# An efficient, one-pot synthesis of polyfunctionalised dihydropyridines catalysed by Agl nanoparticles

## Mohammad Ali Ghasemzadeh\* and Javad Safaei-Ghomi

Department of Chemistry, Qom Branch, Islamic Azad University, Qom, Iran

Polyfunctionalised dihydropyridines were synthesised in high yields and in short reaction times by a four-component reaction of araldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of Agl nanoparticles in aqueous ethanol media under reflux conditions. The catalyst was easily prepared and was recyclable.

Keywords: AgI nanoparticles, hexahydroquinoline, aqueous media, multi-component reaction

Multi-component reactions (MCRs) are special types of synthetically useful organic reactions in which three or more various substrates react to give a final product in a one-pot procedure.<sup>1</sup> Clearly, for multi-step synthetic pathways the number of reaction and purification steps is among the most important criteria for the efficiency and ability of the process and should be as low as possible.<sup>2</sup> Recently, the research and discovery of new MCRs, have gained tremendous importance. In addition the formation of carbon–carbon and carbon–heteroatom bonds by MCRs is known in multitudinous compounds that are of pharmaceutical, biological and material interest.<sup>3</sup>

Nitrogen-containing heterocyclic compounds are widespread in nature and their applications as biologically active pharmaceuticals, agrochemicals and functional materials are becoming more and more important.<sup>4</sup> Therefore, the development of new efficient methods for synthesis of N-heterocycles is a major interest of modern synthetic organic chemistry.<sup>5</sup> The four-component Hantzsch dihydropyridine synthesis is a versatile procedure to achieve a class of pharmaceutically important dihydropyridines including polyhydroquinoline derivatives.

Recently, much attention has been paid to the synthesis of polyhydroquinolines because these compounds possess important pharmaceutical, antifungal, antitumor and other biological properties,<sup>6–8</sup> and have found wide usage as drugs including nifedipine, nicardipine and amlodipine.<sup>9</sup> Consequently, much attention has been paid to the development of new methodologies for the preparation of polyhydroquinoline derivatives.

Indeed, the syntheses of polyhydroquinolines have recently been reported *via* the four-component coupling of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of diverse catalysts such as,  $Yb(OTf)_{3}$ ,<sup>10</sup> molecular iodine,<sup>11</sup> Baker's yeast,<sup>12</sup> ZrCl<sub>4</sub>,<sup>13</sup> *p*-TSA,<sup>14</sup> HClO<sub>4</sub>-SiO<sub>2</sub>,<sup>15</sup> *L*-proline,<sup>16</sup> BF<sub>3</sub>.SiO<sub>2</sub>,<sup>17</sup> and Ni nanoparticles.<sup>18</sup>

Organic reactions in aqueous media have attracted much attention in organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvents but also because it exhibits unique reactivity and selectivity, different from those obtained in conventional organic solvents.<sup>19</sup> The significant enhancement in the rate of reaction has been attributed to hydrophobic packing, solvent polarity, hydration, and hydrogen bonding.<sup>20</sup>

The last decade has witnessed enormous developments in the field of nanoscience and nanotechnology. Several reports show an amazing level of performance of nanoparticles as catalysts in terms of selectivity, reactivity and improved yields of products. In addition, the high surface-to-volume ratio of nanoparticles provides a larger number of active sites per unit area compared to their heterogeneous counter parts.<sup>21,22</sup>Among different metal nanoparticles, silver nanoparticles have received great attention because of their significant properties and potential applications in various reaction types.<sup>23</sup> Silver nanoparticles, generally require only mild reaction conditions to produce high yields of products in short reaction times in comparison with traditional catalysts and can be recycled.<sup>24</sup>

Recently, silver nanoparticles have been used as a robust catalyst in many organic reactions including synthesis of  $\beta$ -enaminones,<sup>25</sup> oxidation reactions,<sup>26</sup> three-component couplings of aldehyde-amine-alkyne,<sup>27</sup> Diels-Alder cycloadditions of 2'-hydroxychalcones,<sup>28</sup> dehydrogenation reactions<sup>29</sup> and carbon-carbon coupling reactions.<sup>30</sup>

In continuation of our previous studies on the applications of heterogeneous nanoparticles in MCRs,<sup>31–36</sup> we report here a highly efficient one-pot synthesis of polyhydroquinolines *via* multi-component coupling in the presence of silver iodide nanoparticles as a recyclable catalyst in aqueous ethanol media (Scheme 1).

### **Results and discussion**

The XRD pattern of AgI nanoparticles is shown in Fig. 1A. All the reflection peaks in Fig. 1A can be readily indexed to pure cubic phase of AgI with F-43m space group (JCDPS No. 78-0641). The crystallite size of AgI was 18 nm.

Figure 1B shows the FT-IR spectrum of AgI nanoparticles. The broad peaks at 3436 cm<sup>-1</sup> and 1628 cm<sup>-1</sup> can be attributed to  $\nu$  (OH) stretching and bending vibrations, respectively, so that, these peaks indicate the presence of physisorbed water on the nanoparticles.



Scheme 1

<sup>\*</sup> Correspondent. E-mail: ghasemzadeh@qom-iau.ac.ir



Fig. 1 The XRD pattern (A) and FT-IR spectrum (B) of silver iodide nanoparticles

The size and morphology of silver iodide nanoparticles were analysed by scanning (SEM) and transmission electron microscopy (TEM). The SEM results (Fig. 2A) show that these catalysts are nanostructures, and that a single phase primary particle is spherical in shape with the average diameter between 40 and 50 nm. The TEM results (Fig. 2B) show that these nanocatalysts consist of spherical particles with the crystallite size between 15 and 20 nm, confirming the results calculated from Scherrer's equation based on the XRD pattern.

Reaction conditions were optimised on the basis of the catalyst, solvent and reactants for carbon–carbon and carbon–heteroatom bonds formation. To test the efficiency of catalytic activity, we focussed our initial studies on a cyclisation model reaction in the presence of different nanocatalysts such as *L*-proline,  $Mn_3O_4$ , MgO, *p*-TSA, and AgI. We selected as the model reaction a four-component MCR consisting of 4-nitrobenzaldehyde 1 (Ar=4-nitrophenyl), dimedone **2**, ammonium acetate **3** and ethyl acetoacetate **4** the yields of which were determined using 20 mol% of various catalysts in aqueous EtOH at reflux (Scheme 1).

The results showed that AgI is the most effective catalyst for this annulation reaction (Table 1, entries 1–5), so we were encouraged to perform the model reaction in the presence of silver iodide nanoparticles. As shown in Table 1 (entry 6), nano AgI afforded an excellent yield in a shorter reaction time in comparison with bulk AgI. Subsequently, we found the use of 10 mol% of this catalyst was sufficient, since an increase in the amount of the catalyst did not change the yield or shorten the reaction time. During optimisation of the reaction conditions, we ran the model reaction using AgI nanoparticles in various solvents and under solvent-free conditions. The results (Table 2) show that a mixture of water/ethanol is the most effective solvent for this multi-component reaction. This is not surprising in view of the fact that the hydrogen bonding between water/ethanol and substrate can prompt the nucleophilic attack of the reactants.

In order to optimise the ratio of reactants, the model reaction was carried out several times using AgI nanoparticles. The best results were obtained when 4-nitrobenzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate were used as substrates in a 1:1:1:1.5 mol ratio. To study the scope of this procedure, next we used a variety of aldehydes in the fourcomponent reaction under the optimum conditions (Scheme 1, Table 3). The data of Table 3 show that araldehydes with electronwithdrawing groups such as NO<sub>2</sub>, Cl and Br (entries 6–9) reacted

Table 1Yields of hexahydroquinoline5gfrom reaction between4-nitrobenzaldehyde 1(Ar=4-nitrophenyl), dimedone 2, ammonium acetate3 and ethyl acetoacetate 4 using 20 mol% of various catalysts in aqueousEtOH at reflux (Scheme 1)

	/		
Entry	Catalyst	Time/h	Yield/% <sup>a</sup>
1	<i>L</i> -proline	2.5	65
2	Mn <sub>3</sub> O <sub>4</sub>	3	45
3	MgO	4	50
4	<i>p</i> -TSA	2	70
5	Agl	1.5	75
6	AgI NPs	0.75	92

alsolated yield.



Fig. 2 SEM (A) and TEM (B) images of Agl nanoparticles.

Table 2Yields of hexahydroquinoline5gfrom reaction between4-nitrobenzaldehyde 1(Ar=4-nitrophenyl), dimedone 2, ammonium acetate3 and ethyl acetoacetate 4 using 10 mol% Agl NPs as catalyst in varioussolvents at reflux and under solvent-free conditions (Scheme 1)

Entry	Solvent	Time/h	Yield/% <sup>a</sup>
1	None <sup>b</sup>	2	50
2	EtOH	2	70
3	DMF	3.5	55
4	Toluene	5	30
5	H <sub>2</sub> O	2.5	65
6	H <sub>2</sub> O/EtOH	0.75	92

<sup>a</sup>lsolated yield.

<sup>b</sup>Solvent-free 120 °C.

Table 3 Yields of hexahydroquinolines 5a-n using 10 mol% AgI NPs as catalysta

Entry	Araldehyde (RCHO)	Product	Time/min	Yield/% <sup>b</sup>	M.p./ºC (lit. /ºC)
1	$C_6H_5$	5a	55	90	201–203 (202–204) <sup>17</sup>
2	$3-CH_{3}C_{6}H_{4}$	5b	60	86	212–214°
3	$4-CH_3C_6H4$	5c	60	88	262–263 (261–263) <sup>17</sup>
4	2-OMeC <sub>6H</sub> 4	5d	75	80	206–208°
5	$4-\mathrm{OMeC}_{6}\mathrm{H}_{4}$	5e	65	85	254–256 (255–257) <sup>17</sup>
6	$3-NO_2C_6H_4$	5f	50	90	173–175 (174–176) <sup>17</sup>
7	$4-\mathrm{NO}_2\mathrm{C}_6\mathrm{H}_4$	5g	45	92	245–247 (244–246) <sup>17</sup>
8	4-BrC <sub>6</sub> H <sub>4</sub>	5h	48	90	252-253 (252-253) <sup>17</sup>
9	$4\text{-}\mathrm{CIC}_{6}\mathrm{H}_{4}$	5i	45	94	245–246 (245–247) <sup>17</sup>
10	$4-FC_6H_4$	5j	50	90	184–185 (185–186) <sup>15</sup>
11	$4\text{-}\mathrm{CHOC}_{6}\mathrm{H}_{4}$	5k	50	90	196 <b>–</b> 197⁰
12	3-0HC <sub>6H</sub> 4	51	70	80	217–219 (218–220) <sup>17</sup>
13	$4-OHC_6H_4$	5m	60	85	231–233 (231–233) <sup>17</sup>
14	$4-N(CH_3)_2C_6H_4$	5n	65	88	231–233 (230–232) <sup>17</sup>

<sup>a</sup>Reaction conditions: araldehyde **1** (1 mmol), dimedone **2** (1 mmol), ammonium acetate **3** (1.5 mmol), ethyl acetoacetate **4** (1 mmol), in  $H_2O/EtOH$  (1:1) at reflux (Scheme 1).

<sup>b</sup>lsolated yield.

°New compounds.

very smoothly to produce polyhydroquinoline derivatives in relatively short reaction times. However, a sterically hindered aldehyde (entry 4) reacted more slowly in comparison with unhindered aldehydes.

In summary an efficient and mild method for the synthesis of hexahydroquinolines has been developed which uses silver iodide nanoparticles as a highly effective, recyclable catalyst in aqueous ethanol media. The products were obtained in excellent yields and the reaction times were significantly reduced in comparison with use of bulk silver iodide.

#### Experimental

Chemicals were purchased from the Sigma-Aldrich and Merck and were used without further purification. All melting points are uncorrected and were determined in capillary tubes on a Boetius melting point microscope. NMR spectra were obtained on a Bruker 400 MHz spectrometer (<sup>1</sup>H NMR at 400 Hz, <sup>13</sup>C NMR at 100 Hz) in CDCl<sub>3</sub> using TMS as internal standard. Chemical shifts ( $\delta$ ) were given in ppm and coupling constants (*J*) in Hz.

FT-IR spectra were recorded on a Magna-IR, 550 Nicolet spectrometer in KBr pellets. The elemental analyses were obtained from a Carlo ERBA Model EA 1108 analyser. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatised Cu K $\alpha$  radiation ( $\lambda$ =1.5406 Å). Microscopic morphology of products was visualised by SEM (LEO 1455VP). Transmission electron microscopy (TEM) was performed with a Jeol JEM-2100UHR, operated at 200 kV.

#### Synthesis of AgI nanoparticles

A solution of 0.415 g KI ( $25 \times 10^{-4}$  mol) in distilled water (25 mL) was added dropwise to a solution of AgNO<sub>3</sub> [0.425 g,  $25 \times 10^{-4}$  mol in distilled water (25 mL)] under ultrasound power in the presence of 0.2 g SDS as surfactant. The yellow as-synthesised precipitate was separated by centrifugation and washed with distilled water and ethanol to remove impurities for several times and then dried.

#### ${\it Synthesis of polyhydroquinolines}\ ({\bf 5a-n}); general procedure$

A mixture of aldehyde (1 mmol), dimedone (1 mmol), ammonium acetate (1.5 mmol), ethyl acetoacetate (1 mmol) and AgI NPs (0.02 g, 0.1 mmol, 10 mol%) in (1:1) EtOH:  $H_2O$  (5 mL) was refluxed in an oil bath for appropriate times. The progress of the reaction was monitored by TLC. After the reaction was complete, the mixture was cooled to room temperature and then centrifuged to separate the catalyst. Then, the solvent was evaporated and the solid obtained recrystallised from ethanol to afford the pure polyhydroquinolines. All of the products were characterised by m.p., <sup>1</sup>H NMR, <sup>13</sup>C NMR and FT-IR techniques.

*Ethyl* 2,7,7-*trimethyl*-5-*oxo*-4-(*m*-*tolyl*)-1,4,5,6,7,8-*hexahydro-quinoline*-3-*carboxylate* (**5b**): Yellow solid, m.p. 212–214 °C (EtOH); FT-IR (cm<sup>-1</sup>): 3322 (NH), 3056, 1694 (C=O), 1612 (C=O), 1548, 1481 (C=C), 1363, 1212 (C–O); <sup>1</sup>H NMR:  $\delta$  0.98 (6H, s, 2 × CH<sub>3</sub>), 1.28 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.22 (3H, s, CH<sub>3</sub><sup>¬</sup>), 2.25–2.29 (4H, m, 2 × CH<sub>2</sub>), 2.33 (3H, s, Ar–CH<sub>3</sub>), 4.21 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.91 (1H, s, CH), 6.11 (1H, s, NH), 7.08 (1H, s, ArH), 7.22–8.43 (3H, m, ArH); <sup>13</sup>C NMR: 14.2, 19.2, 23.1, 27.2, 32.8, 40.3, 44.2, 47.2, 56.1, 102.1, 111.6, 123.8, 125.9, 135.1, 142.2, 145.1, 148.7, 167.2, 191.1. Anal. calcd for C<sub>22</sub>H<sub>27</sub>NO<sub>3</sub> (*M*<sub>r</sub>=353.20): C, 74.76; H, 7.70; N, 3.96; found: C, 74.61; H, 7.78; N, 4.06%.

*Ethyl-4-(2-methoxyphenyl)-2*, 7,7-*trimethyl-5-oxo-1*, 4, 5, 6, 7,8-*hexahydroquinoline-3carboxylate* (5d): Yellow solid, m.p. 206–208 °C (EtOH); FT-IR (cm<sup>-1</sup>): 3311(NH), 3076, 1691 (C=O), 1614 (C=O), 1526, 1485 (C=C), 1379, 1226 (C–O); <sup>1</sup>H NMR:  $\delta$  0.96 (6H, s, 2 × CH<sub>3</sub>), 1.22 (3H, t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.12 (3H, s, CH<sub>3</sub>), 2.22–2.25 (4H, m, 2 × CH<sub>2</sub>), 3.92 (3H, s, OCH<sub>3</sub>), 4.12 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 5.11 (1H, s, CH), 6.16 (1H, s, NH), 6.95–7.13 (4H, m, ArH); <sup>13</sup>C NMR: 14.1, 19.2, 27.3, 32.5, 40.8, 44.1, 47.5, 55.8, 59.8, 106.1, 126.6, 127.3, 128.5, 136.9, 145.2, 145.1, 149.2, 167.1, 195.4. Anal. calcd for C<sub>22</sub>H<sub>27</sub>NO<sub>4</sub> (*M*<sub>r</sub>=369.19): C, 71.52; H, 7.37; N, 3.79; found: C, 71.64; H, 7.28; N, 3.71%.

*Ethyl-4-(4-formylphenyl)-2*,7,7-*trimethyl-5-oxo-1*,4,5,6,7,8-*hexahydroquinoline-3-carboxylate* (**5k**): Yellow solid (recrystallised from ethanol), m.p. 196–197 °C (EtOH); FT-IR (cm<sup>-1</sup>): 3291(NH), 3078, 2873, 1692 (C=O), 1616 (C=O), 1523, 1481 (C=C), 1391, 1282 (C–O); <sup>1</sup>H NMR: δ 0.81 (6H, s,  $2 \times CH_3$ ), 0.98 (3H, t, J=7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.14 (3H, s, CH<sub>3</sub>), 2.42–2.48 (4H, m,  $2 \times CH_2$ ), 4.10 (2H, q, J=7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.82 (1H, s, CH), 6.11(1H, s, NH), 7.13–7.15 (2H, d, J=7.9 Hz, ArH), 7.22–7.24 (2H, d, J=7.9 Hz, ArH), 9.82 (1H, s, CHO); <sup>13</sup>C NMR: 14.2, 19.2, 27.1, 32.3, 40.7, 44.1, 47.1, 60.1, 105.9, 126.1, 126.9, 127.8, 135.1, 144.1, 145.1, 149.5, 167.1, 195.1, 201.3. Anal. calcd for C<sub>22</sub>H<sub>25</sub>NO<sub>4</sub> ( $M_r$ =367.18): C, 71.91; H, 6.86; N, 3.81; found: C, 71.99; H, 6.78; N, 3.73%.

*Recycling and reuse of the catalyst:* The recovered catalyst could be reused five times with only a gradual decrease in the yield from 92 to 91, 89, 88, 86 and 84%.

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