H), 1.09 (t, J = 7.0 Hz, 3H); LCMS: m/z 306 $[M]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14; S, 10.47% Found: C, 58.86; H, 5.98; N, 9.22; S, 10.51%.

Other products (**4**c-h, k-p, s-u, and x) were confirmed with literature data.[10-20]

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