

# Silver iodide nanoparticle as an efficient and reusable catalyst for the one-pot synthesis of benzofurans under aqueous conditions

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**Abstract.** Recyclable heterogeneous AgI nanoparticles were efficiently catalysed one-pot three-component reaction of aldehydes, secondary amines and alkyne in aqueous media. This method provides a novel and improved approach for the synthesis of 2,3-disubstituted benzo[b]furan derivatives to obtain excellent yields, short reaction times and low catalyst loading.

**Keywords.** AgI nanoparticles; heterogeneous catalyst; benzofuran; multicomponent reactions.

## 1. Introduction

One-pot multicomponent reactions (MCRs), where several organic moieties are coupled in one step, for carbon–carbon and carbon–heteroatom bond forming is an attractive synthetic strategy for the synthesis of compound libraries of small molecules for potential applications in medicinal and pharmaceutical chemistry.<sup>1</sup> The research and discovery of new MCRs have gained tremendous importance for the synthesis organic compounds.<sup>2,3</sup> One of the widely used MCRs is three-component coupling of aldehydes, amines and alkynes ( $A^3$  coupling) which are resulting biologically active heterocyclic compounds such as propargylamines, imidazo[1,2a]pyridines and benzofurans.<sup>4</sup>

Benzo[b]furans and their derivatives are of interest, because of their frequent occurrence in nature and their wide range of biological and physiological effects<sup>5</sup> including antifungal,<sup>6</sup> antitumour,<sup>7</sup> and other bioorganic and pharmaceutical properties.<sup>8,9</sup> Consequently, much attention has been paid to develop new methodologies for the preparation of benzofurans. The synthetic routes for the preparation of benzo[b]furans mainly are dehydrative annulation of phenols bearing appropriate ortho vinylic substituents,<sup>10</sup> intramolecular cyclization of substituted allyl-aryl ethers,<sup>11</sup> [3,3]-sigmatropic rearrangement of various arenes,<sup>12</sup> dehydrative cyclization of  $\alpha$ -(phenoxy)-alkyl ketones,<sup>13</sup> reactions of 2-hydroxybenzaldehydes, amines and alkynes using various catalysts,<sup>14–16</sup> Sonogashira cross-coupling reaction of 2-iodonitrophenol acetates<sup>17</sup> and coupling of *o*-iodophenols and aryl acetylenes.<sup>18</sup>

The organic reactions in aqueous media have attracted much attention in the organic synthesis, not only because water is one of the most abundant, cheapest, and environmentally friendly solvents but also because water exhibits unique reactivity and selectivity, different from those obtained in conventional organic solvents.<sup>19</sup>

Last decade has witnessed significant growth in the field of nanoscience and nanotechnology. Several reports showed an amazing level of the performance of nanoparticles as catalyst in terms of selectivity, reactivity, and improved yields of products.<sup>20</sup> In addition, the high surface-to-volume ratio of nanoparticles provides a larger number of active sites per unit area in comparison with its heterogeneous counter parts.

Among various metal nanostructures, silver nanoparticles have received great attention because of their unusual properties and potential applications in diverse fields.<sup>21</sup> In comparison with traditional catalysts, silver nanoparticles, in particular, being available, require only mild reaction conditions to produce high yields of products in short reaction times and can also be recycled.<sup>22</sup>

Recently, silver nanoparticles were used as an active catalysts in many organic reactions such as, three-component coupling of aldehyde-amine-alkyne,<sup>23</sup> carbon–carbon coupling reaction,<sup>24</sup> dehydrogenation reaction,<sup>25</sup> oxidation reaction,<sup>26</sup> Diels–Alder cycloadditions of 2'-hydroxychalcones<sup>27</sup> and synthesis of  $\beta$ -enaminones.<sup>28</sup>

With the aim to develop more efficient synthetic processes, reduce the number of separate reaction steps, minimize by-products and also in continuation of our research on the application of nanocatalysts in MCRs,<sup>29–35</sup> we report here a green, mild, and practical

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method for the preparation of 2,3-disubstituted benzofurans via three-component coupling of aldehydes, amines and alkynes in the presence of AgI nanoparticles (AgI NPs) as an effective and mild catalyst with high specific surface area.

## 2. Experimental

Chemicals were purchased from the Sigma-Aldrich and Merck in high purity. All of the materials were of commercial reagent grade and were used without further purification. Flash-column chromatography was performed by using Merck silica gel 60 with freshly distilled solvents. All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained on Bruker 400 MHz spectrometer with  $\text{CDCl}_3$  as solvent using tetramethylsilane (TMS) as an internal standard, the chemical shift values are in  $\delta$ . FT-IR spectra were recorded on Magna-IR, spectrometer 550 Nicolet in KBr pellets in the range of  $400\text{--}4000\text{ cm}^{-1}$ . The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatized  $\text{Cu K}\alpha$  radiation ( $\lambda = 1.5406\text{ \AA}$ ). Microscopic morphology of the product was visualized by scanning electron microscope (SEM) (LEO 1455VP). Transmission electron microscopy (TEM) was performed with a Jeol JEM-2100UHR, operated at 200 kV.

### 2.1 Preparation of silver iodide nanoparticles

A solution of 0.415 g KI ( $25 \times 10^{-4}$  mol) in 25 ml distilled water was added drop-wise to  $\text{AgNO}_3$  solution (0.425 g,  $25 \times 10^{-4}$  mol in 25 ml distilled water) under ultrasound power in the presence of 0.2 g sodium dodecyl sulphate (SDS) as surfactant. The yellow (as-synthesized) precipitate was separated by centrifugation and washed with distilled water and ethanol to remove impurities for several times and then dried.

### 2.2 General procedure for the synthesis of 2,3-disubstituted benzofuran (**4a-l**)

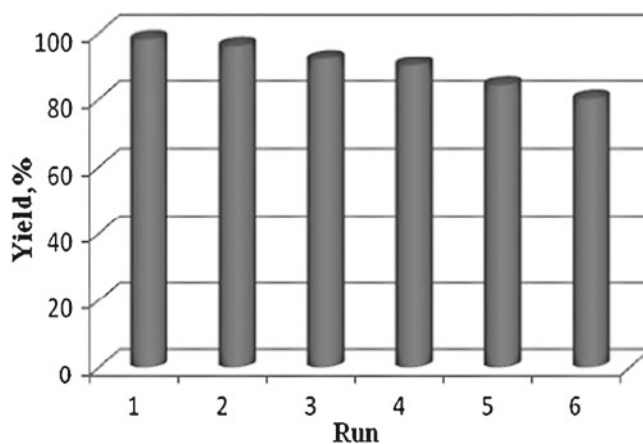
To a solution of the salicylaldehyde (2 mmol), secondary amine (1 mmol) and phenylacetylene (1.5 mmol) in 5 ml of water, was added AgI NPs (0.1 mmol) and  $\text{K}_2\text{CO}_3$  (1.0 mmol) at room temperature. Then the resulting mixture was heated at  $100^\circ\text{C}$

for 1.5 h. Progress of the reaction was continuously monitored by thin-layer chromatography (TLC). When the reaction was complete, the mixture was cooled to room temperature and then was centrifuged to separate the catalyst. Then, the solution was extracted by using ethyl acetate ( $3 \times 5\text{ ml}$ ). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate, filtered, and the solvent was evaporated in vacuum to give the crude product. After removal of the solvent, the residue was purified by column chromatography on silica gel using hexane-ethyl acetate (10:1) as eluent to afford the pure corresponding benzofurans.

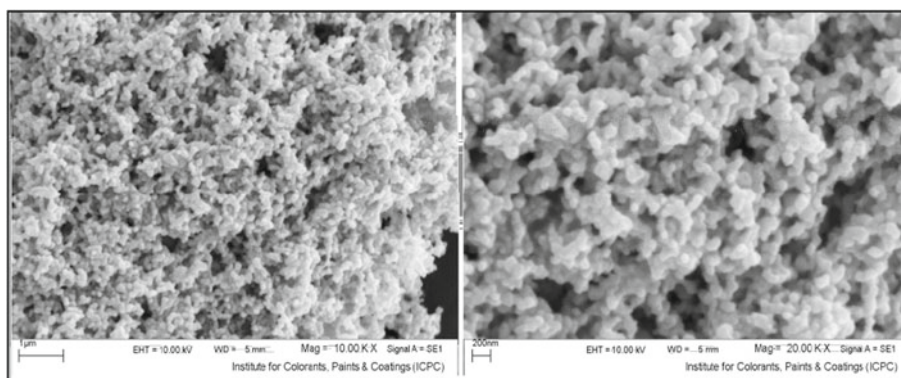
All of the products were identified with m.p.,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and FT-IR spectroscopy techniques. Spectral data of new compounds are listed below:

**2.2a 4-(2-Benzyl-5-chloro-benzofuran-3-yl)-piperidine (4h):** Yellow solid; FT-IR (KBr,  $\text{cm}^{-1}$ ): 3028 (aromatic CH), 2918, 2848, 1606 ( $\text{C}=\text{C}$ ), 1459.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.41–1.63 (2H, m,  $\text{CH}_2$ ) 1.64–1.75 (4H, m,  $J = 5\text{ Hz}$ , 2  $\text{CH}_2$ ), 3.14–3.16 (4H, t,  $J = 5\text{ Hz}$ , 2  $\text{CH}_2\text{-N}$ ), 4.19 (2H, s,  $\text{CH}_2$ ), 7.17–8.14 (7H, m, ArH), 8.54 (1H, s, ArH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 21.9, 26.7, 31.0, 51.3, 111.8, 117.5, 119.1, 124.1, 127.0, 128.0, 129.5, 129.9, 132.1, 139.2, 141.9, 153.2. Anal. Calcd. For  $\text{C}_{20}\text{H}_{20}\text{BrNO}$ : C 64.87, H 5.44, N 3.78. Found C 65.06, H 5.32, N 3.66. MS (EI) ( $m/z$ ): 325 ( $\text{M}^+$ ).

**2.2b N,N-dibenzyl-(2-benzyl-5-nitro-benzofuran-3-yl)-amine (4l):** Yellow oil; FT-IR (KBr,  $\text{cm}^{-1}$ ): 3038 (aromatic CH), 2924, 2851, 1606 ( $\text{C}=\text{C}$ ), 1531 ( $\text{NO}_2$ ), 1442, 1344 ( $\text{NO}_2$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.68 (2H, s,  $\text{CH}_2$ ), 4.24 (4H, s, 2  $\text{CH}_2$ ), 6.82 (2H, s, ArH), 6.84–7.25 (14H, m, ArH), 7.76 (2H, s, ArH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 31.0, 58.1, 111.0, 111.9, 112.1, 115.7, 119.2, 125.9, 126.2, 126.9, 128.1, 128.4, 128.6, 130.1, 135.0,



**Figure 1.** Recoverability of AgI nanoparticles.



**Figure 2.** SEM image of AgI nanoparticles.

137.1, 143.5, 157.1. Anal. Calcd. For  $C_{29}H_{24}N_2O_3$ : C 77.66, H 5.39, N 6.25. Found C 77.85, H 5.24, N 6.14. MS (EI) ( $m/z$ ): 448 ( $M^+$ ).

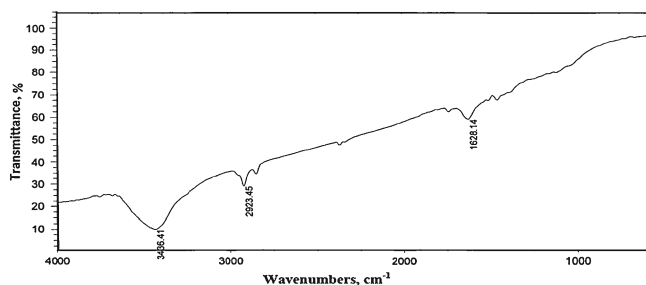
### 2.3 Recycling and reusing of the catalyst

After completion of the reaction, the reaction mixture was centrifuged and the silver iodide nanoparticles were separated, the nanoparticles were washed three to four times with water and chloroform and then dried overnight in an oven at  $70^\circ\text{C}$ . The recovered catalyst was used for six times with a slight decrease in its activity (figure 1).

## 3. Results and discussions

Initially, in order to investigate the morphology and particle size of AgI nanoparticles, SEM image of AgI nanoparticles was presented in figure 2. This result shows that spherical AgI nanoparticles were obtained from  $\text{AgNO}_3$  and KI with particle size 45–50 nm under ultrasound power.

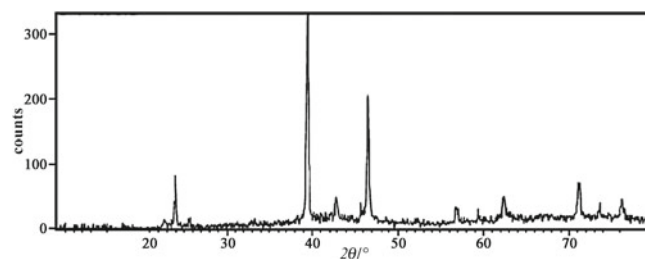
Figure 3 shows the FT-IR spectrum of AgI nanoparticles. The broad peak at  $3436\text{ cm}^{-1}$  and  $1628\text{ cm}^{-1}$  can be attributed to the  $\nu$  (OH) stretching and bending vibrations, respectively. So that, these peaks indicate the presence of physisorbed water linked to nanoparticles,



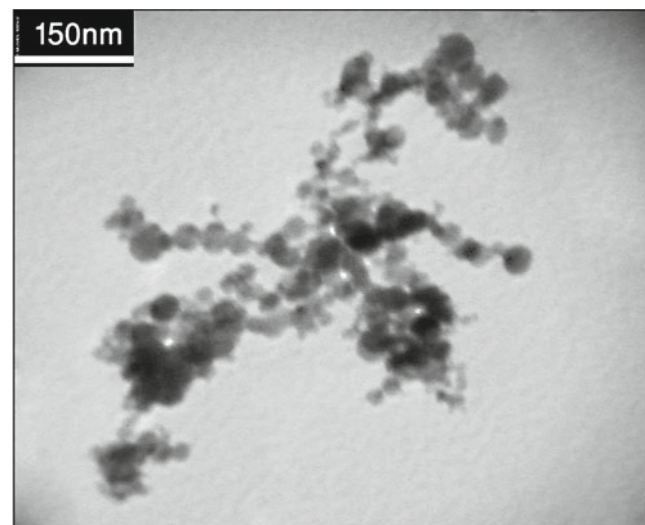
**Figure 3.** FT-IR spectrum of AgI nanoparticles.

the peak corresponding to  $\text{CH}_2$  stretching vibration of SDS (sodium dodecyl sulphate) at  $2923\text{ cm}^{-1}$  can be seen. The appearance of this peak suggests that a trace amount of SDS has been coated on the surface of AgI nanoparticles.

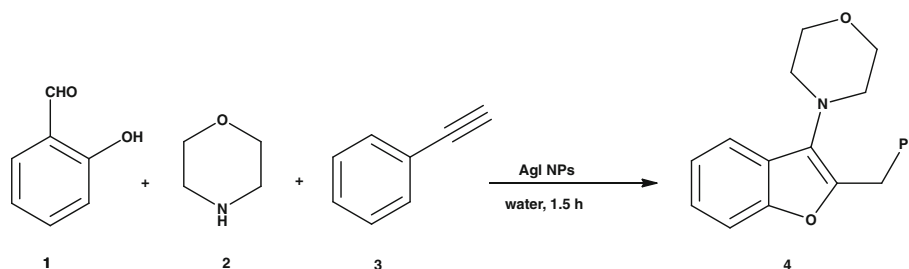
The XRD pattern of AgI nanoparticles was shown in figure 4. All reflection peaks in figure 4 can be readily indexed to pure cubic phase of AgI with F-43m space group (JCDPS No. 78–0641). The crystallite size diameter ( $D$ ) of the AgI nanoparticles has been calculated



**Figure 4.** The XRD pattern of AgI nanoparticles.



**Figure 5.** TEM image of AgI nanoparticles.



**Scheme 1.** The model reaction for the preparation of benzofurans.

by Debye–Scherrer equation ( $D = K\lambda/\beta\cos\theta$ ), where  $\beta$  FWHM (full-width at half-maximum or half-width) is in radian and  $\theta$  is the position of the maximum of diffraction peak,  $K$  is the so-called shape factor, which usually takes a value of about 0.9, and  $\lambda$  is the X-ray wavelength (1.5406 Å for Cu  $K\alpha$ ). Crystallite size of AgI NPs has been found to be 12 nm.

The size and morphology of silver iodide nanoparticles were analysed by transmission electron microscopy (TEM) (figure 5). The results show that these nanocatalysts consist of spherical particles with the crystallite size between 10 and 20 nm, confirming the results calculated from Scherrer's formula based on the XRD pattern.

The reaction conditions were optimized on the basis of catalyst, solvent and reactants at 100°C for carbon–carbon and carbon–heteroatom bonds formation. To test the efficiency of the catalytic activity, we choose to focus our initial studies on the coupling reaction of aldehydes, amines and alkynes in the presence of different catalysts such as CuI, CuCl, AgBr, and AgI in this condensation reaction. The model reaction was performed using salicylaldehyde, morpholine and phenylacetylene under reflux conditions in the presence of each catalyst (20 mol%) separately (scheme 1).

### 3.1 Catalyst effect

The influence of various catalysts on the synthesis of benzofuran 4 is summarized in table 1. As shown, we

**Table 1.** One-pot synthesis of benzofuran 4 by various catalysts.

Entry	Catalyst	Time (h)	Yields <sup>a</sup> (%)
1	CuI	3.5	65
2	CuCl	5	55
3	AgBr	4.5	52
4	AgI	3	60
5	CuI-np	2	86
6	AgI-np	1.5	93

<sup>a</sup>Isolated yields

found that silver iodide is the most effective catalyst for this annulation reaction. When the reaction was conducted in the absence of catalyst, no product was formed. Therefore, in continuation of our research we run the model reaction using silver iodide nanoparticles. Moreover, AgI NPs afforded excellent yields in shorter reaction times in comparison with bulk AgI. The increased catalytic activity of AgI NPs over the commercially available bulk AgI may be attributed to the higher surface area of nanomaterials. This is thought to be due to AgI NPs morphology which has been shown in the SEM image. The optimum ratio of the catalyst was 10 mol% AgI NPs with an increase in the amount of the catalyst did not change the yield and the reaction time.

### 3.2 Solvent effect

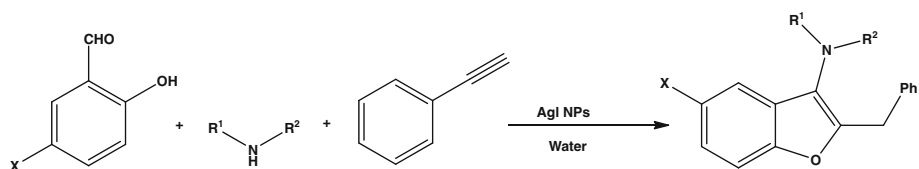
To optimize the reaction conditions on the basis of the solvent, the sample reaction was carried out in different solvents. As shown in table 2, it was found that water is the most effective solvent in comparison with other solvents. This is not surprising in view of the fact that the hydrogen bonding between water and salicylaldehydes and amines can prompt the nucleophilic attack of the reactants.

In the continuation of this research, we used a diversity of salicylaldehydes, amines, and alkynes to investigate three component reactions under the optimized conditions (scheme 2 and table 3). We observed that various salicylaldehyde derivatives easily cyclized to obtain the corresponding products. Table 3 shows salicylaldehydes with electron-withdrawing groups such as

**Table 2.** AgI nanoparticles catalysed A<sup>3</sup> coupling reaction in various solvents.

Entry	Solvent	Time (h)	Yields <sup>a</sup> (%)
1	DMF	4	45
2	Toluene	4	25
3	CH <sub>3</sub> CN	3	65
4	Water	1.5	93

<sup>a</sup>Isolated yields



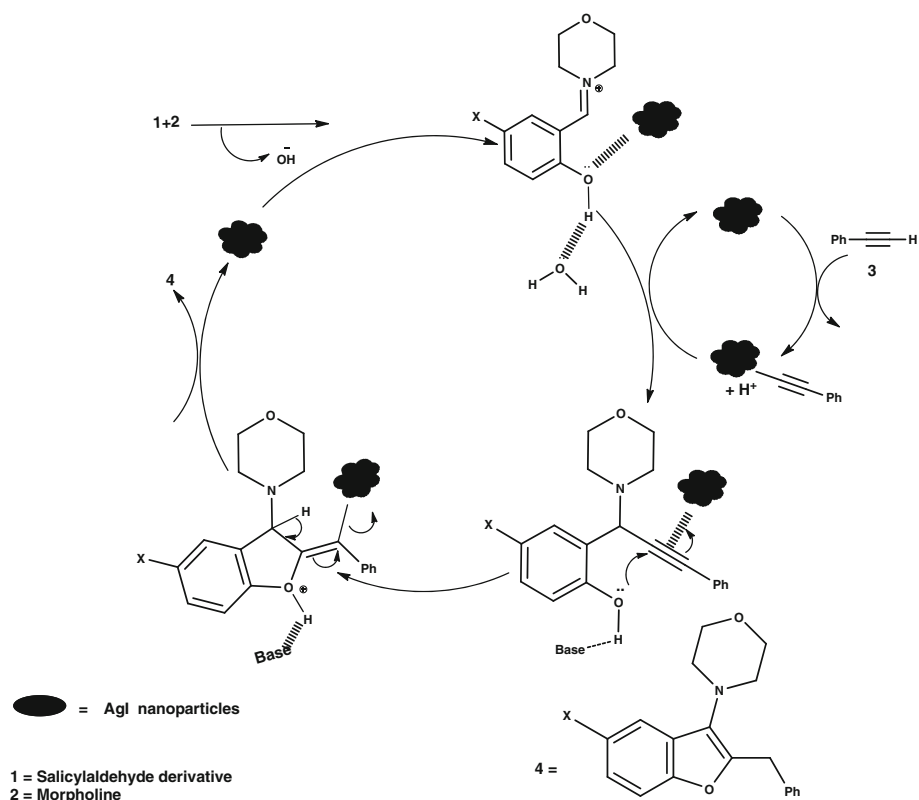
**Scheme 2.** Three-component coupling of salicylaldehydes, amines and phenylacetylene catalysed by silver iodide nanoparticles in water.

**Table 3.** One-pot synthesis of 2,3-disubstituted benzofurans catalysed by AgI NPs.

Entry	Aldehyde (X)	$\begin{matrix} R^1 \\   \\ N-H \\   \\ R^2 \end{matrix}$	Product	Time (min)	Yield (%)	M.p (°C) ref.
1	H	Morpholine	<b>4a</b>	90	93	106–108 <sup>15</sup>
2	H	Piperidine	<b>4b</b>	90	90	74–75 <sup>15</sup>
3	H	Dibenzyl	<b>4c</b>	120	82	..... <sup>a</sup>
4	Br	Morpholine	<b>4d</b>	60	94	110–111 <sup>15</sup>
5	Br	Piperidine	<b>4e</b>	60	92	86–87 <sup>16</sup>
6	Br	Dibenzyl	<b>4f</b>	75	85	..... <sup>a</sup>
7	Cl	Morpholine	<b>4g</b>	54	95	109–111 <sup>14</sup>
8	Cl	Piperidine	<b>4h</b>	58	95	75–78 <sup>14</sup>
9	Cl	Dibenzyl	<b>4i</b>	56	90	..... <sup>a</sup>
10	NO <sub>2</sub>	Morpholine	<b>4g</b>	50	97	119–120 <sup>15</sup>
11	NO <sub>2</sub>	Piperidine	<b>4k</b>	50	95	106–108 <sup>16</sup>
12	NO <sub>2</sub>	Dibenzyl	<b>4l</b>	60	90	..... <sup>a</sup>

All reactions were carried out in the presence of phenylacetylene as alkyne substrate

<sup>a</sup>The products were obtained in viscose form



**Scheme 3.** Proposed reaction pathway for the synthesis of benzofurans using AgI nanoparticles.

NO<sub>2</sub> and Cl reacted very smoothly in short reaction times and high yields. In this research aliphatic alkynes such as 1-octyne and 1-heptyne could not afford the corresponding benzofurans even after 8 h.

Furthermore, different types of secondary amine substrates were explored. Both aliphatic amines (morpholine and piperidine) and aromatic ones such as dibenzylamine were able to generate 2,3-disubstituted benzofurans.

### 3.3 Proposed mechanism

A proposed mechanism on the basis of our experimental results together with some literature for the synthesis of benzofurans in the presence of silver iodide nanoparticles is shown in scheme 3.<sup>36,37</sup> We suppose that AgI NPs generate a silver acetylide intermediate from alkyne, with this intermediate can easily attach to iminium that prepared *in situ* by reaction between salicylaldehyde and amine. Also AgI NPs behaves as a Lewis acid and lead to activation of triple bond to promote cyclization reaction via nucleophilic attack by hydroxyl group. Finally, product 4 was obtained and the AgI NPs catalyst being released for further reaction.

## 4. Conclusion

An efficient, facile and green method for the preparation of benzofuran derivatives has been developed using AgI nanoparticles as a catalyst in aqueous media. The products were obtained in excellent yields and the reaction times were significantly reduced in comparison with using bulk silver iodide. The present protocol represents a simple and efficient method for the three component reactions of aldehydes, amines and phenylacetylene in order to synthesis of some 2,3-disubstituted benzofuran derivatives in the presence of novel nano-scale materials.

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