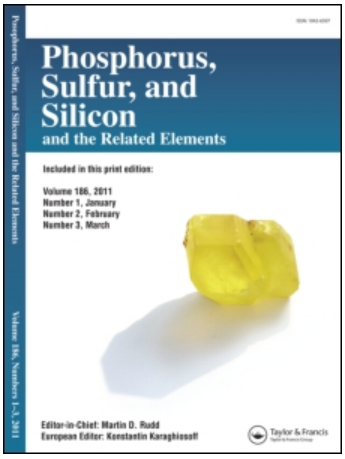

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$NaHSO_4 \cdot H_2O$ as a Heterogeneous Acidic Reagent for Mild and Convenient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Their Sulfur Derivatives

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One-pot cyclocondensation reaction of aromatic aldehydes, 1,3-dicarbonyl compounds and urea / thiourea in the presence of $NaHSO_4 \cdot H_2O$ produced 4-aryl substituted 3,4-dihydropyrimidin-2(1H)-ones and their sulfur analogs in high to excellent yields. The reactions were carried out in refluxing n-hexane and were completed within 2.5–11 h.

Keywords Biginelli synthesis; 3,4-dihydropyrimidin-2(1*H*)-one; heterogeneous; $NaHSO_4 \cdot H_2O$

INTRODUCTION

3,4-Dihydropyrimidin-2(1*H*)-ones and their sulfur analogs have become increasingly significant due to their therapeutic and pharmacological properties.[1] In the past decades, a broad range of biological effects including antiviral, antitumor, antibacterial, antiinflammatory, potent calcium channel blockers, and antihypertensive activities has been ascribed for these compounds.[2] Synthetic strategies for the nucleus of 3,4-dihydropyrimidin-2(1*H*)-ones involve both one-pot and multistep approaches.

The classical Biginelli reaction is the most straightforward and simple protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and involves a one-pot condensation of 1,3-dicarbonyl compounds with aldehydes and urea in ethanol under strong protic acid catalysis.[3] This

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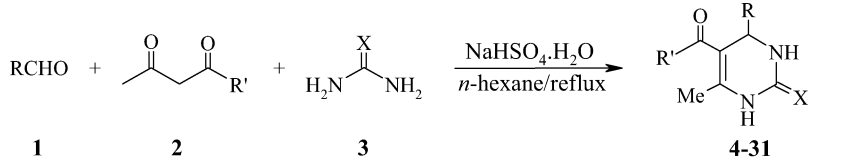
method suffers from long reaction times, harsh reaction conditions, and unsatisfactory yields (10–60%). Complex multistep strategies that produce higher overall yields lack the simplicity of one-pot protocol, however.[4] Furthermore, several marine alkaloids with interesting biological activities containing the 3,4-dihydropyrimidin-5-carboxylate core unit have recently been isolated. Among these, the batzelladine alkaloids were found to be potent HIV gp-120-CD4 inhibitors.[5]

Recently, interest in the one-pot Biginelli synthesis of 3,4-dihydropyrimidones has increased rapidly and several reagents and protocols aiming to improve the efficiency of the reaction have been reported. Modifications and improvements with Lewis acids, acidic catalysts, and metal salts such as $BF_3 \cdot OEt_2$,[6] $BiCl_3$,[7] $FeCl_3 \cdot 6H_2O$,[8] $SnCl_2 \cdot 2H_2O$,[9] $ZrCl_4$,[10] $Mn(OAc)_3 \cdot 2H_2O$,[11] InX_3,[12] $LaCl_3 \cdot 7H_2O$,[13] $La(OTf)_3$,[14] $Yb(OTf)_3$,[15] $Cu(OTf)_2$,[16] $LiClO_4$,[17] *p*-TsOH,[18] Montmorillonite KSF,[19] Envirocat EPZ10,[20] and silica sulfuric acid[21] are examples in this area. In addition, the use of alkali and alkaline earth metal hydrogen sulfates under solvent-free conditions,[22] silica gel–supported $NaHSO_4$,[23] and $KHSO_4$/glycol[24] are other protocols that have been applied for the promotion of Biginelli 3,4-dihydropyrimidone synthesis. The reported methods suffer from the use of expensive reagents, high reaction temperature, cumbersome product isolation, moderate yields, and ecological concerns. Therefore, a need still exists for simple and environmental benign processes that produce 3,4-dihydropyrimidones under milder and practical conditions. In the course of our studies on the use of $NaHSO_4 \cdot H_2O$[25] in organic synthesis and in order to further explore the suitability and efficiency of this mineral acidic reagent for one-pot, three-component Biginelli synthesis we decided to reinvestigate the title reaction under mild and green conditions. Herein we describe a simple and effective method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones as well as their sulfur analogs (**4–31**) by cyclocondensation reaction of aromatic aldehydes (**1**), 1,3-dicarbonyl compounds (**2**), and urea/thiourea (**3**) in the presence of $NaHSO_4 \cdot H_2O$ as a heterogeneous acidic reagent in refluxing *n*-hexane (Scheme 1).



SCHEME 1

TABLE I Synthesis of 3,4-Dihydropyrimidin-2(1H)-one (4) Under Different Conditions[a,b]

$NaHSO_4.H_2O$ (mmol)	Solvent	Time (h)	Conversion (%)
3	EtOH 96%	15	60
3	EtOH-H_2O(1:1)	24	90
3	C_6H_6	10	90
3	C_6H_6-H_2O (3:0.5)	5	0
2.8	*n*-Hexane	7	100
2.5	CH_3CN	10	40
2.5	THF	10	50

[a]Benzaldehyde, ethyl acetoacetate and urea were used in a molar ratio of 1:1:1.2, respectively.

[b]The reactions were carried out under reflux conditions.

RESULTS AND DISCUSSION

Table I shows the results of optimization experiments using various solvents and amounts of $NaHSO_4 \cdot H_2O$ on the rate of reaction to afford 3,4-dihydropyrimidone (**4**). The results show that using 2.8 molar equivalents of $NaHSO_4 \cdot H_2O$ in refluxing *n*-hexane represents the best conditions to complete the reaction of benzaldehyde, ethyl acetoacetate, and urea in a molar ratio of 1:1:1.2, respectively (Table I).

Varieties of substituted aromatic aldehydes, 1,3-dicarbonyl compounds (ethyl/methyl acetoacetate and acetylacetone), and urea were used for the condensation reaction in the presence of $NaHSO_4 \cdot H_2O$ to produce the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones (**4–23**) (Table II). Thiourea has also been used with similar results to provide the corresponding sulfur analogs of 3,4-dihydropyrimidones (**24–31**) (Table II), which are also of great interest with regard to their biological activities.[1] The procedure gives the products in high to excellent yields within 2.5–11 h. The important aspect of this protocol is the tolerance of a variety of functional groups such as, NO_2, Cl, OH, OMe, and C=C under experimental conditions. Furthermore, acid-sensitive aldehydes such as furfural and cinnamaldehyde reacted smoothly without any side products. In order to highlight the advantages of this synthetic method, we compared some of our results with those reported for $NaHSO_4$/solvent-free[22] and $SiO_2/NaHSO_4$.[23] The comparison of the results in Table III shows that our protocol provides excellent yields under green and milder conditions.

In conclusion, we have described a new methodology for the synthesis of 3,4-dihydropyrimidones by one-pot cyclocondensation reaction of aromatic aldehydes, 1,3-dicarbonyl compounds, and urea/thiourea in the

TABLE II Synthesis of 3,4-Dihydropyrimidones and Their 2-Thioxo Derivatives in the Presence of $NaHSO_4.H_2O$[a]

	R	R′	X	Time (h)	Yield (%)[b]	M.p. (°C) Found	M.p. (°C) Reported
4	C_6H_5	OEt	O	7	96	202–203	200–202[16]
5	2-HOC_6H_4	OEt	O	10	94	200–202	200–202[16]
6	3-HOC_6H_4	OEt	O	2.8	95	164–165	164–166[21a]
7	4-HOC_6H_4	OEt	O	4	94	200–201	199–200[16]
8	3-HO-4-MeO-C_6H_3	OEt	O	3.4	95	185–187	185–187[16]
9	2-furyl	OEt	O	5	93	204–206	203–205[16]
10	4-ClC_6H_4	OEt	O	6	95	213–214	212–213[16]
11	4-$O_2NC_6H_4$	OEt	O	4	94	208–210	207–209[16]
12	Ph-CH=CH	OEt	O	3	93	232–234	232–235[21a]
13	4-MeC_6H_4	OEt	O	10	96	213–214	214–216[26]
14	4-$MeOC_6H_4$	OEt	O	10.5	94	201–202	200–201[16]
15	C_6H_5	OMe	O	5.8	95	210–212	209–212[21a]
16	4-ClC_6H_4	OMe	O	6	96	205–207	204–207[21a]
17	4-$O_2NC_6H_4$	OMe	O	4	96	236–238	235–237[21a]
18	4-MeC_6H_4	OMe	O	10	94	202–204	204–206[27]
19	4-$MeOC_6H_4$	OMe	O	11	95	192–194	192–194[21a]
20	C_6H_5	Me	O	7	94	234–236	233–236[21a]
21	2-furyl	Me	O	3.5	93	211–213	210–212[28]
22	4-$O_2NC_6H_4$	Me	O	3.9	94	231(dec)	230 (dec)[21a]
23	4-$MeOC_6H_4$	Me	O	11	95	168–170	168–170[21a]
24	C_6H_5	OEt	s	6.2	96	208–210	208–210[21a]
25	3-HOC_6H_4	OEt	s	2.5	96	185–187	184–186[21a]
26	4-HOC_6H_4	OEt	s	4	97	192–193	193–194[10]
27	4-ClC_6H_4	OEt	s	11	95	192–194	192–194[27]
28	4-$O_2NC_6H_4$	OEt	s	4.7	95	108–110	109–111[27]
29	4-MeC_6H_4	OEt	s	11	97	193–195	192–194[27]
30	4-$MeOC_6H_4$	OEt	s	10	93	149–151	150–152[21a]
31	C_6H_5	Me	s	5.7	92	185 (dec)	185 (dec)[21a]

[a]All reactions were carried out with a molar ratio of aldehyde/β-dicarbonyl/urea (thiourea)/$NaHSO_4$ (1:1:1.2:2.8) in refluxing *n*-hexane.[b] Yields refer to isolated pure products.

presence of $NaHSO_4{\cdot}H_2O$ in a molar ratio of 1:1:1.2:2.8, respectively. Mild reaction conditions, the use of available low-cost reagents and of an ecologically safe solvent, high to excellent yields of the products, the tolerance of various functional groups, and a simple experimental procedure are the main advantages of this protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones as well as of their sulfur analogs.

TABLE III Comparison of Synthesis of 3,4-Dihydropyrimidones and 2-Thioxo Derivatives with $NaHSO_4$ Under Different Conditions

				$NaHSO_4 \cdot H_2O$			$SiO_2/NaHSO_4 \cdot H_2O$[b]			$NaHSO_4$/Solvent-free[c]		
	R	R′	X	Sulfate (mmol)	Time (h)	Yield (%)	Sulfate (mmol)	Time (h)	Yield (%)	Sulfate (mmol)	Time (h)	Yield (%)
4	C_6H_5	OEt	O	2.8	7	96	0.5	1.5	93	1	4	79
10	4-ClC_6H_4	OEt	O	2.8	6	95	0.5	2	89	1	4	75
11	4-$O_2NC_6H_4$	OEt	O	2.8	4	94	0.5	2	85	1	4	68
14	4-$MeOC_6H_4$	OEt	O	2.8	10.5	94	—	—	—	1	4	77
15	C_6H_5	OMe	O	2.8	5.8	95	—	—	—	1	4	75
19	4-$MeOC_6H_4$	OMe	O	2.8	11	95	—	—	—	1	4	78
20	C_6H_5	Me	O	2.8	7	94	—	—	—	1	4	78
23	4-$MeOC_6H_4$	Me	O	2.8	11	95	—	—	—	1	4	61
24	C_6H_5	OEt	s	2.8	6.2	96	0.5	1.5	93	1	4	54
30	4-$MeOC_6H_4$	OEt	s	2.8	10	93	—	—	—	1	4	70

[a]The present protocol; [b]The reactions were carried out in CH_3CN under reflux conditions; [c]The reactions were carried out in oil bath at 80°C under solvent-free conditions.

EXPERIMENTAL

General

All reagents and substrates were purchased from commercial sources with the best quality and used without further purification. Melting points were determined with Philip-Harris melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker Avance spectrometer at 300.13 and 75.46 MHz, respectively. All yields refer to isolated pure products. TLC using silica gel 60 GF_{254} aluminum sheet was applied for determination of the purity of substrates and products as well as monitoring the reaction.

Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Their 2-Thioxo Derivatives in the Presence of $NaHSO_4 \cdot H_2O$: General Procedure

In a round-bottom flask (10 mL) equipped with magnetic stirrer and condenser, a solution of the aldehyde (1 mmol), ethyl or methyl acetoacetate (1 mmol), and urea or thiourea (1.2 mmol) in *n*-hexane (4 mL) was prepared. To this solution, $NaHSO_4 \cdot H_2O$ (0.386 g, 2.8 mmol) was added and the mixture was stirred under reflux for 2.5–11 h (Table II). The progress of the reaction was monitored by TLC (eluent; CCl_4/Et_2O: 5/2). After completion of the reaction the solution was cooled to room temperature and water (5 mL) was added. The reaction mixture was extracted with Et_2O (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-dihydro-pyrimidone or its 2-thioxo analog (Table II).

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