

Ag nanoparticle/melamine sulfonic acid supported on silica gel as an efficient catalytic system for synthesis of dihydropyrimidinthiones

Parya Nasehi^a, Alireza Kiasat^a, Mohammad Kazem Mohammadi^{b,*}

^aDepartment of Chemistry, Science and Research Branch, Islamic Azad University, Ahvaz, Iran

^bDepartment of Chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran

Received: 14 January 2014, Accepted: 16 April 2014, Published: 16 April 2014

Abstract

3,4-Dihydropyrimidin-2(1H)-thiones were synthesized in the presence of Ag nanoparticle/melamine sulfonic acid (MSA) supported on silica gel. The reaction was carried out at 110 °C for 20 min under solvent free conditions. This method has some advantages such as good yield, mild reaction conditions, ease of operation and work up, short reaction time and high product purity.

Keywords: Nanoparticle melamine sulfonic acid.SiO₂; Biginelli reaction; 3,4-dihydropyrimidin-2(1H)-thione; solvent free.

Introduction

3,4-Dihydropyrimidin-2(1H)-thiones were synthesized via Biginelli reaction. This protocol is an acid catalyzed three-component condensation between an aromatic aldehyde, -ketoester or -diketone and thiourea. This

reaction was originally described by Italian chemist Pietro Biginelli in 1893. However, this reaction suffers from the harsh conditions, long reaction times and frequently low yields. Some Biginelli products have potential pharmaceutical applications such as anti-

*Corresponding author: Mohammad Kazem Mohammadi
Tel: +98 (611) 3348329, Fax: +98 (611) 3348329
E-mail: mohammadi@iauahvaz.ac.ir

viral, antitumor, antibacterial, anti-inflammatory and antihypertensive.

Meanwhile, 3,4-dihydropyrimidin-2(1H)-thiones are calcium channel blockers, antihypertensive agents, alpha-1a-antagonists and neuropeptide Y (NPY) antagonists [1]. The most important examples are batzelladine alkaloids, which are potent HIV group-120-CD₄ inhibitors [2].

Many catalysts such as H₃PMO₁₂O₄₀, [3] 12-tungstophosphoric acid [4], chloroacetic acid [5], P-Dodecylbenzenesulfonic acid (DBSA) [6], CuI [7], Fe(CF₃CO₂)₃ [8], ZrCl₄ [9], NH₂SO₃H [10], and Y(NO₃)₃.6H₂O [11] have been applied in Biginelli reaction.

Organic reactions under solvent free condition are of interest from both industrial and academic view points. Due to the medical and chemical importance of Biginelli reaction products, the discovery and introduction of better and milder conditions, using new catalysts, have been under attention. Along this line, using solid acids which are low in toxicity, highly stable towards humidity and high activity, recoverable by simple filtration and very high surface area to volume ratios in nanostructures, has found more attention [12,13].

In this work, we have investigated the application of Ag nanoparticle/MSA.SiO₂ for synthesis of Biginelli-type condensation.

Experimental

General

The materials were purchased from Sigma-Aldrich and Merck and were used without any additional purification. Products were characterized by FT-IR and comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker Equinox 55 spectrometer and the TEM of nanoparticles determined with VEGA/TESCAN scanning electron microscope.

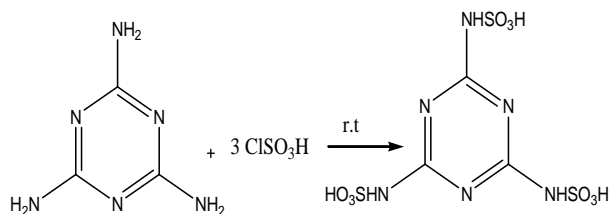
Preparation of Ag nanoparticle supported on silica gel

Aqueous NaBH₄ solution (30 mL, 8 mmol/L) was placed in an ice bath. After cooling, (1.5 g) silica gel was added to the solution. When (10 mL) AgNO₃ solution (1 mmol) was added dropwise to this solution, the color of solution was turned yellow due to the formation of silver particles. After 30 min stirring, the solid was separated from solution by centrifuge. The yellow precipitate was washed by water for several times and oven-dried at 80 °C. The immobilized silver nanoparticle was stored in a dark colored bottle.

Preparation of Melamine sulfonic acid (MSA)

A 50 mL suction flask was equipped with a constant pressure-dropping funnel. The gas outlet was connected to a vacuum system

through adsorbing solution (water) and an alkali trap. Melamine (1.26 g, 10 mmol) was charged in the flask, and Chloro sulfonic acid (3.5 g, 2 mL, 30 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 30 min at room temperature. HCl gas was evolved immediately. After completion of the addition, the mixture was shaken for 2 h while the residual HCl was eliminated by suction. Then, the mixture was washed by excess CH_2Cl_2 to remove the unreacted chlorosulfonic acid. Finally, a white solid powder was obtained (3.3 g, 90%).



Scheme 1. Preparation of MSA

Typical procedures for preparation of 3,4-dihydropyrimidin-2(1H)-thiones in the presence of Ag nanoparticle/MSA.SiO₂ under solvent free condition

A mixture of aldehyde (1 mmol), ethyl acetoacetate or acetyl acetone (1 mmol), thiourea (3 mmol), and 0.2 g melamine sulfonic acid and 0.05 g of Ag nanoparticle.SiO₂ was heated stirring at 110 °C for 20 min. The progress of the reaction was monitored by TLC using (ethyl acetate/hexane (1:4) as elu-

ent). After completion of reaction, the product was washed by crushed ice-cold water and the resultant, separated solid, was filtered to dissolve the excess of thiourea in water. Then, the solid was dissolved in hot ethanol and filtered to remove the catalyst and purified further by recrystallization.

Results and discussion

The Ag nanoparticle immobilized on silica gel was easily prepared by chemical reduction of AgNO_3 by NaBH_4 in water and in the presence of silica gel. The dimensions of nanoparticle were observed with TEM. The sizes of commercial synthesized Ag nanoparticle.SiO₂ are about 53nm (Figure 1).

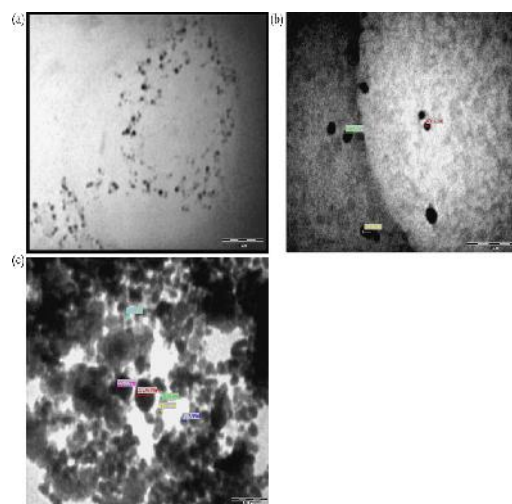


Figure 1. TEM image of synthesized colloidal silver nanoparticle, (b) the Ag nanoparticles immobilized on silica gel (c) aggregated silver nanoparticles

The preparation of Ag nanoparticle was investigated by UV-Vis spectra. The broad peak in 390 nm showed preparation of Ag in nano size (Figure 2).

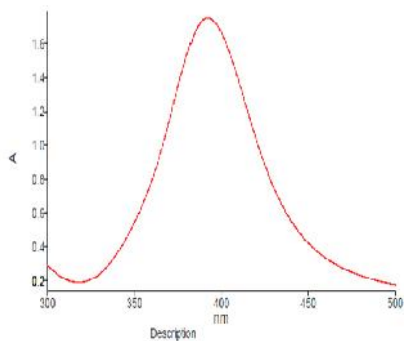


Figure 2. Uv-Vis spectra of Ag nanoparticles

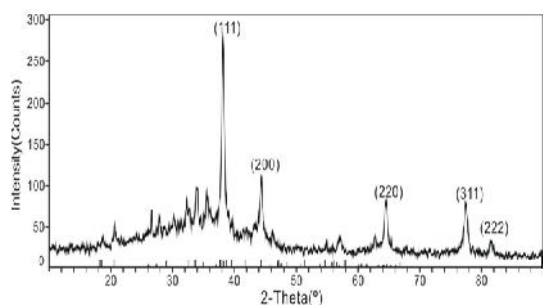
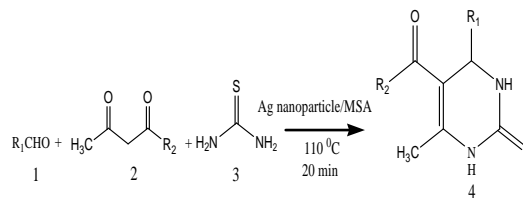


Figure 3. XRD pattern of the silver nanoparticles

The typical powder XRD pattern of the prepared nanoparticles is shown in Figure. 3. The data shows diffraction peaks at $2\theta = 38.2^\circ$, 44.4° , 64.6° , 77.5° , and 81.7° , which can be indexed to (111), (200), (220), (311), and (222) planes of pure silver (PDF 04-

0783). It confirmed that the main composition of the nanoparticles was silver.

In the next steps, we investigated the application of Ag nanoparticle/MSA.SiO₂ for synthesis of various Biginelli type products by condensation of various aromatic aldehyde containing electron donating and withdrawing groups with ethyl acetoacetate or acetyl acetone and thiourea (Table 1). In all cases, the three-component reaction proceeded smoothly to give the corresponding 3,4-dihydropyrimidin-2(1H)-thiones in moderate to good yield. We have found that the best conditions are using 0.2 g MSA, 0.05 g Ag nanoparticle.SiO₂ under solvent free conditions at 110 °C (Scheme 2).

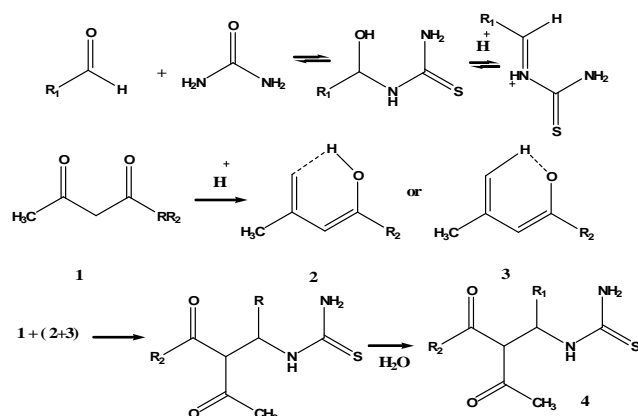


Scheme 2. Preparation of DMPHs

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1H)-thiones in the presence of Ag nanoparticle/MSA.SiO₂

Compound	R ₁	R ₂	Time min	Yield (%)	Mp(°C)	
					Found	Reported
4a	C ₆ H ₅	OC ₂ H ₅	20	73	208-210	209-211[14]
4b	4-Cl C ₆ H ₄	OC ₂ H ₅	20	88	192-194	191-195[14]
4c	4-OMe C ₆ H ₄	OC ₂ H ₅	20	97	152-154	155-156[14]
4d	4-CN C ₆ H ₄	OC ₂ H ₅	20	87	190-193	-
4e	C ₆ H ₄ CH=CH	OC ₂ H ₅	20	82	-	-
4f	C ₆ H ₅	CH ₃	20	77	210-212	214-215[13]
4g	4-Cl C ₆ H ₄	CH ₃	20	87	204-205	208-209[13]
4h	4-OMeC ₆ H ₄	CH ₃	20	84	158-160	161-163[13]
4i	4-CN C ₆ H ₄	CH ₃	20	92	-	-
4j	C ₆ H ₄ CH=CH	CH ₃	20	86	-	-

^aThe yields refer to the isolated pure products which were characterized from their spectral data and were compared with authentic sample.



Scheme 3. Possible mechanism for biginillei reaction

The products have been characterized by comparison of their physical and spectroscopic data with those of the authentic samples. The physical and spectroscopic data of the new compounds are reported below.

Charctristic data for some compounds: Other compounds were charactrisized in refs [3-8].

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione(4a)

Mp 208-210 °C; ¹H NMR(300 MHz): =10.33(s, 1H, NH),9.64 (s, 1H, NH), 7.35-

7.19(m, 5H, C₆ H₅),5.16 (d, J=3.5 Hz, 1H, CH), 4.00 (q, J=7.00Hz, 2H, OCH₂ CH₃), 2.28 (s, 3H, CH₃), 1.09 (t, J=7.0 Hz, 3H, OCH₂ CH₃); IR (KBr): 3312,3186, 2997, 1665, 1191 cm⁻¹ ; MS (70Ev,EI): m/z(%): 306(M, 82), 277 (M-C₂H₅,80), 32(100); Anal.(%): calcd for C₁₅ H₁₈O₃N₂S: C, 58.78; H, 5.93; N,9.15. Found: C, 58.83; H, 5.77; N, 9.03.

4-(4-Chlorophenyl)-5-Ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione(4b)

Mp 192-194⁰C; ¹H NMR (300 MHz): =10.36 (s,1H, NH), 9.65 (s, 1H, NH), 7.43-7.19(m, 4H, C₆ H₄),5.16 (s, 1H, CH), 4.00 (q, J=6.6Hz, 2H, OCH₂ CH₃), 2.28 (s, 3H, CH₃), 1.08(t, J=6.6 Hz, 3H, OCH₂ CH₃); ¹³C NMR(300 MHz): =174.3, 165.0, 145.3, 142.4, 132.3, 128.6, 128.4, 100.4, 59.7, 53.5, 17.2, 14.0; IR (KBr): 3255,1657, 1560 cm⁻¹ ;

MS (70Ev, EI): m/z(%): 310(M, 99), 281 (M-C₂H₅, 82), 199(100); Anal.(%): calcd for C₁₄H₁₅O₂N₂ClS: C, 54.08; H, 4.87; N, 9.02. Found: C, 54.23; H, 4.71; N, 8.99.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4c)

Mp 152-154 °C; ¹H NMR(300 MHz): =10.29(s, 1H, NH), 9.59 (s, 1H, NH), 7.14-6.87(m, 4H, C₆H₄), 5.10 (s, 1H, CH), 3.99 (q, J=7.00Hz, 2H, OCH₂CH₃), 3.71 (s, 3H, OCH₃), 2.27 (s, 3H, CH₃), 1.09(t, J=7.0Hz, 3H, OCH₂CH₃), 3.71(s, 3H, CH₃), 1.09(t, J=7.0 Hz, 3H, OCH₂CH₃); ¹³C NMR(300 MHz): =174.0, 165.2, 158.8, 144.7, 135.8, 127.7, 113.9, 101.1, 59.6, 55.1, 53.5, 17.2, 14.1; IR (KBr): 3250, 1651, 1598, 1561 cm⁻¹; MS (70Ev, EI): m/z(%): 306(M, 82), 277 (M-C₂H₅, 80), 32(100); Anal.(%): calcd for C₁₅H₁₈O₃N₂S: C, 58.78; H, 5.93; N, 9.15. Found: C, 58.83; H, 5.77; N, 9.03.

Ethyl 4-(4-cyanophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

Mp 152-154 °C; ¹H NMR: =10.4(s, 1H,

NH), 9.8 (s, 1H, NH), 7. 43-7.58(m, 4H, C₆H₄), 5.55 (s, 1H, CH), 4 (q, J=7.18Hz, 2H, OCH₂CH₃), 2.04 (s, 3H, CH₃), 1.09(t, J=7.0Hz, 3H, OCH₂CH₃), 3.71(s, 3H, CH₃), 1.09(t, J=7.0 Hz, 3H, OCH₂CH₃); ¹³C NMR(300 MHz): =171.76, 164.4, 144.7, 137.1, 129.52, 128.43, 128.2, 118.1, 109.12, 94.53, 60.06, 54.73, 15.84, 13.95.

4-(5-Acetyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl) benzonitrile (4i)

¹H NMR(300 MHz): =10.98(s, 1H, NH), 10.57 (s, 1H, NH), 7.43-7.62(m, 4H, C₆H₄), 6.02 (s, 1H, CH), 2.35 (s, 3H, CH₃), 1.97(s, 3H, CH₃); ¹³C NMR(300 MHz): =191.81, 172.01, 144.34, 144.25, 132.22, 128.13, 118.9, 118.5, 113.06, 58.21, 29.97, 15.59; IR (KBr): 3278, 3179, 2370, 1608, 1198 cm⁻¹.

It is worthy to note that the catalytic system reused 3 consecutive times with only a slight variation in the yields of the corresponding products. Table 2 demonstrates the usability of the catalyst after three runs in Biginelli condensation reaction.

Table 2. Reusability of the Ag nanoparticle/MSA.SiO₂ catalytic system under solvent free synthesis of DHPMs

Experiment	Cycle	Yield (%) ^a
1	1	97
2	2	95
3	3	94

Reaction conditions: 4-methoxybenzaldehyde (1mmol), ethyl acetoacetate (1mmol), urea (3mmol), Ag nanoparticle/MSA.SiO₂ (0.25 gr), time (20 min).

^aIsolated yield

Conclusion

Ag nanoparticle/MSA.SiO₂ has been applied for the condensation of aromatic aldehydes, ethyl acetoacetate or acetylacetone and thiourea in a simple and straightforward protocol. Short reaction times, good yields, simplicity of operation, easy work up and environmentally friendly procedure are some advantages of this method.

Acknowledgments

We gratefully acknowledge financial support from the Science and Research Branch, Islamic Azad University, Khuzestan, Iran.

References

- [1] B.B. Snider, Z. Shi, *J. Org. Chem.*, **1993**, 58, 3828-3839.
- [2] F. Hojati, M.Gholizadeh, *Bull. Korean-Chem. Soc.*, **2010**, 31, 11, 3238-3240.
- [3] M. M. Heravi, K. Bakhtiari, F. F. Bamoharram, *Catal. Commun.*, **2006**, 7, 373-376.
- [4] M. M. Heravi, F. Derikvand, F. F. Bamoharram, *J. Mol.Catal. A: Chem.*, **2005**, 242,173-175.
- [5] Y.Yu. D. Liu. C. Liu, G.Luo, *Bioorg. Med. Chem. Lett.* **2007** , 17, 3508- 3510.
- [6] H. R. Kalita, P. Phukan, *Catal. Commun.*, **2007**, 8 ,179- 182.
- [7] H. Adibi. H.A. Samimi, M. Beygzadeh, *Catal. Commun.*, **2007**, 8 , 2119- 2124.
- [8] C.V. Reddy, M, Mahesh, P.V.K. Raju, T.R. Bubu, V.V.N. Reddy *Tetrahedron Lett.*,

2002, 43, 2657- 2659.

- [9] J.T. Li, J.F. Han, J.H. Yang, T.S. Li, *UltrasonicsSonochem.*,**2003**, 10,119- 122.
- [10] N.S. Nandurkar. M.J. Bhanushali, M.D. Bhor, B.M. Bhanage, *J. MOL Cata .A: chem.*, **2007**, 271, 14-17.
- [11]B.Sadegi, B.F.Mirjalili, M.M.Hashemi, *Tetrahedron Lett.*,**2008**, 49, 2575- 2575.
- [12] B.F.Mirjalili, A. Bamoniri, A. Akbari, *Tetrahedron Lett.*,**2008**, 49, 6454- 6456.
- [13] B.F.Mirjalili, A. Bamoniri, A. Akbari, *J. Iran. Soc.Chem.*,**2011**, 8, 135- 140.
- [14] M. Zeinal-Dastmalbaf, A.Davoodnia, *Bull.Korean Chem. Soc.*, **2011**, 32, 656-658.