H₂SO₄-Silica Catalyzed One-Pot and Efficient Synthesis of Dihydropyrimidinones Under Solvent-Free Conditions

SEIED ALI POURMOUSAVI* and MARYAM HASANI

School of Chemistry, Damghan University, Damghan-3671641167-Iran
pourmousavi@du.ac.ir

Received 24 February 2011; Accepted 26 April 2011

Abstract: H₂SO₄-Silica efficiently catalyzes the three-component condensation reaction of aldehydes, 1,3-dicarbonyl compounds and urea/thiourea under solvent free conditions to afford the corresponding dihydropyrimidinones and thio-derivatives in high yields. Compared to the classical Biginelli reaction conditions, this new method consistently has the advantage of giving good yields and requiring short reaction times.

Keywords: H₂SO₄-Silica, Aldehydes, 1,3-Dicarbonyl compounds, Dihydropyrimidinone, Biginelli reaction, Solvent free conditions

Introduction

Dihydropyrimidinone derivatives (DHPMs) have attracted considerable interest in recent years because of their promising activities as calcium channel blockers, antihypertensive agents and *R*-1a-antagonists¹⁻². Moreover, several alkaloids containing the dihydropyrimidine unit have been isolated from marine sources, which also exhibit interesting biological properties³. Thus, synthesis of this heterocyclic nucleus is of much current importance. The simple and direct method for the synthesis of dihydropyrimidinones was first reported by Biginelli in 1893, involving a one-pot condensation of an aldehyde, β -ketoester and urea under strongly acidic conditions⁴. However, it suffers from low yields (20–50%) of products. Therefore, in the recent years several improved methodologies mainly using Lewis acids⁵⁻⁸, triflates⁹⁻¹², microwave irradiations¹³⁻¹⁴, ionic liquids¹⁵⁻¹⁶, clay¹⁷, silica-sulfuric acid¹⁸, silica supported sodium hydrogen sulfate¹⁹, heteropoly acids²⁰, iodine-alumina system²¹, poly(4-vinylpyridine-co-divinylbenzene)-Cu(II) complex²², iodotrimethylsilane²³, solid super acid²⁴, ion-exchange resins²⁵, *L*-proline²⁶, polyoxometallates²⁷, LaCl₃-graphite²⁸, trifluoroacetic acid²⁹ and thiamine hydrochloride³⁰ have been reported in the literature. However, many of these methods are associated with expensive and toxic reagents, stoichiometric amount of catalyst, unsatisfactory yields, incompatibility with other functional

groups and involve difficult product isolation procedures. Thus, there is still a need for a simple and general procedure for one-pot synthesis of dihydropyrimidinone and thiones under mild conditions.

In recent years, use of eco-friendly applicable industrial and green catalysts has been of interest. Thus, green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials³¹.

Experimental

Chemicals were purchased from Fluka and Merck chemical companies. Silica gel 60, 0.063-0.200 mm was applied as support. The structures of known compounds were identified by comparison of their spectral data with those in the authentic samples. The ¹H NMR (250 MHz) was run on a Bruker Avance DPX-250 FT-NMR spectrometer (δ in ppm). H₂SO₄-Silica was prepared according to our previously reported method³².

General procedure for the preparation of DHPMs

A mixture of aldehyde (2 mmol), ethyl acetoacetate or acetylacetone (2 mmol), urea or thiourea (3 mmol) and H₂SO₄-Silica (0.15 mmol) was stirred at 50-55 °C under solvent-free conditions. The reaction mixture was left stirring and the progress of the reaction was monitored by TLC using cyclohexane/ethylacetate (7:3) as eluent. After completion of the reaction, the mixture was cooled to room temperature and poured on to ice-water (20 mL). The resulting solid product was filtered and washed with water (2×5 mL) and then recrystallized from ethanol to give the pure products.

Selected spectral data of the products

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, Entry 2): ¹H-NMR (DMSO-d₆) δ : 1.09 (t, 3H, J = 7.1 Hz, CH₃), 2.25 (s, 3H, CH₃), 3.97 (q, 2H, J = 7.1 Hz, OCH₂), 5.05 (d, 1H, J = 2.15 -CH), 7.28 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.20 (s, 1H, NH); IR ($\nu_{\max}$; KBr, cm⁻¹): 3240, 1722, 1638.

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, Entry 8): ¹H-NMR (DMSO-d₆) δ : 1.15 (t, 3H, J = 7.12 Hz, CH₃), 2.33 (s, 3H, CH₃), 3.78 (s, 3H, -OCH₃), 4.06 (q, 2H, J = 7.12 Hz, OCH₂), 5.34 (d, 1H, J = 2.28 -CH), 6.82 (d, 2H, J = 8.60, Ar-H), 7.22 (d, 2H, J = 8.60, Ar-H), 7.76 (s, 1H, NH), 9.26 (s, 1H, NH); IR ($\nu_{\max}$; KBr, cm⁻¹): 3232, 1720, 1638.

5-(Ethoxycarbonyl)-4-(2,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, Entry 11): ¹H-NMR (DMSO-d₆) δ : 1.14 (t, 3H, J = 7.2 Hz, CH₃), 2.40 (s, 3H, CH₃), 3.54 (s, 3H, CH₃), 3.90 (s, 3H, CH₃), 4.05 (q, 2H, J = 7.2 Hz, OCH₂), 5.63 (d, 1H, J = 2.30, -CH), 5.83 (s, 1H, NH), 6.34-6.52 (m, 2H, Ar-H), 6.95 (m, 1H, Ar-H), 8.23 (s, 1H, NH); IR ($\nu_{\max}$; KBr, cm⁻¹): 3255, 1731, 1651.

Results and Discussion

Noting recent reports on the use of sulfuric acid immobilized on silica (H₂SO₄-Silica)³³⁻³⁵ and in continuation of our research to develop new reagent for organic transformation^{32,36-37}, we now wish to report a three component Biginelli-type reaction by this catalyst. The Biginelli reaction was carried out with urea, ethyl acetoacetate or acetylacetone, aldehydes and a catalytic amount of H₂SO₄-Silica as a non-toxic, inexpensive and easily available catalyst, under solvent-free conditions at 50-55 °C. The reaction mixture was converted to the corresponding DHPMs and the products were obtained in good to high yields under solvent free conditions (Scheme 1).

Scheme 1

To optimize the reaction conditions, we tried to convert a mixture of benzaldehyde, ethyl acetoacetate and urea to its corresponding DHPMs under solvent-free conditions, in various solvents and also various catalytic amounts of H_2SO_4 -Silica (Table 1).

Table 1. Effect of solvent and catalyst amounts of H_2SO_4 -Silica on the yield of the DHPMs^a

Entry	Solvent	Catalyst Amounts, mol %	Time, h	Yield ^b
1	-	2.5	6	40
2	-	5	3	55
3	-	7.5	2	80
4	-	10	2	80
4	THF	7.5	3	30
5	Ethyl acetate	7.5	3	30
6	Ethanol	7.5	2	55
7	Acetonitrile	15	1	40
8	Dichloromethane ^c	7.5	1	10
9	Chloroform	7.5	3	30

^abenzaldehyde/ ethyl acetoacetate /Urea (1:1:1.5 mmol). ^bThe yields refer to isolated pure products.

^cThe reaction was carried out under reflux conditions

As shown in Table 1, in comparison to conventional methods in solution the yield of the reaction under solvent-free conditions is higher and the reaction time is shorter. It is remarkable to note that the condensation proceeded with a low catalyst concentration (7.5 mol% of H_2SO_4 -Silica) and gave 3,4-dihydropyrimidin-2(1H)-ones in good yield. Higher amounts of the catalyst did not improve the yields. In a control experiment, we observed that the reaction does not take place in the absence of H_2SO_4 -Silica.

Therefore, we employed the above conditions for the conversion of various aldehydes to the corresponding DHPMs under solvent-free conditions at 50-55 °C. Under the given reaction conditions several aromatic aldehydes containing electron donating as well as electron withdrawing groups with diverse substitution pattern were effectively cyclized to give DHPMs. The results are summarized in Table 2.

Table 2. H₂SO₄-Silica catalyzed Biginelli reaction under solvent free conditions^a

Entry	R ¹	R ²	R ³	X	Time, h	Yield ^b , %
1	Me	Me	C ₆ H ₅ -	O	1.5	82
2	Me	OEt	C ₆ H ₅ -	O	2	80
3	Me	Me	C ₆ H ₅ -	S	3	72
4	Me	Me	2-MeOC ₆ H ₄ -	O	2.5	73
5	Me	OEt	2-MeO C ₆ H ₄ -	O	2	73
6	Me	Me	2-HO C ₆ H ₄ -	O	6.5	76
7	Me	OEt	2-HO C ₆ H ₄ -	O	6	84
8	Me	OEt	4-MeO C ₆ H ₄ -	O	2	93
9	Me	OEt	4-MeO C ₆ H ₄ -	S	6	72
10	Me	OEt	4-Cl C ₆ H ₄ -	O	0.5	50
11	Me	OEt	2,4-(MeO) ₂ C ₆ H ₃ -	O	2	80
12	Me	OEt	2,4-(MeO) ₂ C ₆ H ₃ -	S	2	53
13	Me	OEt	4-HO C ₆ H ₄ -	O	2	70
14	Me	OEt	4-HO-3-MeO C ₆ H ₃ -	S	4	50
15	Me	OEt	3,4,5-(MeO) ₃ C ₆ H ₂ -	O	2	66

^aA mixture of Aldehyde (1 mmol) and 1,3-diketone or Ethylacetoacetate (1 mmol) with urea (1.5 mmol) in the presence of H₂SO₄-Silica (0.075 mmol) was heated at 50-55 °C. ^bThe yields refer to isolated pure products

As can be seen from Table 2, aldehydes, 1,3-dicarbonyl compounds and urea or thiourea in the presence of a catalytic amount of H₂SO₄-Silica gave the corresponding dihydropyrimidinones and thioderivatives in good yields under solvent-free conditions. In most cases, after completion of reaction and washing with H₂O the crude products were purified by recrystallization from ethanol. An important feature of this method is that aromatic aldehydes carrying either electron-donating or electron-withdrawing groups afforded good yields of products in high purity.

Conclusion

In conclusion, we have demonstrated a very simple, efficient, and practical method for the synthesis of dihydropyrimidinones and thioderivatives through a one-pot, three-component condensation of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea catalyzed by H₂SO₄-Silica under solvent-free conditions. The main features of our new reaction are as follows: (1) The simplicity of the system; (2) the condensation reaction could be performed exclusively using cheap, commercially available chemicals; (3) easy separation of products from the reaction mixture (4) The method is cost-effective and environmentally benign.

Acknowledgment

We gratefully acknowledge the funding support received for this project from the Damghan University IR Iran.

References

1. Atwal K S, Rovnyak G C, Kimball S D, Floyd D M, Moreland S, Swanson B N, Gougoutas J Z, Schwartz J, Smillie K M and Malley M F, *J Med Chem.*, 1990, **33**, 2629.
2. Atwal K S, Swanson B N, Unger S E, Floyd D M, Moreland S, Hedberg A and O'Reilly B C, *J Med Chem.*, 1991, **34**, 806 and references therein.
3. Overman L E, Rabinowitz M H and Renhowe P A, *J Am Chem Soc*, 1995, **117**, 2657.
4. Biginelli P, *Gazz Chim Ital.*, 1893, **23**, 360.
5. Reddy C V, Mahesh M, Raju P V K, Babu T R and Reddy V V N, *Tetrahedron Lett.*, 2002, **43**, 2657.
6. Fu N Y, Yuan Y F, Cao Z, Wang S W, Wang J T and Peppe C, *Tetrahedron*, 2002, **58**, 4801.
7. Ramalinga K, Vijyalakshmi P and Kaimal T N B, *Synlett.*, 2001, **6**, 863-865.
8. Yadav J S, Reddy B V S, Srinivas R, Venugopal C and Ramalingam T, *Synthesis*, 2001, **9**, 1341-1345.
9. Lu J and Bai Y, *Synthesis*, 2002, **4**, 466-470.
10. Ma Y, Qian C, Wang L and Yang M, *J Org Chem.*, 2000, **65**, 3864-3868.
11. Adapa S R, Alam M M and Varala R, *Synlett.*, 2003, **1**, 67.
12. Paraskar A S, Dewkr G K and Sudailal A, *Tetrahedron Lett.*, 2003, **44**, 3305.
13. Mishar A K, Agnihotri G and Madhusudan S K, *Indian J Chem.*, 2004, **43B**, 2018.
14. Yadav J S, Reddy B V S, Reddy K B, Raj K S and Prasad A R, *J Chem Soc Perkin Trans I*, 2001, **42**, 7975.
15. Peng J J and Chin Deng Y-Q, *J Org Chem.*, 2002, **22**, 71.
16. Shaabani A and Rahmati A, *Catal Lett.*, 2005, **25**, 1062.
17. Peng J and Deng Y, *Tetrahedron Lett.*, 2001, **42**, 34, 5917-5919.
18. Salehe P, Dabiri M, Zolfigol M A and Fard M A B, *Heterocycles*, 2003, **60**, 2435.
19. Saxena I, Borah D C and Sarma J C, *Tetrahedron Lett.*, 2005, **46**, 1159.
20. Chari M A and Syamasunder K J, *Mol Catal A Chem.*, 2004, **221**, 137.
21. Yarapathi R V, Kurya S and Tammishetti S, *Catal Commun.*, 2004, **5**, 511.
22. Yadav J S, Kumar S P, Kondaji G, Rao R S and Nagaiah K, *Chem Lett.*, 2004, **33**, 1168.
23. Yadav J S, Reddy B V S, Sridhar P, Reddy J S S, Nagaiah K, Lingaiah N and Saiprasad P S, *Eur J Org Chem.*, 2004, **3**, 552.
24. Kappe C O, Kumar D and Verma R S, *Synthesis*, 1999, **10**, 1799.
25. Joseph J K, Jain S L and Sain B, *J Mol Catal A Chem.*, 2006, **247**, 99-102.
26. Gohain M, Prajapati D and Sandhu J S, *Synlett.*, 2004, **2**, 235-238.
27. Fazaeli R, Tangestaninejad S, Aliyan H and Moghadam M, *Appl Catal A Gen.*, 2006, **309**, 44.
28. Khabazzadeh H, Saidi K and Sheibani H, *Bioorg & Med Chem Lett.*, 2008, **18**, 278-280.
29. Shobha D, Adharvana Chari M and Ahn K H, *Chinese Chemical Lett.*, 2009, **20(9)**, 1059-1061.
30. Mandhane P G, Joshi R, S, Nagargoje D R and Gill C. H. *Tetrahedron Lett.*, 2010, **51**, 3138-3140.
31. Clark J H, *Green Chem.*, 1999, **1**, 1.
32. Pourmousavi S A and Zinati Z, *Turk J Chem.*, 2009, **33**, 385-392.
33. Mukhopadhyay B, *Tetrahedron Lett.*, 2006, **47**, 4337-4341.
34. Rajput V K, Roy B and Mukhopadhyay B, *Tetrahedron Lett.*, 2006, **47**, 6987.
35. Rajput V K and Mukhopadhyay B, *Tetrahedron Lett.*, 2006, **47**, 5939-5941.
36. Pourmousavi S A and Salehi P, *Bull Korean Chem Soc.*, 2008, **29**, 1332.
37. Pourmousavi S A and Salehi P, *Acta Chim Slov.*, 2009, **56**, 734-739.