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Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

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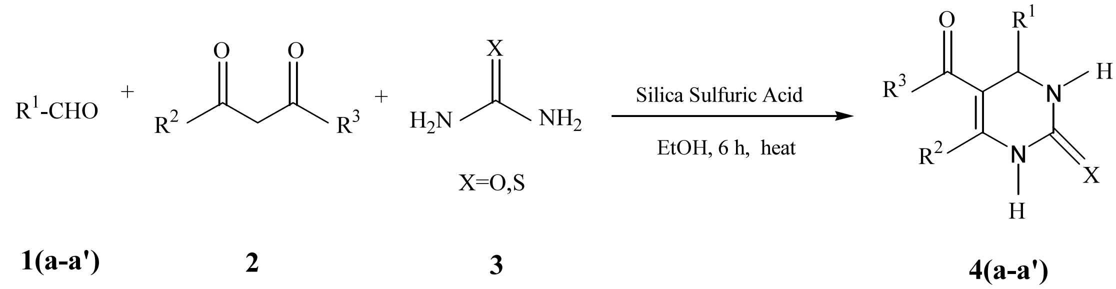
Abstract—Silica sulfuric acid efficiently catalyzes the three-component Biginelli reaction between an aldehyde, a β-dicarbonyl compound and urea or thiourea in refluxing ethanol to afford the corresponding dihydropyrimidinones in high yields. The catalyst is reusable and can be applied several times without any decrease in the yield of the reactions. © 2003 Elsevier Science Ltd. All rights reserved.

3,4-Dihydropyrimidin-2(1*H*)-ones and their sulfur analogs (DHPMs) have been reported to possess diverse pharmacological activities such as antiviral, antibacterial and antihypertensive activity,[1] as well as efficacy as calcium channel modulators and α_{1a}-antagonists.[2] The biological activity of some alkaloids isolated recently has also been attributed to the dihydropyrimidinone moiety.[3]

The simple and direct method for the synthesis of DHPMs reported by Biginelli in 1893 involves the one-pot condensation of an aldehyde, a β-ketoester and a urea under strongly acidic conditions.[4] However, this method suffers from low yields especially in the cases of aliphatic and some substituted aromatic aldehydes. The Biginelli reaction has been reviewed.[5] Several improved protocols for the preparation of DHPMs have recently been reported, either by modification of the classical one-pot condensation approach itself,[6–10] or by the development of novel, but more complex, multi-step strategies.[11] However, some of the newer reported methods also suffer from drawbacks such as unsatisfactory yields, cumbersome product isolation procedures and environmental pollution.[6,12–17] Moreover some of the methods are only practical for aromatic aldehydes.[6,11d,15,17] Therefore, a need still exists for versatile, simple and environmentally friendly processes whereby DHPMs may be formed under milder and practical conditions.



Scheme 1.

Keywords: Biginelli reaction; silica sulfuric acid; dihydropyrimidinones; catalysis; solid phase.

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Table 1. Reaction of benzaldehyde, ethyl acetoacetate and urea under different conditions

Entry	Solvent[a]	Catalyst	Yield (%)
1	$CHCl_3$	Silica sulfuric acid	35
2	THF	Silica sulfuric acid	77
3	C_2H_5OH	Silica sulfuric acid	91, 92, 90, 93, 90[b]
4	CH_3CN	Silica sulfuric acid	91
5	Toluene	Silica sulfuric acid	90
6	H_2O	Silica sulfuric acid	15
7	C_2H_5OH[c]	None	26

[a] Refluxed for 6 h.

[b] The same catalyst was used for each of the five runs.

[c] Refluxed for 24 h.

Recently, we reported the preparation of silica sulfuric acid as a stable acidic reagent and showed its catalytic activity in synthetic methodology.[18] Here we wish to report the ability of this reagent as a reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones in high yields (Scheme 1).

We started to study the three-component Biginelli condensation catalyzed by silica sulfuric acid by examining the conditions required for the reaction involving benzaldehyde, urea and ethyl acetoacetate to afford the DHPM **4a** (R^1 = Ph, R^2 = Me, R^3 = OEt, X = O). A summary of the results obtained is provided in Table 1. Entries 1–6 show the effect of various solvents on the yield of the reaction. Although acetonitrile and toluene afforded the product in high yields, we chose ethanol for its cheapness and environmental acceptability. Entry 3 describes the yields of five consecutive condensations leading to **4a**. In these experiments the product was isolated by filtration and washing the solid residues with ethyl acetate, the remaining catalyst being reloaded with fresh reagents for further runs. No decrease in the yield was observed demonstrating that silica sulfuric acid can be reused as a catalyst in Biginelli condensations. Entry 7 shows the catalytic effect of silica sulfuric acid in the three-component condensation of benzaldehyde, urea and ethyl acetoacetate.

The reactions proceeded smoothly in refluxing ethanol and were completed within 6 h. Table 2 shows the generality of the present protocol, which is equally effective for urea or thiourea, and also for aromatic and aliphatic aldehydes. Under these conditions, the yields were significantly better in comparison with the classical Biginelli procedure.

Several aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the *ortho*, *meta* and *para* positions afforded high yields of the products. An important feature of this procedure is

Table 2. Synthesis of dihydropyrimidin-ones and -thiones (DHPMs) by the condensation of aldehydes, β-dicarbonyls and urea or thiourea catalyzed by silica sulfuric acid in ethanol

Entry	DHPM[a]	R^1	R^2	R^3	X	Yield (%)[b]	Mp (°C)	
							Found	Reported
1	**4a**	C_6H_5	Me	OEt	O	91	206	202–204[6]
2	**4b**	$4\text{-}O_2N\text{-}C_6H_4$	Me	OEt	O	94	209–212	208–211[6]
3	**4c**	$4\text{-}Cl\text{-}C_6H_4$	Me	OEt	O	95	209–212	213–215[6]
4	**4d**	$4\text{-}CH_3O\text{-}C_6H_4$	Me	OEt	O	95	205–207	201–203[6]
5	**4e**	$4\text{-}F\text{-}C_6H_4$	Me	OEt	O	92	182–184	185–186[6]
6	**4f**	$3\text{-}O_2N\text{-}C_6H_4$	Me	OEt	O	93	227–229	226–227[11d]
7	**4g**	$3\text{-}HO\text{-}C_6H_4$	Me	OEt	O	93	167–170	164–166[14]
8	**4h**	$2\text{-}CH_3O\text{-}C_6H_4$	Me	OEt	O	92	259–260	262[20]
9	**4i**	$2\text{-}O_2N\text{-}C_6H_4$	Me	OEt	O	87	208–210	206–208[17]
10	**4j**	$3,4\text{-}(CH_3O)_2\text{-}C_6H_3$	Me	OEt	O	94	175–177	178[12]
11	**4k**	$C_6H_5\text{-}CH{=}CH$	Me	OEt	O	90	230–232	232–235[13]
12	**4l**	$n\text{-}C_3H_7$	Me	OEt	O	86	154	157–158[21]
13	**4m**	$n\text{-}C_6H_{13}$	Me	OEt	O	84	152–154	151–152[12]
14	**4n**	C_6H_5	C_6H_5	OEt	O	87	155–157	157–159[6]
15	**4o**	C_6H_5	Me	OMe	O	96	210–212	209–212[6]
16	**4p**	$4\text{-}Cl\text{-}C_6H_4$	Me	OMe	O	94	203–205	204–207[6]
17	**4q**	$4\text{-}CH_3O\text{-}C_6H_4$	Me	OMe	O	95	189–192	192–194[6]
18	**4r**	$4\text{-}O_2N\text{-}C_6H_4$	Me	OMe	O	95	233–235	235–237[6]
19	**4s**	$2,4\text{-}(Cl)_2\text{-}C_6H_3$	Me	OMe	O	96	252–253	254–255[13]
20	**4t**	C_6H_5	Me	Me	O	87	229–231	233–236[8]
21	**4u**	$4\text{-}CH_3O\text{-}C_6H_4$	Me	Me	O	86	170–172	168–170[14]
22	**4v**	$4\text{-}O_2N\text{-}C_6H_4$	Me	Me	O	92	229 (dec)	230 (dec)[13]
23	**4w**	C_6H_5	Me	OEt	S	93	209–211	208–210[16]
24	**4x**	$3\text{-}O_2N\text{-}C_6H_4$	Me	OEt	S	91	203–205	206–207[11c]
25	**4y**	$3\text{-}HO\text{-}C_6H_4$	Me	OEt	S	92	183–184	184–186[22]
26	**4z**	$4\text{-}CH_3O\text{-}C_6H_4$	Me	OEt	S	84	153–155	150–152[16]
27	**4a′**	C_6H_5	Me	Me	S	93	183 (dec)	185 (dec)[23]

[a] Products were characterized by comparison of their spectroscopic data (^{1}H NMR and IR) and mps with those reported in the literature.

[b] Isolated yield.

the survival of a variety of functional groups such as ethers, nitro groups, hydroxy groups, halides, etc. under the reaction conditions. Another advantage of this method is its efficiency for the high yield synthesis of DHPMs from aliphatic aldehydes.

Thiourea was used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones which are also of interest with regard to their biological activities. For example monastrol **4y**, a mitotic kinesin Eg5 motor protein inhibitor and a potential new lead for the development of anticancer drugs, was obtained in a 92% yield (Table 2, entry 25).[19]

In conclusion, the present procedure provides an efficient and improved modification of the Biginelli reaction. Mild reaction conditions, ease of workup, high yields, and stability and recyclability of the reagent are features of this new procedure. Moreover, this method has the ability to tolerate a wide variety of substituents in all three components. The results are reproducible and the reactions can be carried out on a gram scale.

General procedure for the synthesis of DHPMs

A mixture of the aldehyde (2 mmol), the β-dicarbonyl compound (2 mmol), urea or thiourea (3 mmol) and silica sulfuric acid (0.23 g, equal to 0.6 mmol H^+) in ethanol (10 ml) was refluxed for 6 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The solid mixture was washed with cold water (20 ml) to remove the excess of urea or thiourea and then filtered. The remaining solid material was washed with hot ethyl acetate (30 ml). The filtrate was concentrated and the solid product was recrystallized from ethyl acetate/*n*-hexane or ethanol.

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