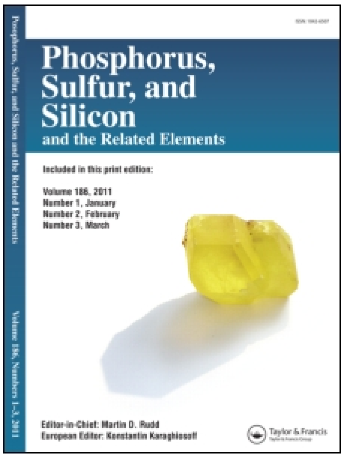

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One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Their Sulfur Derivatives with H_2SO_4 Supported on Silica Gel or Alumina

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The one-pot condensation of aromatic aldehydes, β-dicarbonyl compounds, and urea or thiourea in the presence of H_2SO_4 supported on silica gel or alumina (80% m/m) in refluxing n-hexane produces 3,4-dihydropyrimidin-2(1H)-ones and their sulfur derivatives in high to excellent yields.

Keywords Alumina; Biginelli reaction; 3,4-dihydropyrimidin-2(1*H*)-one; H_2SO_4; silica gel

INTRODUCTION

3,4-Dihydropyrimidin-2-(1*H*)-ones and their sulfur analogs have recently attracted considerable interest due to their therapeutic and pharmacological activities, including antiviral, antitumoral, and antihypertensive activity as well as their ability to act as potent calcium channel modulators.[1] Dihydropyrimidines have also been found in natural marine alkaloids such as batzelladine A and B, which are the potent HIV gp-120-CD4 inhibitors.[2]

Synthetic strategies for the synthesis of the dihydropyrimidine nucleus involve one-pot and multistep approaches. The one-pot synthesis of 3,4-dihydropyrimidones (DHPMs) was first reported by Biginelli in 1893, using hydrochloric acid as catalyst for a three-component condensation reaction of aldehydes, ethyl acetoacetate, and urea or thiourea

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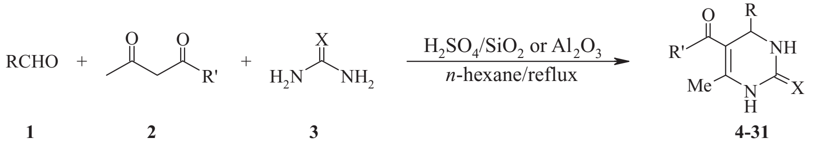
in ethanol.[3] However, this reaction suffers from the harsh reaction conditions and long reaction times. Furthermore, the reaction of substituted aromatic or aliphatic aldehydes results in low to moderate yields of products (20–60% and 10%, respectively). In this context, several new methods have been reported in the literature, involving either the modification of the classical one-pot condensation approach or the development of novel multistep strategies. Most of the reported methods have been devoted to one-pot approach because of the simplicity and high yields.

$FeCl_3 \cdot 6H_2O$,[4] $SnCl_2 \cdot 2H_2O$,[5] $CoCl_2 \cdot 6H_2O$,[6] $ZrCl_4$,[7] $LaCl_3 \cdot 7H_2O$,[8] $BF_3 \cdot OEt_2$,[9] $CeCl_3 \cdot 7H_2O$,[10] $CuCl_2$,[11] $LiClO_4$,[12] $Mn(OAc)_3 \cdot 2H_2O$,[13] $Zn(OTf)_2$,[14] $Cu(OTf)_2$,[15] $La(OTf)_3$,[16] $Bi(OTf)_3$,[17] $KHSO_4$,[18] *p*-TsOH,[19] Montmorillonite KSF,[20] Envirocat EPZ10,[21] and silica sulfuric acid[22] are the catalysts or promoters, which have been recently used for the synthesis of 3,4-dihydropyrimi-din-2(1*H*)-ones. Although most of the reported reagents are efficient for the Biginelli synthesis, the difficult or expensive preparation of some of the reagents, their availability, and ecological concerns encourage chemists to develop new protocols for this transformation.

On the other hand, over the last two decades, inorganic solid supports, especially silica gel and alumina, have become popular and have been used for supporting various reagents due to their characteristic properties such as ease of manipulation, the ability to support moisture-sensitive reagents, to enhance the selectivity of reactions, to require milder reaction conditions, and finally due to straightforward work-up procedures. Numerous reviews and articles have demonstrated the importance of these solid supports and their applications in organic synthesis.[23] We are interested in developing strategies for the synthesis of biologically important 3,4-dihydropyrimidin-2(1*H*)-ones. Here we report a general and practical methodology to effectively promote Biginelli synthesis using sulfuric acid supported on readily available silica gel or alumina in refluxing *n*-hexane (Scheme 1).



SCHEME 1

TABLE I Synthesis of 3,4-Dihydropyrimidone (4) with H_2SO_4 Supported on SiO_2 or $A1_2O_3$ Under Different Conditions[a]

Support	SiO_2/Al_2O_3 (g)	H_2S0_4 (g)	H_2SO_4/SiO_2 or Al_2O_3 (% m/m)	Solvent	Time (h)	Conversion (%)
a) SiO_2	—	0.3	—	*n*-Hexane	10	45
	0.2	0.16	80	C_2H_5OH	5	15
	0.2	0.16	80	CH_3CN	5	40
	0.2	0.16	80	THF	5	30
	0.2	0.16	80	*n*-Hexane	7	85
	0.5	0.25	50	*n*-Hexane	7	55
	0.5	0.4	80	*n*-Hexane	7	100
	0.5	0.4	80	C_6H_6	10	100
b) Al_2O_3	0.5	0.4	80	*n*-Hexane	2	100
	0.5	0.4	80	C_6H_6	3	100

[a] All reactions were carried out with 1 mmol of benzaldehyde in 5 mL of solvent under reflux conditions.

RESULTS AND DISCUSSION

We first studied the promotion of a three-component Biginelli synthesis with H_2SO_4/SiO_2 or H_2SO_4/Al_2O_3 to examine the conditions for the reaction of benzaldehyde, ethyl acetoacetate, and urea to afford 3,4-dihydropyrimidone (**4**). A summary of the optimization experiments is provided in Table I. The effect of various solvents, sulfuric acid alone, and its supported form on silica gel or alumina was investigated. The results show that when using sulfuric acid alone, the reaction remains incomplete under the defined conditions with only 45% conversion after 10 h (Table I). However, the supported form of sulfuric acid on silica gel or alumina accelerated the rate of reaction, which was complete within 2–10 h in refluxing *n*-hexane or benzene. It is noteworthy that the reaction in *n*-hexane was more efficient than in benzene. Thus using 80% m/m (mass ratio) of H_2SO_4/SiO_2 or H_2SO_4/Al_2O_3 (SiO_2 or Al_2O_3, 0.5 g, H_2SO_4 98%, 0.4 g) in refluxing *n*-hexane affords the best yield of 3,4-dihydropyrimidone (**4**) from the reaction of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1.2 mmol) (Table I).

To explore the further utility of this protocol, a variety of substituted aromatic aldehydes and β-dicarbonyl compounds, such as ethyl or methyl acetoacetate and acetylacetone together with urea, were subjected to H_2SO_4/SiO_2 (80% m/m) to give the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones (**4–23**) in refluxing *n*-hexane (Table II). The reactions were completed within 1–8 h with high to excellent yields. The important aspect of this protocol is the tolerance of a variety of functional groups, including NO_2, Cl, OH, OMe, and C=C, under

TABLE II Synthesis of 3,4-Dihydropyrimidones and 2-Thioxo Derivatives with H_2SO_4 Supported on SiO_2 or Al_2O_3[a]

				H_2SO_4/SiO_2		$H_2SO_4/A1_2O_3$		M.p.(°C)	
R	R′	X	DHPMs	Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]	Found	Reported
C_6H_5	OEt	O	**4**	7.2	93	2	95	202–203	200–202[15]
2-OHC_6H_4	OEt	O	**5**	3.4	94	3	94	200–202	200–202[15]
3-OHC_6H_4	OEt	O	**6**	1.2	92	0.9	91	164–165	164–166[22a]
4-OHC_6H_4	OEt	O	**7**	2	95	1.5	94	200–201	199–200[15]
3-OH-4-MeO-C_6H_3	OEt	O	**8**	1	90	0.8	90	185–187	185–187[15]
2-furyl	OEt	O	**9**	2.4	89	1.8	91	204–206	203–205[15]
4-ClC_6H_4	OEt	O	**10**	2.5	96	2.3	97	213–214	212–213[15]
4-$NO_2C_6H_4$	OEt	O	**11**	2.3	93	1.8	94	208–210	207–209[15]
Ph-CH=CH	OEt	O	**12**	1.3	93	1	92	232–234	232–235[22a]
4-MeC_6H_4	OEt	O	**13**	5.3	94	4	96	213–214	214–216[24]
4-$MeOC_6H_4$	OEt	O	**14**	2.3	92	1.3	93	201–202	200–201 [15]
C_6H_5	OMe	O	**15**	8	94	5	94	210–212	209–212[22a]
4-ClC_6H_4	OMe	O	**16**	2.6	96	2	98	205–207	204–207[22a]
4-$NO_2C_6H_4$	OMe	O	**17**	2.3	95	1.6	95	236–238	235–237[22a]
4-MeC_6H_4	OMe	O	**18**	3	90	4.3	93	202–204	204–206[25]
4-$MeOC_6H_4$	OMe	O	**19**	1.6	95	1	97	192–194	192–194[22a]
C_6H_5	Me	O	**20**	5.3	92	3.3	92	234–236	233–236[22a]
2-furyl	Me	O	**21**	2.6	90	1.3	89	211–213	210–212[26]
4-$NO_2C_6H_4$	Me	O	**22**	1.9	93	1.3	95	231 (dec)	230 (dec)[22a]
4-$MeOC_6H_4$	Me	O	**23**	2	93	0.7	92	168–170	168–170[22a]
C_6H_5	OEt	S	**24**	6.3	96	1.8	96	208–210	208–210[22a]
3-OHC_6H_4	OEt	S	**25**	0.9	93	0.8	93	185–187	184–186[22a]
4-OHC_6H_4	OEt	S	**26**	1.9	95	1.2	92	192–193	193–194[7]
4-ClC_6H_4	OEt	S	**27**	2.6	96	2.5	97	192–194	192–194[25]
4-$NO_2C_6H_4$	OEt	S	**28**	2.2	93	1.7	94	108–110	109–111[25]
4-MeC_6H_4	OEt	S	**29**	4.7	96	3.7	95	193–195	192–194[25]
4-$MeOC_6H_4$	OEt	S	**30**	1.8	92	0.9	93	149–151	150–152[22a]
C_6H_5	Me	S	**31**	4.5	90	5.5	90	185 (dec)	185 (dec)[22a]

[a] All reactions were carried out with a molar ratio of aldehyde/β-dicarbonyl/urea (thiourea) of 1:1:1.2 in refluxing *n*-hexane.

[b] Yields refer to isolated pure products.

the experimental conditions. Thiourea has also been used to provide the corresponding sulfur analogs of 3,4-dihydropyrimidones (**24–31**), which are also of much interest because of their biological activities[1] (Table II). The reactions were completed within 0.9–6.3 h with 90–96% yields of the thiocarbonyl products. The Biginelli synthesis of 3,4-dihydropyrimidones and their sulfur analogs was also promoted by H_2SO_4/Al_2O_3 (80% m/m) in refluxing *n*-hexane (Table II). Comparison of the results shows that reactions were generally faster using H_2SO_4/Al_2O_3 compared to H_2SO_4/SiO_2. However, the efficiency of both solid supported systems is high and nearly the same.

TABLE III Comparison of Synthesis of 3,4-Dihydropyrimidones and 2-Thioxo Derivatives with H_2SO_4 Supported on SiO_2/Al_2O_3 and Silica Sulfuric Acid[a]

				H_2SO_4/SiO_2		H_2SO_4/Al_2O_3		Silica sulfuric acid[22a]	
R	R′	X	DHPMs	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
C_6H_5	OEt	O	**4**	7.2	93	2	95	6	91
4-$MeOC_6H_4$	OEt	O	**14**	2.3	92	1.3	93	6	95
C_6H_5	OMe	O	**15**	8	94	5	94	6	96
4-ClC_6H_4	OMe	O	**16**	2.6	96	2	98	6	94
C_6H_5	Me	O	**20**	5.3	92	3.3	92	6	87
4-$NO_2C_6H_4$	Me	O	**22**	1.9	93	1.3	95	6	92
C_6H_5	OEt	S	**24**	6.3	96	1.8	96	6	93
C_6H_5	Me	S	**31**	4.5	90	5.5	90	6	93

[a] The reactions with H_2SO_4/SiO_2 or Al_2O_3 and silica sulfuric acid were carried out in refluxing *n*-hexane and ethanol, respectively.

In order to highlight the advantages of H_2SO_4/SiO_2 or Al_2O_3, we compared some of our results with the reported silica sulfuric acid (SiO-SO_3H)[22a] (Table III). It becomes evident that, from the point of view of rate enhancement, efficiency, and the use of nonpolar solvents, our promoters and especially H_2SO_4/Al_2O_3 show the best results.

In conclusion, we have presented a new protocol for the promotion of the Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and their sulfur analogs by one-pot cyclocondensation reaction of aromatic aldehydes, *β*-dicarbonyl compounds, and urea/thiourea using H_2SO_4/SiO_2 and H_2SO_4/Al_2O_3 (80% m/m) in refluxing *n*-hexane. Supporting of sulfuric acid on Al_2O_3 resulted in higher reaction rates than supporting on SiO_2. Mild reaction conditions, the use of available low-cost reagents to afford high to excellent yields as compared to the classical Biginelli reaction, tolerance of various functional groups, and a simple experimental procedure are the advantages, which could make this protocol a useful addition to the present methodologies.

EXPERIMENTAL

All reagents and substrates were purchased from commercial sources with the best quality and used without further purification. SiO_2 and Al_2O_3 were used in a grade for column chromatography and were obtained from Merck. The products were characterized by their ^1H, ^{13}C NMR, or IR spectra, which were recorded with a 300 MHz Bruker spectrometer and a Thermo Nicolet Nexus 670 FT-IR spectrophotometer, respectively. All yields refer to isolated pure products. TLC was applied for the purity determination of the substrates, products, and for monitoring the reactions, using silica gel 60 F_{254} aluminum sheets.

Supporting of H_2SO_4 on Alumina or Silica Gel

In a round-bottomed flask (10 mL) charged with Al_2O_3 or SiO_2 (0.5 g), H_2SO_4 (98%, 0.4 g) was added, and the mixture was stirred magnetically for 2 min to afford H_2SO_4/Al_2O_3 or H_2SO_4/SiO_2 (80% m/m).

Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones (4–23) and 2-Thioxo Derivatives (24–31) with H_2SO_4/Al_2O_3 or H_2SO_4/SiO_2: General Procedure

In a round-bottomed flask (10 mL) charged with freshly prepared H_2SO_4/Al_2O_3 or H_2SO_4/SiO_2 (0.9 g, 80% m/m), *n*-hexane (5 mL) was added, and the reaction mixture was stirred magnetically at room temperature for 2 min. To the resulting mixture, the aldehyde (1 mmol), ethyl or methyl acetoacetate (1 mmol), and urea or thiourea (1.2 mmol) were added, and the mixture was stirred under reflux conditions for the appropriate time (Table II). The progress of the reaction was monitored by TLC (eluent CCl_4:Et_2O 5:3). After completion of the reaction, the solution was cooled to the room temperature and cold sodium bicarbonate (5%, 10 mL) was added. The mixture was stirred for 10 min and then filtered. The filtrate was extracted with CH_2Cl_2 (3 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent CCl_4:Et_2O 5:3) affords the pure 3,4-dihydropyrimidone or 2-thioxo derivative in high to excellent yield (Table II).

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