# Monolayer-protected silver nanoparticles: an efficient and versatile reagent for the synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones (thiones) Bahareh Sadeghi<sup>a\*</sup>, Salehe Zavar<sup>a</sup> and Alireza Hassanabadi<sup>b</sup>

<sup>a</sup>Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran <sup>b</sup>Department of Chemistry, Islamic Azad University, Zahedan Branch, PO Box 98135-978, Zahedan, Iran

Silver nanoparticles has been prepared and shown to efficiently catalyse the one-pot, three-component reaction of an aromatic aldehyde, urea or thiourea and a 1,3-diketone at reflux, to afford the corresponding 3,4-dihydropyrimidine-2-(1*H*)-ones in high yield.

Keywords: silver nanoparticles, 1,3-diketones, aromatic aldehyde, Biginelli reaction, 3,4-dihydropyrimidine-2-(1H)-ones

3,4-Dihydropyrimidine-2-(1H)-ones (DHPMs) have received considerable attention due to their interesting pharmacological properties.1-5 These compounds can be easily prepared the Biginelli reaction, a one-pot condensation using  $\beta$ -dicarbonyl compounds with aldehydes (aromatic and aliphatic aldehydes) and urea or thiourea. Since Biginelli<sup>6</sup> first reported this method using strongly acidic conditions, improvements in the syntheses have been made in order to keep the simplicity of the original one-pot Biginelli protocol and at the same time overcome its drawbacks such as low yields, especially in the case of substituted aromatic and aliphatic aldehydes<sup>7</sup>. Recently, modifications and improvements have included the use of Lewis acids as well as Br¢nsted acids/bases, primary amines, chlorotrimethylsilane and hexaaquaaluminium tetrafluoroborate as a propagator.8-21 Many other synthetic methods have been reported including the use of the classical conditions with microwave<sup>22,23</sup> and ultrasound irradiation.<sup>24-26</sup>

Over the past decade, nanomaterials have attracted interest due to their potential applications in microelectronics, catalysis and optics. metallic nanoparticles show unique properties which differ from those of the bulk species because of their singular electronic structure and extremely large surface area.27-29 Silver nanoparticles have been of interest due to their size-dependent optical and surface plasmon properties, including surface-enhanced Raman effects.<sup>30</sup> Silver nanoparticles are mostly synthesised by various colloidal processes giving surfactant-stabilized silver nanoparticles in liquid phases and involving the chemical reduction of silver salts in aqueous solutions. With some exceptions, most of these synthetic approaches are based on the reduction of water-soluble silver salt precursors, such as AgNO<sub>3</sub> and its derivatives, using boron hydrides, sodium citrate, ascorbate and LiAlH<sub>4</sub>.<sup>31,32</sup> The size distributions of these nanoparticles are often broad and the stability of these colloids has been problematic, as they aggregate and precipitate out over time from aqueous solution. In continution of our investigations of the application of solid acids in organic synthesis,<sup>33–35</sup> we have investigated the synthesis of silver nanoparticles as a catalyst and applied them to the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones (thiones).

## **Results and discussion**

We attempted to synthesise organic-soluble silver nanoparticles using silver nitrate as a precursor by adsorption method for use in an organic phase as a versatile reagent for the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones (thione). This synthesis involved the three-component condensation of an aromatic aldehyde 1, 1,3-diketones 2, and urea or thiourea 3 (Scheme 1).

The stable catalyst was easily prepared and used for preparation of 3,4-Dihydropyrimidine-2-(1H)-ones (thiones) (Figs 1–5).

Initially, the fully organic phase system contained silver nitrate as a silver precursor, *n*-butylamine  $(CH_3(CH_2)_3NH_2)$  as a solvent for dissolving the silver salt, dodecanoic acid  $(CH_3(CH_2)_{10}CO_2H)$  [DDA] as a capping molecule, toluene as a reaction medium, and NaBH<sub>4</sub> as the reducing reagent. The silver NPs which were synthesized were used without further purification. The dodecanoic acid was held as a silver salt and the mechanistic role of the silver ions was used to stabilise the enolates of the 1,3-dicarbonyl compound that are required for the reaction. A scheme for the direct synthesis of silver nanoparticles from silver nitrate in the organic phase is illustrated in Fig. 1. The formation of silver nanoparticles was observed with UV spectroscopy, which showed surface plasmon peaks in the range between 380 and 450 nm in Fig. 2.

The product was characterised by SEM in Fig. 3. The SEM image showed that the particle size was between 70 and 100nm. The nanoparticles were typically dispersed in toluene for further characterization using field emission transmission TEM. TEM samples were prepared by placing a drop of the colloidal dispersion in toluene on an amorphous carbon-coated grid in Fig. 4. The TEM image showed nanopores with a size of 5 nm. The molecular structure of the capping molecule on the synthesised nanoparticles was investigated through <sup>1</sup>H NMR in Fig. 5. It shows that there were no protons in polar groups such as amino or carboxylic acid, but only in hydrocarbon (C–H).

To optimise the reaction conditions, the reaction of 4nitrobenzaldehyde, ethyl acetoacetate and urea was used as a



Scheme 1 Synthesis of 3,4-dihydropyrimidine-2-(1*H*)-ones (thiones) in the presence of silver NPs as catalyst.

<sup>\*</sup> Correspondent. E-mail: bsadeghia@gmail.com



Formation of silver-alkyl ligand complex

Exchange of alkyl ligand with capping molecule

Fig. 1 Experimental schemes for direct synthesis of silver nanoparticles in fully organic phase through *in situ* ligand exchange.



Fig. 2 UV–Vis spectrum for silver nanoparticles dissolved into toluene.



Fig. 3 The SEM images of silver nanoparticles.



Fig. 4 The TEM images of silver nanoparticles.



**Fig. 5** The <sup>1</sup>H NMR spectrum of silver nanoparticles dissolved into deuteriatedchloroform.

 Table 1
 Evaluation of the activity of different catalysts for the synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3-4-dihydropyrimidin-2(1H)-one

Entry	Catalyst	Time /min	Yieldª /%	
1	-	10	8	
2	$Ni(NTf_2)_2$	10	28	
3	CeCl <sub>3</sub>	10	15	
4	$AI(H_2O)_6(BF_4)_3$	10	71	
5	Yb(OTf) <sub>3</sub>	10	54	
6	Cu(OTf) <sub>2</sub>	10	32	
7	BiONO <sub>3</sub>	10	10	
8	BiCl <sub>3</sub>	10	24	
9	NiCl <sub>2</sub> .6H <sub>2</sub> O	10	11	
10	BF <sub>3</sub> .Ēt <sub>2</sub> O	10	48	
11	CuCl/HOAc	10	30	
12	FeCl <sub>3</sub> .6H <sub>2</sub> O	10	35	
13	$Zn(OTf)_2$	10	52	
14	SbCl <sub>3</sub>	10	45	
15	Silver NPs	10	92	
16	[DDPA][HSO₄]	10	76	

<sup>a</sup> Isolated yield.

model reaction. In order to establish the high catalytic activity of silver NPs, we have compared the reaction using other catalysts at reflux and for 10 min. The results are listed in Table 1. The problems of the reported protocols such as prolonged reaction time and poor yields prompted us to explore this solid phase catalyst for the synthesis of 3,4-dihydropyrimidine-2-(1H)-ones.

In order to determine the optimum quantity of NPs silver, the reaction of 4-nitrobenzaldehyde, ethyl acetoacetate and urea (1 mmol each) was carried out at reflux in EtOH (10 mL) using different quantities of silver NPs (Table 2). A concentration of silver NPs of 0.002 g gave an excellent yield in 10 min (Table 2, entry 4).

The above reaction was also examined in various solvents (Table 3). The results indicated that different solvents affected the efficiency of the reaction. Most of these solvents required a longer time and gave moderate yields. The best results were obtained when ethanol was used as solvent (Table 3, entry 4).

 Table 2
 Optimisation amount of NPs silver for the synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3-4-dihydropy-rimidin-2(1H)-one

Entry	Catalyst	Time/min	Yieldª/%	
1	0.008	10	93	
2	0.004	10	92	
3	0.003	10	90	
4	0.002	10	90	
5	0.001	10 40		

<sup>a</sup>lsolated yield.

 
 Table 3
 Effect of the solvent on the synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3-4-dihydropyrimidin-2(1H)one by silver NPs

Entry	Solvent	Time /min	Yieldª/%	
1	CH <sub>2</sub> Cl <sub>2</sub>	15	80	
2	H₂Õ	10	80	
3	CH₃CN	10	87	
4	EtŐH	10	90	
5	CH₃COOH	25	60	

<sup>a</sup> Isolated yield.

 Table 4
 Optimisation of temperature using silver NPs as catalyst

Entry	Temperature /°C	Time /min	Yield <sup>a</sup> /%	
1	25	240	50	
2	60	120	65	
3	Reflux	10	90	

<sup>a</sup> Isolated yield.

To optimise the temperature in the mentioned reaction, we have carried out a model study with a 4-nitrobenzaldehyde, ethyl acetoacetate and urea using 0.002 g of catalyst at various temperatures (Table 4). Table 4 clearly demonstrates that reflux is an effective temperature in terms of reaction time and yield.

 Table 5
 Condensation of an aromatic aldehyde, 1,3-diketones, and urea or thiourea in the presence of silver NPs catalyst in ethanol at reflux<sup>a</sup>

 O
 Ar

	Ar H + 1	$ \begin{array}{c} 0 & 0 \\ \hline 2 \\ \end{array} $ R	+ H <sub>2</sub> N	$\frac{X}{MH_2}$ Et	NPs Silver (0 OH (10 ml), 1	0.002 g) 0 min, reflux	$\begin{array}{c} 0 & Ar \\ R & H_{3}C & N \\ H_{3}C & H \\ 4 \end{array}$	NH X
Entry	Ar	Ar R	Х	Product	Time/min	Yield/% <sup>b</sup>	M.p./°C	
							Found	Reported <sup>[Ref.]</sup>
1	C <sub>6</sub> H <sub>5</sub>	OEt	0	4a	10	96	206–207	206–207 <sup>36</sup>
2	4-MeOČ <sub>6</sub> H₄	OEt	0	4b	10	93	202-203	203–204 <sup>36</sup>
3	$4 - NO_2C_6H_4$	OEt	0	4c	10	90	212-214	212-213 <sup>36</sup>
4	4-CIC <sub>6</sub> H <sub>4</sub>	OEt	0	4d	10	86	213–214	213–214 <sup>36</sup>
5	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	OEt	0	4e	10	80	255–257	256-258 <sup>37</sup>
6	3-MeOC <sub>6</sub> H <sub>4</sub>	OEt	0	4f	10	85	220-222	220-221 <sup>36</sup>
7	4-MeC <sub>6</sub> H <sub>4</sub>	OEt	0	4g	10	83	213–214	215-216 <sup>36</sup>
8	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	OEt	S	4ĥ	10	90	207-208	209-210 <sup>38</sup>
9	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	S	4i	10	91	192–194	192–194 <sup>36</sup>
10	4-CIC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	S	4j	10	88	210-211	208-209 <sup>36</sup>
11	4-MeOC <sub>6</sub> H₄	CH <sub>3</sub>	S	4k	10	83	160–161	161–163 <sup>36</sup>
12	4-MeC <sub>6</sub> H <sub>4</sub>	OEt	S	41	10	85	192–194	191–193 <sup>36</sup>

<sup>a</sup>The compounds **4a-I** were known and their structures were deduced by comparison of melting points and spectral data with authentic samples.

<sup>b</sup>Yields refer to the pure isolated products.

To study the scope of the reaction, a series of aromatic aldehydes, methyl or ethylacetoacetate and urea (thiourea) catalysed by silver NPs as catalyst were examined. The results are shown in Table 5. In all cases, aromatic aldehyde substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave the expected products in good yields.

The compounds **4a–I** were characterised by <sup>1</sup>H, <sup>13</sup>C NMR and IR spectroscopy and elemental analyses.<sup>36–38</sup>

In summary, we have prepared silver NPs and shown that they have advantages in the preparation of 3,4-dihydropyrimidine-2-(1H)-ones (thiones) such as shorter reaction times, simple work-up, and affording excellent yield.

## Experimental

Melting points were determined with an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer for solutions in d<sub>6</sub>-DMSO using TMS as an internal standard. The morphologies of the products were observed using a Philips CM10 TEM and a Holland Philips XL30 SEM microscope with an accelerating voltage of 20 kV. The chemicals for this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

### Synthesis of silver nanocrystals

Silver nitrate (1 mol) and dodecanoic acid DDA (0.3 mol) were dissolved into *n*-butylamine (2 mol)/toluene (300 mL) completely, which resulted in a molar concentration [Ag] above 2 M. After addition of an equimolar amount of reductant, the solution became dark brown and then was refluxed for 1 h. After completion of the reaction, products were precipitated by addition of an acetone/methanol mixture. The precipitates were collected through a glass funnel filter and then washed several times with methanol and acetone.

#### General procedure

Silver NPs (0.002 g) was added to a stirred mixture of the aromatic aldehyde (1 mmol), 1,3-diketones (1 mmol) and urea or thiourea (1 mmol) in EtOH (10 mL). The reaction mixture was then stirred for 10 min at reflux. The progress of the reaction was followed by TLC (*n*-hexane:ethylacetate). After completion of the reaction, the mixture was filtered to remove the catalyst. After evaporation of the solvent, the crude product was recrystallised from hot ethanol to obtain the pure compound.

We gratefully acknowledge financial support from the Research Council of Islamic Azad University of Yazd and The Islamic Azad University of Zahedan of Iran.

## Received 4 February 2012; accepted 15 March 2012 Paper 1201147 doi: 10.3184/174751912X13352025454801 Published online: 4 June 2012

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