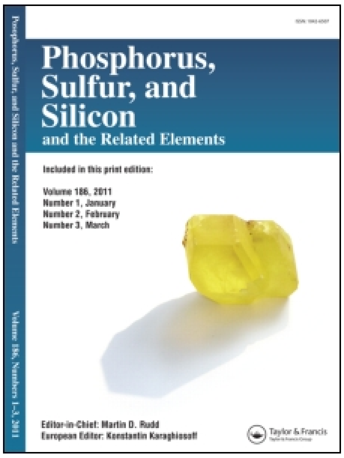

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$Al(HSO_4)_3$ and Al_2O_3-SO_3H as Efficient Catalysts for Modified Preparation of 3,4-Dihydropyrimidin-2 (1*H*)-ones/thiones

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An environmentally friendly procedure for the preparation of dihydropyrimidinone derivatives or their sulfur analogues under thermal solvent-free conditions in the presence of aluminium hydrogen sulfate [$Al(HSO_4)_3$] and alumina sulfuric acid (Al_2O_3-SO_3H) as heterogeneous catalysts was developed.

Keywords Aluminium hydrogen sulfate; alumina sulfuric acid; Biginelli reaction; 3,4-dihydropyrimidin-2(1*H*)-ones/thiones

INTRODUCTION

Dihydropyrimidinones (DHPMs) and their derivatives have attracted interest in medicinal chemistry because they exhibit a wide range of biological, pharmacological, and therapeutic properties.[1] DHPMs can serve as the integral backbones of several calcium channel blockers.[2] They are also reported to have antibacterial, antioxidant, antiviral, antitumor, anti-inflammatory, α-1a-antagonist, and neuropeptide Y (NPY) antagonist activities.[3–6]

The classical Biginelli reaction of an aldehyde, 1,3-dicarbonyl, and urea or thiourea requires strongly acidic conditions with relatively low yields, high reaction times, and harsh conditions.[7] In order to improve the efficiency of Biginelli reaction, a number of catalysts have been developed. These include ammonium chloride,[8] $ZrCl_4$ or $ZrOCl_2$,[9]

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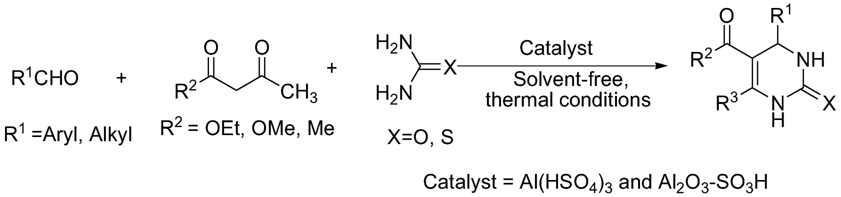
vanadium(III) chloride,[10] chloroacetic acid,[11] graphite-supported lanthanum chloride,[12] alkylammonium and alkylimidazolium perhaloborates, phosphates, and aluminates,[13] 1,1,3,3-tetrametylguanidinium trifluoroacetate,[14] ferric chloride and boric acid,[15] sulphamic acid,[16] tetrabutyl ammonium hydrogensulfate,[17] and polyphosphate ester (PPE).[18] However, many of these methods suffer from the drawbacks inconsistent with green chemistry, such as the use of toxic chemicals and heavy metals. Therefore utilization of clean processes as well as eco-friendly and green catalysts has been a subject of intense research. The demand for environmentally benign procedures with heterogeneous catalysts prompted us to develop a safe alternate method for the synthesis of dihydropyrimidinones (DHPMs) as biologically important compounds in the presence $Al(HSO_4)_3$ and alumina sulfuric acid (Al_2O_3-SO_3H) as heterogeneous catalysts (Scheme 1).



SCHEME 1 The synthesis of dihydropyrimidinones (DHPMs) in the presence of aluminum hydrogen sulfate and alumina sulfuric acid as catalysts.

In this research, $Al(HSO_4)_3$ and alumina sulfuric acid (Al_2O_3-SO_3H) as heterogeneous solid acid catalysts deserve special mention. These catalysts are safe, easy to handle, environmentally benign, and present fewer disposal problems. $Al(HSO_4)_3$[19] and alumina sulfuric acid (0.2 g of alumina sulfuric acid equal to 0.6 mmol H^+)[20] were prepared according to the reported procedures.

RESULTS AND DISCUSSION

In order to be able to carry out Biginelli condensation in a more efficient way and minimizing the time, temperature, and amount of the catalyst, the reaction of benzaldehyde, ethyl acetoacetate, and urea was selected as a model system to investigate the effects of the catalyst at different reaction temperatures (50, 60, 100, and 120°C) and different amounts of catalyst (5, 10, 15, 20, 25, and 30 mol%). The best result was obtained by carrying out the reaction with 1:1.2:1.5 molar ratios of aldehyde, 1,3-dicarbonyl compound, urea and 10 mol% of $Al(HSO_4)_3$ at 100°C under thermal solvent-free conditions. We also used alumina sulfuric acid (Al_2O_3-SO_3H) as catalyst in the model system to find optimization conditions at the same molar ratios. The best result was obtained by using 15 mol% of Al_2O_3-SO_3H at 120°C.

Using these optimized reaction conditions, the scope and efficiency of these procedures were explored for the synthesis of a wide variety of substituted 3,4-dihydropyrimidin-2(1*H*)-ones or their sulfur analogues. The results are summarized in Table I.

As shown in Table I, aromatic aldehydes with both electron-withdrawing and electron-donating substituents reacted efficiently with urea/thiourea and methyl/ethyl acetoacetate or acetylacetone in the presence of a catalytic amount of $Al(HSO_4)_3$ (10 mol %) or Al_2O_3-SO_3H (15 mol%), forming the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones/thiones without the formation of any side products, in good to high yields (Table I).

TABLE I Synthesis of 3,4-Dihydropyrimidin- 2(1*H*)-ones/thiones

Entry	R^1	R^2	X	$Al(HSO_4)_3$ Time (min)/ Yield (%)[a]	Al_2O_3-SO_3H Time (h)/ Yield (%)[a]	mp°C (lit mp°C)
1	C_6H_5	C_2H_5O	O	35/79	2.1/88	203–205 (200–202)[8]
2	4-ClC_6H_4	C_2H_5O	O	55/90	1.6/94	210–212 (209–211)[8]
3	$(CH_3)_2CH$	C_2H_5O	O	150/55	3.3/69	195–197 (196–197)[11]
4	C_6H_5	C_2H_5O	S	30/80	2.7/81	205–207 (205–206)[8]
5	3-ClC_6H_4	C_2H_5O	S	110/83	1.5/81	196–198 (192–196)[9]
6	4-$NO_2C_6H_4$	C_2H_5O	S	90/79	2.5/83	108–110 (107–108)[14]
7	3-$OMeC_6H_4$	C_2H_5O	S	100/76	1.7/73	150–152 (150–152)[12]
8	4-HOC_6H_4	C_2H_5O	S	50/60	2.1/75	194–196 (193–195)[11]
9	2,4-$Cl_2C_6H_3$	CH_3O	O	20/92	1.7/85	252–254 (252–253)[11]
10	3-$NO_2C_6H_4$	CH_3O	O	15/74	2.7/74	276–278 (279–280)[8]
11	C_6H_5	CH_3O	S	10/87	1.8/84	221–223 (221–222)[11]
12	3-$NO_2C_6H_4$	CH_3O	S	30/86	2.7/68	237–239 (237)[16]
13	4-HOC_6H_4	CH_3O	S	10/77	1.1/81	226–228 (227)[16]
14	4-$(Me)_2NC_6H_4$	CH_3O	S	110/67	1.5/70	152–154 (152–153)[12]
15	C_6H_5	CH_3	O	20/90	0.6/93	234–236 (232–235)[8]
16	C_6H_5	CH_3	S	15/91	1.1/93	216–217 (214–215)[9]
17	2-ClC_6H_4	CH_3	S	40/82	1.6/88	173–174 (173–174)[9]
18	3-ClC_6H_4	CH_3	S	15/80	1.1/87	244–246 (243–245)[9]
19	4-FC_6H_4	CH_3	S	25/92	0.7/93	209–211 (209–212)[13]
20	4-$NO_2C_6H_4$	CH_3	S	25/74	1.6/81	207–209 (207–209)[13]

[a] Yields refer to the pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of melting points, and IR and NMR spectra with authentic samples.[8–18]

TABLE II Comparison of the Results of $Al(HSO_4)_3$ and Al_2O_3-SO_3H with Other Catalysts Reported in the Literature

Entry	Catalyst (mol %)	Conditions (molar ratio)[a]	Time/Yield (%)
1	$Al(HSO_4)_3$ (10)	Solvent-free/100°C (1/1.2/1.5)	10–150 min/55–92
2	Al_2O_3-SO_3H(15)	Solvent-free/120 °C (1/1.2/1.5)	0.6–3.3 h/68–94
3	NH_4Cl (40)	Solvent-free/100°C (1/1/1.5)	3 h/42–92
4	$ZrOCl_2.8H_2O$ (15)	Solvent-free/90–100°C (1/1/1.3)	30–180 min/40–99
5	VCl_3 (10)	CH_3CN/Reflux (1/1/1.5)	2 h/65–96
6	Chloroacetic acid (10)	Solvent-free/90 °C (1/1.1/1.5)	3 h/47–98

[a] The molar ratio of aldehyde/1,3-dicarbonyl compounds/urea or thiourea.

To show the merit of the present work in comparison with reported results in the literature, we compared results of aluminium hydrogen sulfate and alumina sulfuric acid with ammonium chloride,[8] $ZrOCl_2$,[9] vanadium(III) chloride,[10] and chloroacetic acid[11] in the synthesis of Biginelli compounds. As shown in Table II, $Al(HSO_4)_3$ and Al_2O_3-SO_3H can act as effective catalysts with respect to reaction times, yields, and the obtained products.

In conclusion, we have developed a simple, cost-effective, and green procedure for the synthesis of 3,4-dihydropyrimidinones/thiones using aluminium hydrogen sulfate and alumina sulfuric acid as heterogeneous catalysts under thermal solvent-free conditions.

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR and ^1H NMR spectra). The NMR spectra were recorded on a Bruker Avance DPX 300 MHz instrument. Mass spectra were recorded on an Agilent Technologies 5973 network mass selective detector (MSD) operating at an ionization potential of 70 eV. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica-gel polygram SIL G/UV 254 plates.

Typical Experimental Procedure for the One-Pot Preparation of 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

A mixture of benzaldehyde (4 mmol), ethyl acetoacetate (4.8 mmol), urea (6 mmol), and $Al(HSO_4)_3$ (0.4 mmol) at 100°C or Al_2O_3-SO_3H

(0.2 g, 0.6 mmol H^+) at 120 °C was stirred in an oil bath for the appropriate time (Table I). After completion of the reaction as indicated by TLC, the resulting solidified mixture was diluted with ethyl acetate (5 mL), and the catalyst was separated by simple filtration and washed with ethyl acetate (2 × 5 mL). The filtrate obtained was washed with water (2 × 10 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure yielded crude product, which was purified by recrystallization with ethanol to afford pure 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (Table I, Entry 1).

The desired pure products were characterized by comparison of their physical data with those of known 3,4-dihydropyrimidin-2(1*H*)-ones/thiones, which are reported in the litrature.[8–18]

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