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# Silicagel supported sodium hydrogensulfate as a heterogenous catalyst for high yield synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones

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**Abstract**

Silicagel supported sodium bisulfate catalyzes efficiently the three component condensation reaction of aldehyde, β-ketoester and urea in refluxing acetonitrile to afford the corresponding dihydropyrimidinones. Compared to the classical Biginelli reaction conditions, this new approach consistently has the advantage of excellent yields (84–93%) and short reaction times 1–2.5 h.


*Keywords:* Biginelli reaction; Silicagel supported sodium bisulfate; Dihydropyrimidinones

## 1. Introduction

Many aryl substituted 3,4-dihydropyrimidin-2-ones (DHPMs) and their derivatives are an important class of compounds in the field of drugs and pharmaceuticals [1]. They are found to exhibit a wide range of biological activities [2] such as antibacterial, antiviral, antitumour, antiinflammatory properties. Most of the DHPMs and their derivatives are medicinally important as calcium channel blockers, antihypertensive agents $\alpha_{1a}$-antagonists and anti HIV agents [3]. The biological activities of some marine alkaloids isolated recently have been attributed to the presence of a dihydropyrimidinone moiety [4]. The simplest and the most straightforward approach for DHPMs involve one pot condensation of an aldehyde, β-ketoester and urea or thiourea in the presence of acid catalyst [5]. However, this so-called Biginelli reaction often suffer from low yields practically in case of substituted aromatic and aliphatic aldehydes [6]. Even though, high yields could be achieved by following complex multi-step procedures [7] these methods lack the simplicity of original one-pot Biginelli protocol. Therefore, Biginelli reaction continues to attract the attention of researchers for the discovery of milder and efficient procedures for the synthesis of dihydropyrimidinones.

In recent years, several synthetic procedures for preparing of DHPMs have been reported including classical conditions with microwave irradiation [8] and by using Lewis acids as well as protic acids as promoters such as concentrated HCl [9], $BF_3$, $OEt_2$ [10], polyphosphonate ester (PPE) [11], montmorillonite [12], $InCl_3$ [13], $LaCl_3$, [14] lanthanide triflate [15], $H_2SO_4$ [16], ceric ammonium nitrate [17], $Mn(OAc)_3$ [18], ion-exchange resin [19], 1-*n*-butyl-3-methyl imidazolium tetra fluoroborate (BMImBF4) [20], $BiCl_3$ [21], $LiClO_4$ [22], $InBr_3$ [23], $FeCl_3$ [24], $ZrCl_4$ [25], $Cu(OTf)_2$ [26], $Bi(OTf)_3$ [27], LiBr [28], yutterbium triflate [29], $NH_4Cl$ [30], etc. are found to be effective. In spite of their potential utility many of these methods involve expensive reagents, strongly acidic conditions, long reaction times, high temperatures, stoichiometric amounts of catalysts and unsatisfactory yields. Therefore the discovery of new and an inexpensive catalyst for the preparation of 3,4-dihydropyrimidin-2-ones under neutral and mild conditions is of prime importance.

Recently, the use of solid supported reagents [31] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Par-

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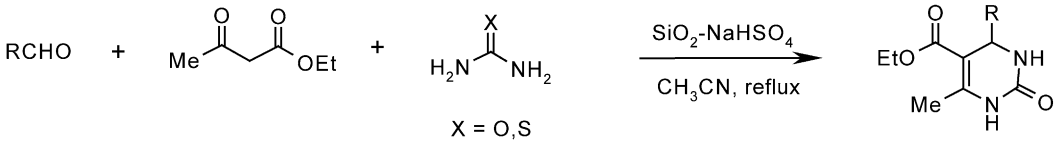


Scheme 1.

ticularly, silica gel impregnated with sodium bisulfate [32,33] has advantages of low cost, ease of preparation, and catalyst recycling. Since the reaction is heterogenous in nature, the catalyst can conviniently be separated by simple filtration.

In view of recent surge in the use of heterogeneous catalysts [34], we wish to report a simple, convenient and efficient method for the preparation of DHPMs using a solid supported reagent, $SiO_2$–$NaHSO_4$, as an inexpensive and eco-friendly catalyst. This method not only afforded the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. The reaction of benzaldehyde (1 mmole), ethyl acetoacetate (1.2 mmol) and urea or thiourea (1.2 mmole) in the presence of 10 mol% $SiO_2$–$NaHSO_4$ in refluxing acetonitrile (7 ml) resulted in the formation of dihydropyrimidinone in 93, 87, 85, and 81% yields over four cycles. Similarly, several aromatic, aliphatic and heterocyclic aldehydes reacted well under the reaction conditions to give the corresponding dihydropyrimidinones in excellent yields (Scheme 1).

## 2. Experimental

### 2.1. Preparation of the catalyst

The catalyst was prepared by mixing silica gel (1.5 g, Merck grade 60, 230–400 mesh) with a solution of $NaHSO_4 \cdot H_2O$ (0.7 g, 5 mmol) in distilled water (10 ml). The resulting mixture was stirred for 30 minutes to absorb $NaHSO_4$ on surface of silica gel. After removal of water in a rotary evaporator, the solid powder was dried at 120 °C for 2 to 3 h under reduced pressure. The drying temperature was maintained below the decomposition temperatures of the salts.

### 2.2. Typical procedure

A solution of ethyl acetoacetate (156 mg, 1.2 mmole), aldehyde (1.0 mmol) and urea (72 mg 1.2 mmole) in acetonitrile (8 ml) was heated under reflux conditions in the presence of catalyst (10 mol%) for 2 h. The completion of the reaction was monitored by TLC. The reaction mixture was then poured onto crushed ice and the solid product separated was filtered and recrystallised from methanol. The spectral data of some of the compounds are given below. Compound 12: Solid, m.p. 193–194 °C. $^1$H NMR (DMSO-$d_6$): δ 1.14 (t, 3H, $J$ = 6.8 Hz), 2.36 (s, 3H), 4.10 (q, 2H, $J$ = 6.8 Hz), 5.35 (s, 1H), 5.80 (brs, NH), 6.85 (m, 1H), 7.05 (m, 5H), 7.45 (m, 3H), 8.40 (brs, NH). EIMS: $m/z$ 352 ($M^+$), 323, 279, 183, 155, 137, 91, 69. IR (KBr): υ 3242, 3112, 2981, 1712, 1654, 1582, 1487, 1245, 1097, 786. **13**: Solid, m.p. 229–231 °C (lit., 232–235). $^1$H NMR (DMSO-$d_6$): δ 1.06 (t, 3H, $J$ = 7.0 Hz), 2.50 (s, 3H), 3.95 (q, 2H, $J$ = 7.0 Hz), 4.24 (d, 1H, $J$ = 6.0 Hz), 6.05 (dd, 1H, $J$ = 16.4 Hz), 6.2 (d, 1H, $J$ = 16.4 Hz), 7.25 (m, 5H), 7.45 (d, NH, $J$ = 1.7 Hz), 8.95 (brs, NH). EIMS: $m/z$ 286 ($M^+$), 252, 224, 196, 149, 84. IR (KBr): υ 3335, 3242, 3098, 2978, 1689, 1642, 1492, 1373, 1218, 1121, 785. All other products were characterised by spectral (NMR and IR) data and by comparision with those of authentic samples and also by the mixed melting points with the authentic samples.

Table 1
$SiO_2$–$NaHSO_4$ catalyzed synthesis of dihydropyrimidinones and thioderivatives

| Entry | R | X | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | $C_6H_5$ | O | 1.5 | 93 |
| 2 | 4-$ClC_6H_4$ | O | 2.0 | 89 |
| 3 | 3,4-$Cl_2C_6H_5$ | O | 2.0 | 91 |
| 4 | 2-$(OH)C_6H_3$ | O | 1.5 | 90 |
| 5 | 3-$(OH)C_6H_4$ | O | 1.5 | 88 |
| 6 | 4-$(MeO)C_6H_4$ | O | 2.0 | 90 |
| 7 | 2-Naphthyl | O | 2.5 | 84 |
| 8 | 4-$MeC_6H_4$ | O | 2.5 | 88 |
| 9 | 4-$NO_2C_6H_4$ | O | 2.0 | 85 |
| 10 | 2-Furfuryl | O | 2.5 | 85 |
| 11 | Cyclohexyl | O | 2.5 | 80 |
| 12 | 3-(OPh)-$C_6H_4$ | O | 2.5 | 91 |
| 13 | $C_6H_5CH$=CH | O | 2.5 | 85 |
| 14 | 3,4,5-$(OH)C_6H_2$ | O | 2.5 | 85 |
| 15 | $C_6H_5$ | S | 1.5 | 93 |
| 16 | 4-$ClC_6H_4$ | S | 2.0 | 90 |
| 17 | 2-$(OH)C_6H_4$ | S | 2.0 | 90 |

## 3. Results and discussion

Several examples illustrating this novel and general method for the synthesis of dihydropyrimidinones are summarized in Table 1. This three-component condensation proceeded smoothly in refluxing acetonitrile and also complete with in 1–2 h of reaction time. Many of the pharmacological relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Aromatic aldehydes carrying either electron donating or withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehyde such as furfural (Entry 10) is also worked well without the formation of any side products, which are normally observed either in the presence of protic or Lewis acids. In addition to

its simplicity and milder reaction conditions, this method is effective even with aliphatic and α,β-unsaturated aldehydes which are normally produce poor yields in the presence of either protic or Lewis acids due to thier decomposition or polymerization under acidic conditions. Another important feature of this procedure is survival of a variety of functional groups such as olefins, ethers, esters, nitro and halides under the reaction conditions. This procedure not only preserves the simplicity of Biginelli reaction but also produces excellent yields of the DHPMs. Thus this procedure offers an easy access to substituted DHPMs with a variety of substitution patterns. Among various solvents like acetonitrile, methanol, ether and THF used for this transformation, methanol and acetonitrile were the best choice. Thiourea has been used to get the corresponding thio-derivatives of dihydropyrimidinones which are possessing good biological activities.

## 4. Conclusion

We have developed a simple, convenient and effective method for the synthesis of 3,4-dihydropyrimidinones by using $NaHSO_4$–$SiO_2$ under slightly acidic conditions. This method is applicable for a wide range of substrates including aromatic, aliphatic, α,β-unsaturated and heterocyclic aldehydes. The operational simplicity of the procedure is also attractive. The catalyst can be prepared easily with readily available inexpensive reagents, which is heterogenous and non-hazardous. To our knowledge, this is first time report of an efficient general method for the synthesis of DHPMs by using a simple catalyst.

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