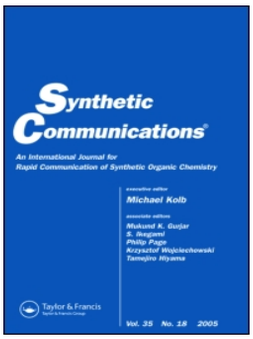

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XANTHAN SULFURIC ACID: A NEW AND EFFICIENT BIOSUPPORTED SOLID ACID CATALYST FOR THE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1H)-ONES

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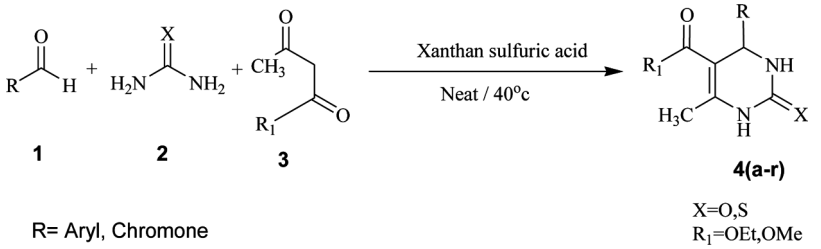
GRAPHICAL ABSTRACT



Abstract *Xanthan sulfuric acid (XSA) is employed as a recyclable catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones. These syntheses were performed via a one-pot, three-component condensation of aldehydes, amines, and urea/thiourea under solvent-free conditions.*

Keywords Biginelli reaction; 3,4-dihydropyrimidin-2(1H)-ones; one-pot synthesis; solvent-free conditions

INTRODUCTION

Evolution of organic synthesis involving environmentally clean protocols under solvent-free conditions has emerged as an area of great interest from both environmental and economical points of view.[1] 3,4-Dihydropyrimidin-2(1H)-ones attract increasing interest because of their diverse therapeutic and pharmacological properties.[2,3] They are also reported to serve as calcium channel blockers, antihypertensive agents, α_{1a} antagonists, and anti-HIV agents.[4] The biological activities of some marine alkaloids isolated recently have been attributed to the presence of a dihydropyrimidinone moiety.[5] To prepare the compounds, the first protocol was presented by Biginelli[6] more than a century ago, a one-pot condensation of

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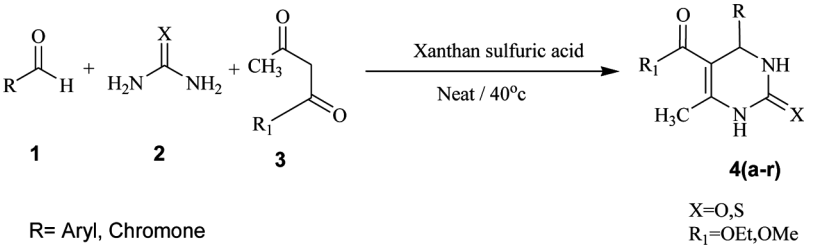

1 2 3 4(a-r)

Scheme 1. Synthesis of 3,4-dihydropyrimidine-2(1H)-ones using xanthan sulfuric acid.

β-ketoester, aldehyde, and urea under strongly acidic conditions. This method has its own merits and drawbacks. A major drawback of the classical Biginelli reaction is poor to moderate yields, particularly when the reaction is performed with an aliphatic aldehyde.[7] To improve the efficiency of the Biginelli reaction, a number of Lewis acids as well as protic acids as promoters such as BF_3 etherate / copper (II) acetate,[8] polyphosphonate ester (PPE),[9] montmorillonite,[10] $InCl_3$,[11] lanthanide triflate,[12] H_2SO_4,[13] ion-exchange resin,[14] 1-*n*-butyl- 3-methyl imidazolium tetra fluoroborate ($BMImBF_4$),[15] $BiCl_3$,[16] $LiClO_4$,[17] $InBr_3$,[18] $FeCl_3$,[19] $ZrCl_4$,[20] $Cu(OTf)_2$,[21] $Bi(OTf)_3$,[22] ytterbium triflate,[23] NH_4Cl[24] have been used. However, many of these protocols have some drawbacks, such as use of expensive, highly acidic catalysts and prolonged reaction times. In addition, the yields of the corresponding 3,4-dihydropyrimidin-2(1H)-ones are not always satisfactory. Because of the importance of the Biginelli reaction, milder, faster, and more ecofriendly methods accompanied by higher yields are need to be introduced. Therefore, the search continues for a better catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones in terms of operational simplicity, reusability of catalyst, low cost, and greater selectivity.

Xanthan and its derivatives[25–27] have some unique properties, which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Xanthan is the most abundant bacterial exopolysaccharide in the world and is produced through fermentation. It has been widely studied during the past decades, as it is a biodegradable material and a renewable resource. Unlike other gums, it is very stable under a wide range of temperatures and pH values. Xanthan sulfuric acid can be easily prepared by the reaction of xanthan with chlorosulfonic acid; the number of acidic (H^+) sites in xanthan sulfuric acid is determined by acid–base titration to be 0.6 meq/g.

In continuation of our efforts to improve the Biginelli reaction,[28] and as part of our ongoing interest, we here report a straightforward and versatile method to afford 3,4-dihydropyrimidin-2(1H)-ones in good yield by employing xanthan sulfuric acid, as a mild acid catalyst.

RESULTS AND DISCUSSION

Preparations of biologically important compounds are in high demand in organic chemistry. Therefore here we describe a mild and efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones using xanthan sulfuric acid[29] as a catalyst under

Table 1. Effect of various solvents[a]

Entry	Solvent	Yields[b] (%)
1	Neat	95[c]
2	Acetonitrile	75
3	Ethanol	92
4	Dichloroethane	50
5	Toluene	82
6	Methanol	86

[a]Reaction conditions: benzaldehyde (1 mmol), EAA (1 mmol), urea (1.5 mmol), and xanthan sulfuric acid (0.1 g) stirred at 40 °C under solvent-free conditions.
[b]Isolated yields.
[c]The same catalyst was used for four runs.

Table 2. Results of recyclability of the xanthan sulfuric acid[a]

Run	Cycle	Time (min)	Yield (%)
1	0	20	95
2	1	20	94
3	2	20	91
4	3	20	84

[a]Reaction conditions: benzaldehyde (1 mmol), EAA (1 mmol), urea (1.5 mmol), and xanthan sulfuric acid (0.1 g) stirred at 40 °C under solvent-free conditions.

solvent-free conditions. We explore catalytic properties of xanthan sulfuric acid under solvent-free conditions for the Biginelli reaction. The reaction proceeded smoothly without any solvent at 40 °C with a catalytic amount of xanthan sulfuric acid. Yields are excellent with high purity.

The model reaction was also examined in various solvents as well as under solvent-free conditions in the presence of 0.1 g of xanthan sulfuric acid (Table 1). The results showed that the efficiency and the yield of the reaction under solvent-free conditions were better than those obtained in other solvents.

We can easily separate xanthan sulfuric acid from the reaction medium by washing it with $CHCl_3$ and drying in an oven (50 mm Hg pressure) at 60 °C for 3 h prior to use in the other reaction. The recovered catalyst can be reused at least three additional times in subsequent reactions without significant loss in product yield (Table 2).

EXPERIMENTAL

All the melting points are uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC). Infrared (IR) spectra (KBr) were recorded on a Shimadzu Fourier transofrm (FTIR)–model 8010 spectrometer, and the ^{1}H NMR spectra were recorded on a Varian Gemini 200-MHz spectrometer using tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. All solvents and reagents were purchased from Aldrich and Fluka.

Typical Procedure for Synthesis of Dihydropyrimidinones (4a–r)

Xanthan sulfuric acid (0.1 g) was added to the mixture of aldehyde (1 mmol), 1,3-dicarbonyl compound (1 mmol), and urea or thiourea (1.5 mmol). The reaction mass was stirred at 40 °C for an appropriate time (Table 3). The reaction progress was checked by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and $CHCl_3$ (15 ml) was added. The catalyst was filtered off, the solid was washed with $CHCl_3$ (5 ml), and the combined $CHCl_3$ solution was concentrated in a vacuum to afford the crude product. The pure product was obtained by further recrystallization from ethanol.

We examined the amount of catalyst loading in reaction. The best results were obtained by using 0.1 g of catalyst (yield 95%). If the catalyst is less than 0.1 g, poor yields are obtained. In the absence of catalyst, yields are in traces (Table 4).

Product Characterization Data

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (Table 1, Entry 4a). Mp 201–203 °C. ^{1}H NMR: δ 9.21 (s, 1H, NH), 7.73 (s, 1H, NH), 7.27 (m, 5H, Ar-H), 5.14 (s, 1H,CH), 3.99 (q, 2H, OCH_2), 2.23 (s, 3H, CH_3), 1.08 (t, 3H, CH_3); IR (KBr): 3243, 1722, 1639 cm^{-1}. EIMS, 70 ev, m/z: 260 (M^+). Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.72; H, 6.29; N, 10.66.

Table 3. Xanthan sulfuric acid–catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions

Product	Aldehyde	R_1	X	Time (min)	Yield[b] (%)
4a	Benzaldehyde	OEt	O	20	95
4b	4-Methoxybenzaldehyde	OEt	O	30	94
4c	4-Nitrobenzaldehyde	OEt	O	25	91
4d	4-Chlorobenzaldehyde	OEt	O	20	92
4e	4-Fluorobenzaldehyde	OEt	O	25	90
4f	2,4-Dichlorobenzaldehyde	OEt	O	30	89
4g	2-Bromobenzaldehyde	OEt	O	30	92
4h	4-Hydroxybenzaldehyde	OEt	S	20	90
4i	4-Methyoxybenzaldehyde	OEt	S	40	93
4j	Benzaldehyde	OMe	O	25	90
4k	4-Methoxybenzaldehyde	OMe	O	20	89
4l	4-Nitrobenzaldehyde	OMe	O	20	88
4m	2,4-Dichlorobenzaldehyde	OMe	O	20	81
4n	4-Flourobenzaldehyde	OMe	O	30	83
4o	6-Nitro-4-oxo-*4H*-chromene-3-carbaldehyde	OEt	O	20	74
4p	2-Naphthaldehyde	OEt	S	25	78
4q	4-Hydroxy-2-oxo-2H-chromene-8-carbaldehyde	OEt	O	40	72
4r	4-Oxo-*4H*-chromene-3-carbaldehyde	OEt	O	30	76

[a]All the compounds are known; characterized by IR, ^{1}H NMR, and mass spectral analysis; and compared with the authentic samples.

[b]Isolated yields.

Table 4. Influence of xanthan sulfuric acid on reaction rates and yields[a]

Entry	Catalyst (g)	Time (min)	Yield (%)[b]
1	None	120	Trace
2	0.01	20	25
3	0.04	20	51
4	0.08	20	81
5	0.1	20	95
6	0.1	40	95

[a]Reaction conditions: Mixture of benzaldehyde (1 mmol), EAA (1 mmol), urea (1.5 mmol), and xanthan sulfuric acid (0.1 g) stirred at 40 °C under solvent-free conditions.
[b]Isolated yield.

Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(6-nitro-4-oxo-4H-chromen-3-yl)-2-oxopyrimidine-5-carboxylate (Table 3, Entry 4o). Mp 90 °C. ^{1}H NMR (DMSO-d_6): δ 9.13 (bs, 1H, NH), 7.92 (bs, 1H, NH), 7.12–7.25 (m, 3H, Ar-H), 7.02 (s, 1H, CH), 5.18 (s, 1H, C_4-H), 4.09 (q, 2H, OCH_2), 2.40 (s,3H, CH_3), 1.75 (t, 3H, CH_3); IR (KBr): 3250, 3196, 1734, 1716, 1652 cm^{-1}. EIMS, 70 ev, m/z: 373 (M^+). Calcd. for $C_{17}H_{15}N_3O_7$: C, 54.69; H, 4.05; N, 11.26. Found: C, 54.62; H, 4.16; N, 11.06.

Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(naphthalen-6-yl)-2-thioxopyrimidine-5-carboxylate (Table 3, Entry 4p). Mp 149–150 °C. ^{1}H NMR (DMSO-d_6): δ 9.27 (bs, 1H, NH), 7.52 (bs, 1H, NH), 7.20–7.81 (m, 7H, CH), 5.19 (s, 1H, C_4-H), 3.97 (q, 2H, OCH_2), 2.25 (s,3H, CH_3), 1.10 (t, 3H, CH_3); IR (KBr) : 3245, 3170, 1723, 1639 cm^{-1}. EIMS, 70 ev, m/z: 326 (M^+). Calcd. for $C_{17}H_{15}N_3O_7$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.31; H, 5.44; N, 8.62.

Ethyl 1,2,3,4-tetrahydro-4-(7-hydroxy-2-oxo-2H-chromen-8-yl)-6-methyl-2-oxopyrimidine-5-carboxylate (Table 3, Entry 4q). Mp 121–122 °C. ^{1}H NMR (DMSO-d_6): δ 9.23 (bs, 1H, NH), 8.01 (d, 1H, C_4-H), 7.90 (bs,1H, NH), 7.57 (d, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 6.35 (d, 1H), 5.12 (d, 1H, C_4-H), 3.97 (q, 2H, OCH_2), 2.20 (s,3H, CH_3), 1.17 (t, 3H, CH_3); IR (KBr): 3415, 3,315, 1728, 1710, 1690 cm^{-1}. EIMS, 70 ev, m/z: 344 (M^+). Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.37; H, 4.54; N, 8.09.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(4-oxo-4H-chromen-3-yl) pyrimidine-5-carboxylate (Table 3, Entry 4r). Mp 110 °C. ^{1}H NMR (DMSO-d_6): δ 9.40 (bs, 1H, NH), 8.20 (d, 1H, Ar-H), 7.90 (bs, 1H, NH), 7.45-7.60 (m, 3H, Ar-H), 6.95 (1H, CH), 5.10 (s, 1H, C_4-H), 4.12 (q, 2H, OCH_2), 2.20 (s, 3H, CH_3), 1.25 (t, 3H, CH_3); IR (KBr): 3310, 3170, 1734, 1710, 1695 cm^{-1}. EIMS, 70 ev, m/z: 328 (M^+). Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.27; H, 4.83; N, 8.59.

CONCLUSION

In conclusion, we have developed a mild, simple, cost-effective procedure for the synthesis of 3,4-dihydropyrimidinones/thiones using a reusable solid acid

catalyst. Moreover, the mild reaction conditions, good yield of products, easy work-up, ready availability of the catalyst, and the ecologically clean procedure make the present method a useful and important addition to the present methodologies for the Biginelli synthesis.

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