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EFFICIENT SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES OVER SILICA SULFURIC ACID AS A REUSABLE CATALYST UNDER SOLVENT-FREE CONDITIONS

Peyman Salehi,[a,]* Minoo Dabiri,[b] Mohammad Ali Zolfigol,[c] and Mohammad Ali Bodaghi Fard[b]

a.Department of Phytochemistry, Aromatic and Medicinal Plants and Drug Research Institute, Shahid Beheshti University, Evin, Tehran, P.O.Box 19835-389, Iran, E-mail: p-salehi@cc.sbu.ac.ir, Fax:+98-21-2418679
b.Department of Chemistry, Faculty of Science, Shahid Beheshti University, Evin, Tehran 1983963113, Iran
c.Department of Chemistry, Faculty of Science, Bu-Ali Sina University, Hamadan 65174, Iran

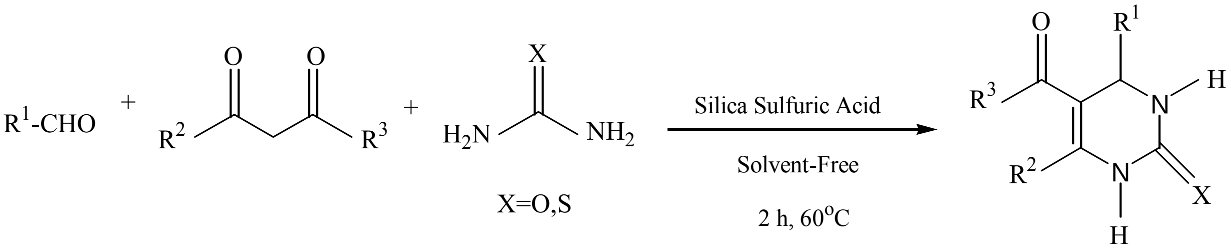
Abstract- 3,4-Dihydropyrimidin-2(1*H*)-ones and their sulfur analogues are efficiently synthesized by the three-component condensation of β-dicarbonyl compounds, aromatic and aliphatic aldehydes, and urea or thiourea in the presence of catalytic amounts of silica sulfuric acid under solvent-free conditions in high yields. The catalyst is recyclable and can be used several times without any decrease in the products yields.

The Biginelli reaction was first reported more than a century ago and recently has been reviewed.[1,2] Dihydropyrimidinones (DHPMs), the products of Biginelli reaction, and their derivatives have attracted considerable interest in recent times because of the interesting pharmacological properties, such as efficacy as calcium channel modulators and α_{1a}-adreno acceptor-selective antagonists;[3] antihypertensive agents and neuropeptide Y (NPY) antagonists.[4] Also the anti-HIV activity in some marine natural products containing the DHMPs skeleton, such as the alkaloid batzalladine B, is observed.[5] Therefore, the discovery of milder and practical routes for the synthesis of dihydropyrimidinones by the Biginelli reaction continues to attract the attention of scientists.

The simple method reported by Biginelli involving three-component condensation reaction often suffers from low yields, practically in cases of aliphatic and some substituted aromatic aldehydes.

Several improved procedures for the preparation of DHPMs have recently been reported, either by modification of the classical one-pot Biginelli approach itself,[6-10] or by the development of novel, but more complex multi-step strategies.[11] However, in spite of their potential utility, some of the newer reported methods also suffer from drawbacks such as long reaction times, unsatisfactory yields, cumbersome product isolation procedures and environmental contamination.[6,12-17] Moreover some of the methods are only practical for aromatic aldehydes.[6,11d,15,17]

Recently, we reported the preparation of silica sulfuric acid and some of its applications in synthetic methodology.[18] In an effort we reported the efficient synthesis of dihydropyrimidinones in solution using silica sulfuric acid as catalyst.[19] According to our experience in solvent-free reactions,[20] we decided to improve the reaction conditions by conducting three-component Biginelli condensation in the absence of solvent. Here we report another remarkable catalytic activity of silica sulfuric acid for the one-pot solvent-free synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones (Scheme 1).



1(a-a') **2** **3** **4(a-a')**

Scheme 1

We started to optimize the conditions by examining 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. Entry 7 describes the yields of five consecutive condensations leading to **4a** under solvent-free conditions. In these experiments the product was isolated by filtration and washing the solid residues with ethyl acetate, and the remaining catalyst was reused for new runs. No decrease in the yield was observed demonstrating that silica sulfuric acid can be recycled as catalyst in a Biginelli condensation with zero-discharge to the environment. Entry 8 shows the catalytic effect of silica sulfuric acid in the Biginelli reaction.

Table 2 shows the generality of the present protocol, which equally effective for urea and thiourea, and also for aromatic and aliphatic aldehydes. Under these conditions, the reactions time shortened significantly in comparison with similar reactions performed in solution.[19]

Several aromatic aldehydes containing electron-donating or electron-withdrawing groups were examined under the optimized conditions. In all cases the reactions with β-dicarbonyl compounds proceeded smoothly within 2 h at 60°C to give the corresponding dihydropyrimidinones in high yields (Table 2). One of the outstanding advantages of this method is its efficiency for conversion of aliphatic aldehydes into their corresponding DHPMs in good yields (Table 2, Entries 12, 13). Satisfactory yields of **4l** and **4m** were obtained at 100°C after 2 h.

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	"	77
3	EtOH	"	91
4	CH_3CN	"	91
5	Toluene	"	90
6	H_2O	"	15
7	None[b]	"	96,94,94,95,93[c]
8	None[d]	None	56

[a] Refluxed for 6 h.

[b] 60°C for 2 h.

[c] Catalyst was reused for five runs.

[d] 100°C for 2 h.

A wide variety of different groups in β-dicarbonyl compounds were tolerated in this procedure. Ethyl acetoacetate, methyl acetoacetate, ethyl benzoylacetate and acetylacetone were used satisfactorily as the model compounds. Thiourea was also used with similar success to provide the corresponding 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 90% yield (Table 2, Entry 25).[21]

In conclusion the present procedure provides an efficient and improved modification of the Biginelli reaction. In addition to its simplicity, milder reaction conditions, stability and recyclability of the reagent, shorter reaction periods, higher yields and ease of work-up, the method enjoys the chemical and environmental advantages of solvent-free reactions.[22]

EXPERIMENTAL

All of the products are known compounds and characterized by comparison of their spectroscopic data (IR, ^{1}H NMR) and melting points with those reported in the literature. Melting points were obtained in open capillaries on an Electrothermal 9200 melting point apparatus and are not corrected. Silica sulfuric acid was prepared according to our reported procedure.[18a] Progresses of the reactions were followed by dissolving a sample in ethyl acetate and monitoring on precoated TLC aluminum sheets (eluent: hexane/ ether: 1/1). Yields refer to isolated products.

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 under solvent-free conditions

Entry	**DHPM**[a]	R^1	R^2	R^3	**X**	**Yield**[b] **(%)**	**Mp(°C)**	
							Found	**Reported**
1	**4a**	C_6H_5	Me	OEt	O	96	203-205	202-204[6]
2	**4b**	$4\text{-}O_2N\text{-}C_6H_4$	Me	OEt	O	92	210-213	208-211[6]
3	**4c**	$4\text{-}Cl\text{-}C_6H_4$	Me	OEt	O	93	208-210	213-215[6]
4	**4d**	$4\text{-}MeO\text{-}C_6H_4$	Me	OEt	O	94	202-204	201-203[6]
5	**4e**	$4\text{-}F\text{-}C_6H_4$	Me	OEt	O	94	181-183	185-186[6]
6	**4f**	$3\text{-}O_2N\text{-}C_6H_4$	Me	OEt	O	90	224-226	226-227[11d]
7	**4g**	$3\text{-}HO\text{-}C_6H_4$	Me	OEt	O	93	168-170	164-166[14]
8	**4h**	$2\text{-}MeO\text{-}C_6H_4$	Me	OEt	O	91	260-262	262[23]
9	**4i**	$2\text{-}O_2N\text{-}C_6H_4$	Me	OEt	O	89	203-205	206-208[17]
10	**4j**	$3,4\text{-}(MeO)_2\text{-}C_6H_3$	Me	OEt	O	93	176-178	176-177[12]
11	**4k**	$C_6H_5\text{-}CH{=}CH$	Me	OEt	O	92	230-232	232-235[13]
12	**4l**	*n*-Pr	Me	OEt	O	83[c]	153-154	157-158[24]
13	**4m**	$n\text{-}C_6H_{13}$	Me	OEt	O	80[c]	152-154	151-152[12]
14	**4n**	C_6H_5	C_6H_5	OEt	O	90[d]	154-156	157-159[6]
15	**4o**	C_6H_5	Me	OMe	O	95	210-213	209-212[6]
16	**4p**	$4\text{-}Cl\text{-}C_6H_4$	Me	OMe	O	97	205-209	204-207[6]
17	**4q**	$4\text{-}MeO\text{-}C_6H_4$	Me	OMe	O	96	190-193	192-194[6]
18	**4r**	$4\text{-}O_2N\text{-}C_6H_4$	Me	OMe	O	91	238-240	235-237[6]
19	**4s**	$2,4\text{-}(Cl)_2\text{-}C_6H_3$	Me	OMe	O	96	256-258	254-255[13]
20	**4t**	C_6H_5	Me	Me	O	89	230-232	233-236[8]
21	**4u**	$4\text{-}MeO\text{-}C_6H_4$	Me	Me	O	83	170-172	168-170[14]
22	**4v**	$4\text{-}O_2N\text{-}C_6H_4$	Me	Me	O	91	228(decomp)	230(decomp)[13]
23	**4w**	C_6H_5	Me	OEt	S	95	210-212	208-210[16]
24	**4x**	$3\text{-}O_2N\text{-}C_6H_4$	Me	OEt	S	93	204-206	206-207[11c]
25	**4y**	$3\text{-}HO\text{-}C_6H_4$	Me	OEt	S	90	182	184-186[25]
26	**4z**	$4\text{-}MeO\text{-}C_6H_4$	Me	OEt	S	95	155-156	150-152[16]
27	**4a´**	C_6H_5	Me	Me	S	93	182-184(decomp)	185(decomp)[26]

[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 (60°C, 2 h).

[c] The reaction was performed at 100°C for 2 h.

[d] The reaction was performed at 100°C for 3 h.

General Procedure for the Synthesis of DHPMs

Urea or thiourea (3 mmol) was grinded with silica sulfuric acid (0.23 g, equal to 0.6 mmol H^+). Then aldehyde (2 mmol) and β-dicarbonyl compound (2 mmol) were added to the mixture and the whole was heated at 60°C for 2 h. The mixture was washed with cold water (20 mL) to remove the excess of urea and 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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