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An Efficient Synthesis of Multi-Substituted 3,4-Dihydropyrimidin-2(1H)-ones/thiones Under Solvent-Free Microwave Irradiation Using Alumina Sulfuric Acid

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A new and efficient method for the synthesis of multi-substituted dihydropyrimidinone derivatives or their sulfur analogs has been developed under solvent-free microwave irradiation conditions in the presence of alumina sulfuric acid ($Al_2O_3 \cdot SO_3H$) as an environmentally friendly heterogeneous recyclable catalyst, in high yields and short reaction time.

Keywords Biginelli reaction; dihydropyrimidinone/thione; heterogeneous catalyst; microwave; multi-component reaction; solvent-free

INTRODUCTION

Dihydropyrimidinones (DHPMs) and their derivatives have attracted interest in medicinal chemistry, as 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, antiviral, antitumor, antiinflammatory, α -1a-antagonist, and neuropeptide Y (NPY) antagonist activities.³ Recently, structurally simple DHPM derivatives have emerged as a mitotic kinesin Eg5 motor protein inhibitor for the development of anticancer drugs.⁴ Furthermore, the dihydropyrimidinone moiety in batzelladine alkaloids A and B inhibit the binding of HIV envelope protein gp-120 to human CD4 cells, so that they are potential compounds in

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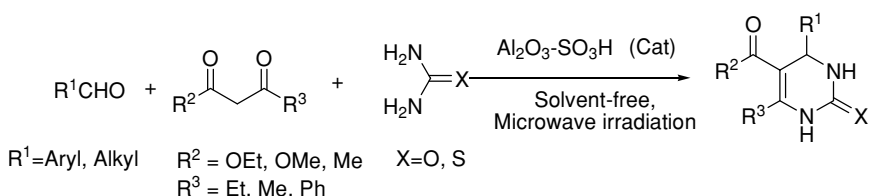
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AIDS therapy.⁵ In addition, the antioxidant activity of this ring system has been reported for retarding a variety of human diseases, including diabetes and various neurodegenerative diseases.⁶

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, many Lewis and Brønsted catalysts, such as chlorotrimethylsilane,⁸ ferric chloride/tetraethyl orthosilicate,⁹ ruthenium(III) chloride,¹⁰ N-bromosuccinimide,¹¹ ferric and nickel chloride hexahydrates,¹² ammonium chloride,¹³ polystyrenesulfonic acid (PSSA),¹⁴ Yb(III)-resin and polymer-supported scavengers,¹⁵ ZrCl₄ or ZrOCl₂,¹⁶ vanadium(III) chloride,¹⁷ sulfonic acid functionalized silica,¹⁸ ion exchange resins,¹⁹ Ziegler–Natta,²⁰ PW, PMo, SiW,²¹ chloroacetic acid,²² ferric chloride and boric acid,²³ iron(III) trifluoroacetate and trifluoromethanesulfonate,²⁴ sulphamic acid,²⁵ alkylammonium and alkylimidazolium perhaloborates, phosphates, and aluminates,²⁶ 1,1,3,3-tetramethylguanidinium trifluoroacetate,²⁷ and LaCl₃-graphite²⁸ have been developed. However, many of these methods are not green, as they use toxic chemicals, have low yields and very long reaction times, and also use heavy metallic salts that pollution environment. Hence, there is a clear need for a simple and practical methodology for the synthesis of this useful class of molecules on a large scale. Therefore, introducing clean processes and utilizing eco-friendly and green catalysts that can be simply recycled at the end of reactions have been under constant attention. The demand for an environmentally benign procedure with a heterogeneous and reusable catalyst prompted us to develop a safe alternate method for the synthesis of DHPMs as biologically important compounds in the presence of Al₂O₃-SO₃H as catalyst (Scheme 1).

This catalyst is safe, easy to handle, environmentally benign, presents fewer disposal problems, and is stable in reaction media. Alumina sulfuric acid was prepared according to the preparation of silica sulfuric acid.²⁹ It has been used in some organic reactions, such as



SCHEME 1

esterification of carboxylic acids^{30a} and synthesis of keto- and ald-oximes in Beckman rearrangement.^{30b}

RESULTS AND DISCUSSION

In order to be able to carry out Biginelli condensation in a more efficient way that minimizes time, microwave power irradiation, and the amount of catalyst, the reaction of benzaldehyde, ethyl acetoacetate, and urea was selected as a model. 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 15 mol% of $\text{Al}_2\text{O}_3\text{-SO}_3\text{H}$ at 180W microwave power in solvent-free conditions.

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(1H)-ones or their sulfur analogs. 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 and methyl/ethyl acetoacetate, or acetylacetone in the presence of catalytic amount of $\text{Al}_2\text{O}_3\text{-SO}_3\text{H}$ (15 mol %) gave the corresponding 3,4-dihydropyrimidin-2(1H)-ones without the formation of any side products, in high to excellent yields (Table I, Entries 1–5, 11–15, and 20–23). Under the optimized reaction conditions, by using thiourea in place of urea, aldehydes were transformed to their corresponding 3,4-dihydropyrimidin-2(1H)-thiones in high yield (Table I, Entries 6–10, 16–19, and 24–33), which are also of interest for their biological activities. The aliphatic aldehydes, which are known to be less reactive under conventional Biginelli reaction conditions, also reacted smoothly to afford high yields (Table I, Entries 5 and 15). This protocol significantly improves the yields of Biginelli products, and the reaction was carried out under solvent-free conditions without using any toxic solvents that pollute the environment.

The suggested mechanism of the $\text{Al}_2\text{O}_3\text{-SO}_3\text{H}$ -catalyzed transformation is shown in Scheme 2. The first step in the mechanism is the condensation between the aldehyde and urea/thiourea, with some similarities to Mannich condensation. The acyl imine intermediate generated acts as an electrophile for the nucleophilic addition of the keto enol ether, and the carbonyl ketone of the resulting adduct undergoes condensation with the urea NH_2 to give the cyclized Biginelli product.

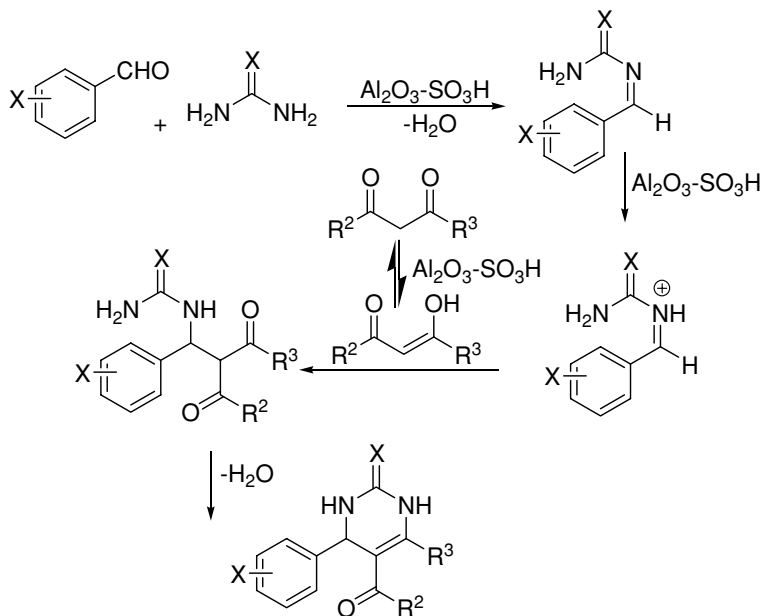
In conclusion, we have described a rapid and highly efficient method for the green synthesis of multi-substituted 3,4-dihydropyrimidinones/thiones using reusable alumina sulfuric acid as

TABLE I Al₂O₃-SO₃H-Catalyzed Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones/thiones Under Solvent-Free Microwave Irradiation Conditions

Entry	R ¹	R ²	R ³	X	Time (min) /Yield (%) ^a	m.p.°C (lit. m.p) ^{ref}
1	C ₆ H ₅	C ₂ H ₅ O	CH ₃	O	2 / 88	205–207 (205–206) ¹⁶
2	4-ClC ₆ H ₄	C ₂ H ₅ O	CH ₃	O	1.5 / 93	211–213 (209–211) ¹³
3	1-Naphthyl	C ₂ H ₅ O	CH ₃	O	2 / 79	255–257 (256–258) ²⁰
4	Ph-CH=CH	C ₂ H ₅ O	CH ₃	O	2.5 / 80	232–234 (230–232) ²⁰
5	(CH ₃) ₂ CH	C ₂ H ₅ O	CH ₃	O	3 / 72	195–197 (196–197) ²²
6	C ₆ H ₅	C ₂ H ₅ O	CH ₃	S	2.5 / 80	206–207 (206–207) ¹⁶
7	3-ClC ₆ H ₄	C ₂ H ₅ O	CH ₃	S	1.5 / 81	196–198 (192–196) ¹⁶
8	4-NO ₂ C ₆ H ₄	C ₂ H ₅ O	CH ₃	S	2.5 / 83	108–110 (107–108) ²⁷
9	3-MeOC ₆ H ₄	C ₂ H ₅ O	CH ₃	S	1.5 / 74	150–152 (150–152) ²⁰
10	4-HOC ₆ H ₄	C ₂ H ₅ O	CH ₃	S	2 / 87	194–196 (193–195) ²²
11	C ₆ H ₅	CH ₃ O	CH ₃	O	1.5 / 79	210–212 (207–209) ¹³
12	2,4-Cl ₂ C ₆ H ₃	CH ₃ O	CH ₃	O	1.5 / 82	252–254 (252–253) ²²
13	3-NO ₂ C ₆ H ₄	CH ₃ O	CH ₃	O	2.5 / 74	276–278 (279–280) ¹³
14	4-MeC ₆ H ₄	CH ₃ O	CH ₃	O	1.5 / 89	208–210 (210–213) ²²
15	(CH ₃) ₂ CH	CH ₃ O	CH ₃	O	3 / 69	215–217 (217–218) ²²
16	C ₆ H ₅	CH ₃ O	CH ₃	S	1.5 / 84	221–223 (221–222) ²²
17	3-NO ₂ C ₆ H ₄	CH ₃ O	CH ₃	S	2.5 / 68	237–239 (237) ²⁵
18	4-HOC ₆ H ₄	CH ₃ O	CH ₃	S	1 / 92	226–228 (227) ²⁵
19	4-(Me) ₂ NC ₆ H ₄	CH ₃ O	CH ₃	S	1.5 / 90	152–154 (152–153) ²⁰
20	C ₆ H ₅	CH ₃	CH ₃	O	0.5 / 91	234–236 (235–236) ²⁶
21	3-ClC ₆ H ₄	CH ₃	CH ₃	O	1 / 87	233–235 (229–231) ¹⁶
22	4-NO ₂ C ₆ H ₄	CH ₃	CH ₃	O	1.5 / 80	230(dec) (229(dec)) ²⁷
23	4-MeOC ₆ H ₄	CH ₃	CH ₃	O	1 / 93	177–179 (175–178) ²⁷
24	C ₆ H ₅	CH ₃	CH ₃	S	1 / 91	216–217 (214–215) ¹⁶
25	2-ClC ₆ H ₄	CH ₃	CH ₃	S	1.5 / 89	173–174 (173–174) ¹⁶
26	3-ClC ₆ H ₄	CH ₃	CH ₃	S	1 / 86	244–246 (243–245) ¹⁶
27	4-FC ₆ H ₄	CH ₃	CH ₃	S	0.5 / 93	209–211 (209–212) ²⁶
28	4-NO ₂ C ₆ H ₄	CH ₃	CH ₃	S	1.5 / 81	207–209 (207–209) ²⁶
29	C ₆ H ₅	C ₂ H ₅ O	C ₆ H ₅	S	2 / 74	179–181 (183–185) ¹⁶
30	4-MeOC ₆ H ₄	C ₂ H ₅ O	C ₆ H ₅	S	1.5 / 80	147–149 (151–152) ¹⁶
31	C ₆ H ₅	CH ₃ O	C ₂ H ₅	S	1.5 / 80	166–168 (168–169) ²³
32	2-ClC ₆ H ₄	CH ₃ O	C ₂ H ₅	S	1.5 / 86	183–185 (183–185) ²³
33	3-NO ₂ C ₆ H ₄	CH ₃ O	C ₂ H ₅	S	2 / 67	200–202 (201–203) ²³

^aYields refer to the pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of melting points, IR, and NMR spectra with authentic samples.^{8–28}

a catalyst under heterogeneous catalysis conditions and also under solvent-free microwave irradiation reaction conditions. With such successful results, this convenient and efficient protocol should provide a superior alternative to the existing methods because of its fast and

**SCHEME 2**

clean reactions and high yields. Furthermore, its simple work-up procedure will make the present method a useful and important for Biginelli synthesis.

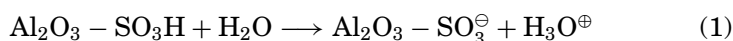
EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and were used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectral data (IR, ^1H NMR spectra). The NMR spectra were recorded on a Bruker Avance DPX 500 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.

Preparation of Alumina Sulfuric Acid

The idea for synthesis of alumina sulfuric acid is based on the preparation of silica sulfuric acid that it was first synthesized by Zolfigol²⁹ as following procedure.

A 500 mL suction flask was used. It was equipped with a constant pressure-dropping funnel containing chlorosulfonic acid (14 mL, 210 mmol) and a gas inlet tube for conducting HCl gas over adsorbing solution, e.g., water. Charged alumina (51 g, 510 mmol) was placed into it. Chlorosulfonic acid was added dropwise over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After the addition was complete, the mixture was shaken for 60 min. A white solid alumina sulfuric acid (0.2 g, 0.6 mmol) of 67.0 g was obtained. The amount of H⁺ in the alumina sulfuric acid was determined by acid-base titration according to the reaction in Equation 1.



The librated H₃O⁺ was titrated by standard NaOH, and the amount of H⁺ in alumina sulfuric acid was calculated (0.2 g of alumina sulfuric acid equal to 0.6 mmol).

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

A mixture of benzaldehyde (10 mmol), ethyl acetoacetate (12 mmol), urea (15 mmol), and Al₂O₃-SO₃H (0.5 g, 1.5 mmol H⁺) was placed in a microwave oven (Samsung, model KE300R) and heated at 180 W for the appropriate time. See 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 MgSO₄. 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(1H)-one in 88% yield (Table I, Entry 1); ¹H NMR (DMSO-d₆, 300 MHz): δ = 9.21 (s, 1H), 7.76 (s, 1H), 7.42–7.27 (m, 5H), 5.19 (d, *J* = 2.7 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 2.29 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H) ppm; IR (KBr, cm⁻¹): 3250, 2940, 2900, 1720, 1690, 1630, 1210, 750.

Similarly, other aldehydes were reacted with urea/thiourea and β-dicarbonyl compounds to obtain the corresponding

3,4-dihydropyrimidin-2(1H)-ones/thiones. The Biginelli pure product(s) was characterized by comparison of their physical data with those of authentic samples. The spectral data of some representative products are given below.

5-(Ethoxycarbonyl)-6-methyl-4(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (Table I, Entry 2)

¹H NMR (DMSO-d₆, 300 MHz): δ = 9.27 (s, 1H), 7.78 (s, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 5.14 (d, J = 3.6 Hz, 1H), 3.53 (s, 3H), 2.25 (s, 3H) ppm; IR (KBr, cm⁻¹): 3243, 3238, 3114, 2950, 2875, 1702, 1645, 840.

5-(Ethoxycarbonyl)-6-methyl-4(naphthalen-1-yl)-3,4-dihydropyrimidin-2(1H)-one (Table I, Entry 3)

¹H NMR (DMSO-d₆, 300 MHz): δ = 9.28 (s, 1H), 8.31 (d, J = 7.9 Hz, 1H), 7.95 (m, 2H), 7.78 (s, 1H), 7.55 (m, 4H), 6.09 (d, J = 2.7 Hz, 1H), 3.82 (q, J = 7.03 Hz, 2H), 2.39 (s, 3H), 0.83 (t, J = 7.03 Hz, 3H) ppm; IR (KBr, cm⁻¹): 3423, 3252, 2978, 1701, 1596.

5-(Ethoxycarbonyl)-6-methyl-4(cinnamyl)-3,4-dihydropyrimidin-2(1H)-one (Table I, Entry 4)

¹H NMR (DMSO-d₆, 300 MHz): δ = 9.13 (s, 1H), 7.54 (s, 1H), 7.19-7.40 (m, 5H), 6.35 (d, J = 15.9, 1H), 6.18 (dd, J = 15.9, 15.5 Hz, 1H), 4.72 (dd, J = 5.5, 3.4 Hz, 1H), 3.06 (q, J = 7.2 Hz, 2H), 2.20 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H) ppm; IR (KBr, cm⁻¹): 3246, 2979, 1704, 1650.

5-(Methoxycarbonyl)-6-methyl-4-(2,4-dichlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (Table I, Entry 12)

¹H NMR (DMSO-d₆, 300 MHz): δ = 9.34 (s, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz), 5.60 (s, 1H), 3.48 (s, 3H), 2.57 (s, 3H) ppm; IR (KBr, cm⁻¹): 3362, 1697, 1647, 845, 820.

5-(Methoxycarbonyl)-6-methyl-4-(4-(N,N-dimethylamino)phenyl)-3,4-dihydropyrimidin-2(1H)-thione

¹H NMR (DMSO-d₆, 300 MHz): δ = 9.95 (s, 1H), 9.30 (s, 1H), 7.16 (d, J = 9.1 Hz, 2H), 6.62 (d, J = 9.1 Hz, 2H), 5.13 (s, 1H), 3.60 (s, 3H), 2.92 (s, 6H), 2.30 (s, 3H) ppm; IR (KBr, cm⁻¹): 3280, 3185, 2928, 1710, 1651.

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