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Short communication

Green synthesis and characterization of silver nanoparticles (Ag NPs) from extract of plant *Radix Puerariae*: An efficient and recyclable catalyst for the construction of pyrimido[1,2-*b*]indazole derivatives under solvent-free conditions

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ABSTRACT

We have developed a green and environmentally friendly approach for the synthesis of silver nanoparticles (Ag NPs) using *Radix Puerariae* plant extract via a novel chemical route. The prepared Ag NPs has been characterized by TEM, XRD, SEM, DLS, EDX, and UV–Vis. Further, catalytic application of this fascinating nanomaterial has been utilized in the synthesis of biologically important pyrimido[1,2-*b*]indazole derivatives via one-pot three-component coupling reaction between aldehydes, alkynes and amines with excellent yields under solvent-free conditions. After completion of the catalytic reaction, the Ag NPs could be easily recovered and reused for four times without significant loss in its catalytic activity.

1. Introduction

In the past few years, the preparation and application of noble metal nanoparticles in catalysis have attracted emerging attention from the scientific community. Owing to their fabulous properties and diversity of applications [1]. As research in this area moves forward, scientists are discovering novel application possibilities by varying size, shape, composition, or local environment presents them with unusual capabilities [2]. By manipulating the chemical composition of the materials at the nanoscale, their electrical, chemical, optical, and other properties can be manipulated precisely. Importantly, among the metal-based nanoparticles, silver nanoparticles catalysis have been of great interest in organic synthesis and has expanded promptly in the past few years because of nanosilver catalysts unique reactivity, selectivity, and stability, as well as recyclability in catalytic reactions [3–5]. Therefore, silver nanoparticles have become the focus of intensive research due to their catalytic properties for some important organic reactions such as multi component (A^3-coupling) reactions [6], Diels − Alder [4 + 2]Cycloaddition reactions [7] etc. One of the main important aims of the green chemistry is environmental protection. Green chemistry emphasizes the deployment of a set of principles that reduce or eliminate the use or generation of hazardous substances in chemical reactions [8]. In this direction, synthetic communities paying more attention to the development of new, efficient and environmentally benign alternatives for traditionally environmentally unfriendly processes. Now-a-days researchers are focusing on the green and shape controlled synthesis of Ag nanoparticles for various practical applications and to minimize the effect of hazardous chemicals. Therefore, the creation of nanoparticles using green synthesis approaches has achieved significant research interests due to their relative simplicity, environmental sustainability, cost-effectiveness and reproducibility compared to physical and chemical based methods [9]. In recent years, the natural polymers like starch, leaf extracts, root extracts, fruit extracts [10] etc. have been extensively used for the green nanoparticles synthesis as plants are widely available, safe to handle and possess a variety of metabolites that function as reducing agents in nanoparticle synthesis [11]. The *Radix Puerariae* has been used historically for the treatment of diarrhea, acute dysentery, and cardiovascular disease in China, Japan, Korea [12]. Several studies have been carried out to identify the chemical constituents of *Radix Puerariae* which confirms that polyphenolic compounds, especially isoflavones are in abundant content and responsible for the reduction [13]. A motive to exploit the unique catalytic properties of Ag nanoparticles led us to flourish a new method to synthesize green Ag nanoparticles using the dried root of

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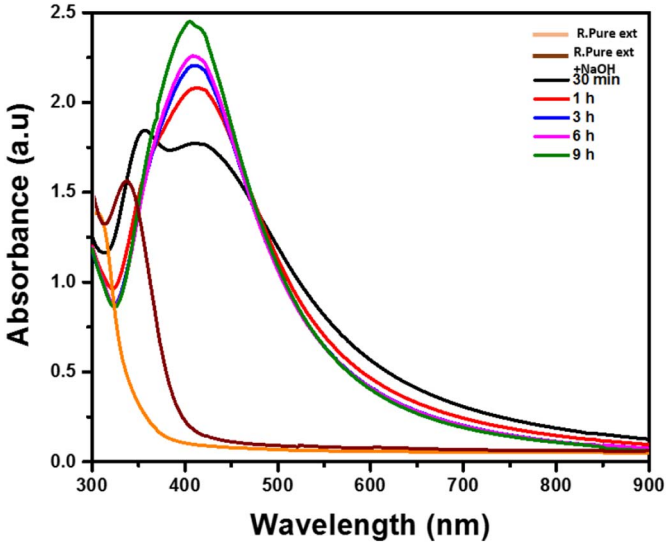


Fig. 1. UV–Vis spectra of Ag NPs synthesized with *Radix Puerariae* extract.

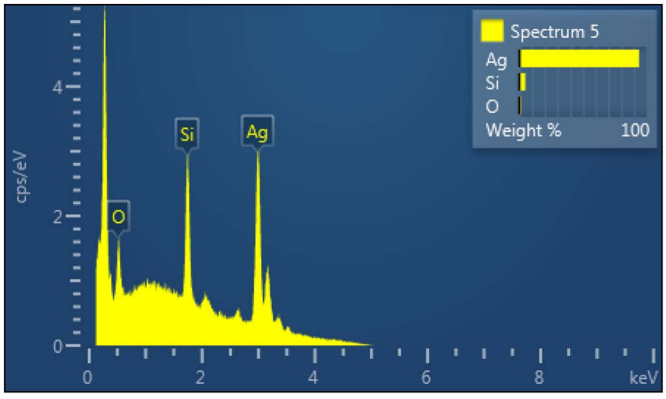


Fig. 3. The EDX spectrum of Ag NPs synthesized with *Radix Puerariae* extract.

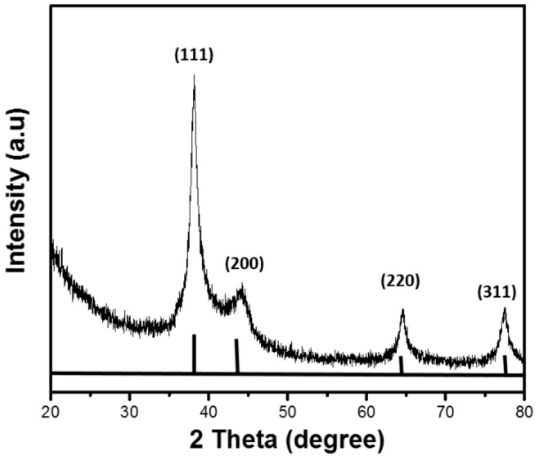


Fig. 4. The XRD spectrum of Ag NPs synthesized with *Radix Puerariae* extract.

plant *Radix Puerariae* by the simple sonication method. And its catalytic activity has been tested for one-pot multi-component (A^3-coupling) reactions for the synthesis of biologically important pyrimido[1,2-*b*] indazoles under solvent-free conditions.

Pyrimido[1,2-*b*]indazole which incorporate both indazole and pyrimidine moieties, have aroused considerable interests in the fields of medicinal chemistry and material science [14]. For instance, some pyrimido[1,2-*b*]indazole considered to be active as protein kinase inhibitors [15], cancer cell proliferative disorders [16], Alzheimer's diseases [17], viral infections [18], auto-immune diseases, and neurodegenerative disorders. These examples emphasize the vital importance of pyrimido[1,2-*b*]indazole as key pharmacophores in bioactive molecules. Although these fused indazole and pyrimidine moieties are important, efficient synthetic approaches to substituted pyrimido[1,2-*b*] indazole have rarely been documented. However, these methodologies suffer from some shortcomings due to their tedious procedures [19], restricted efficacy [20], uses of corrosive and toxic reagents [21], high reaction temperature, longer reaction time, non-compatible solvents and low yields. Therefore, developing convenient and efficient approaches to a diverse range of substituted pyrimido[1,2-*b*]indazoles from simple and readily available starting materials are highly desirable.

In continuation of our studies for the development of new and efficient methods for heterocyclic synthesis [22] and nanocatalysts preparation, we here report an efficient Ag NPs catalyzed three component synthesis of pyrimido[1,2-*b*]indazole, by the coupling of reaction of amine, acetylene and various aldehydes under solvent-free conditions (Table 2).

2. Experimental

2.1. Synthesis and characterization of catalyst

2.1.1. Preparation of Radix Puerariae extract

1 g of Radix Puerariae powder was dissolved in 100 mL of water and boiled at 100 °C for 2 h. After cooling the mixture at room temperature, the mixture was centrifuged at 3000 rpm for 15 min followed by filtering the mixture. The filtrate was used as *Radix Puerariae* extract for the synthesis of Ag nanoparticles.

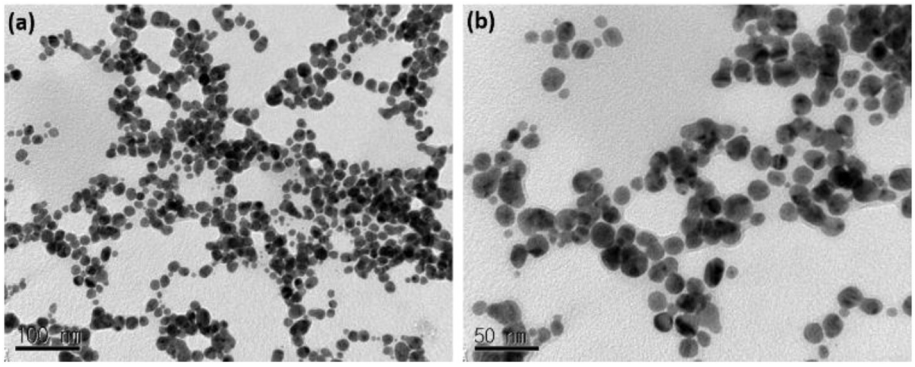
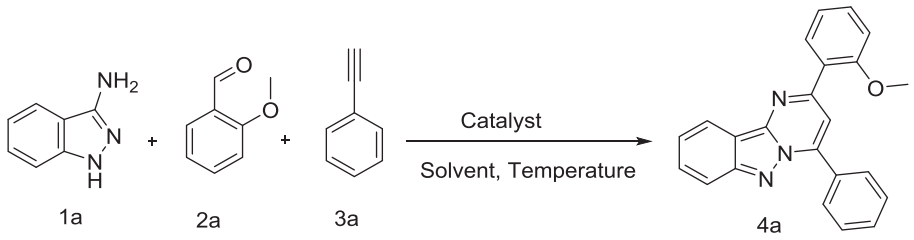


Fig. 2. TEM images of Ag NPs synthesized with *Radix Puerariae* extract. (a) With magnification 100 nm and (b) with 50 nm.

Table 1
Optimization of the reaction conditions for the synthesis of compound **4a**[a].



Entry	Catalyst (mol%)	Solvent	Time (h)	Temp (°C)	Yield[b] (%)
1	Ag NPs (0.5)	Acetonitrile	6	Reflux	74
2	Ag NPs (0.5)	Toluene	8	Reflux	67
3	Ag NPs (0.5)	Ethanol	6	Reflux	69
4	Ag NPs (0.5)	THF	6	Reflux	58
5	Ag NPs (0.5)	Dioxane	8	Reflux	56
6	Ag NPs (0.5)	Water	6	Reflux	44
7	Ag NPs (0.5)	DMF	8	Reflux	63
8[c]	Ag NPs (0.5)	Solvent-free	1	80	96,91,89,85
9	Ag NPs [1]	Solvent-free	1	80	95
10	Ag NPs [5]	Solvent-free	1	80	96
11	Ag NPs (0.1)	Solvent-free	1	80	78
12	Ag NPs (0.5)	Solvent-free	1	110	94
13	Ag NPs (0.5)	Solvent-free	3	80	95
14	CuI [10]	Solvent-free	6	80	24
15	$CuSO_4$. $5H_2O$ [10]	Solvent-free	6	80	48
16	$Cu(OTf)_2$ (10)	Solvent-free	6	80	61

[a] Reaction conditions: 3-aminoindazoles (1, 1 mmol), 2-methoxybenzaldehyde (2, 1 mmol) and ethynylbenzene (3, 1 mmol).
[b] Isolated yield.
[c] Catalyst was reused three times.

2.1.2. Synthesis of Ag nanoparticles

In a typical synthesis, 5 mL of 20 mM $AgNO_3$ was mixed with 2 mL of *Radix Puerariae* extract in a glass vial. The pH of the reaction mixture was adjusted to 9 by adding sufficient quantity of 100 mM NaOH solution. Then the vial was kept in the sonication bath for 9 h. The synthesis of Ag nanoparticles was monitored by UV–Vis spectroscopy at regular time intervals. Reaction was stopped after 9 h. and the product was centrifuged at 12500 rpm for 20 min, (three times) to remove the *Radix Puerariae* extract from Ag nanoparticles.

2.2. Characterization techniques

2.2.1. UV–Vis spectroscopy

The synthesis of Ag NPs by using *Radix Puerariae* extract was monitored by UV–Vis spectroscopy. For the UV–Vis analysis the sample was taken out after regular time intervals from the reaction solution exactly 200 μL and diluted up to 2 mL. The UV–Vis spectroscopy analysis was carried in range 300–900 nm.

UV–Vis spectroscopy is an essential analytical technique for determining the AgNP formation, which is related to LSPR of Ag NPs size, shape and dielectric medium surrounding the Ag NPs. The UV–Vis spectra were analyzed at different time intervals during the synthesis are shown in Fig. 1. The spectra of *Radix Puerariae* extract do not show any peak in the range 300–900 nm. When, NaOH was added to the *Radix Puerariae* extract, a peak at 350 nm was appeared. After, 30 min the characteristic peak of Ag nanoparticles at 430 nm was appeared. The peak at 350 nm was shifted to 370 nm, and disappeared as the reaction progresses. The absorption peak is observed around 400–430 nm, indicating the formation of Ag NPs. The reaction peaks shifted towards the shorter wavelength with increasing time, this may be due to decrease in size of Ag NPs. Similarly the absorption intensities were also increased as the time increased, this may be attributed to increase in concentration of Ag NPs with time.

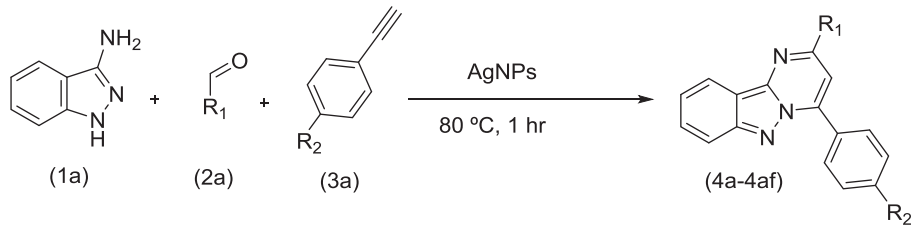
2.2.2. TEM analysis

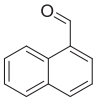
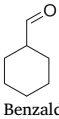
The morphological studies of Ag NPs were performed on Tunneling Electron Microscopy instrument operating at 120 kV. The TEM samples were prepared by freshly prepared Ag NPs washed three times with distilled water and centrifuged at 13500 rpm for 20 min. The Ag NPs were prepared by dropping a small amount of Ag NP solution on copper grid a drying at room temperature. The morphology of Ag NPs synthesized with *Radix Puerariae* extract was investigated by TEM. Fig. 2 shows the TEM image of Ag NPs synthesized with different magnification (a) 100 nm and (b) 50 nm. The TEM image demonstrates monodisperse Ag NPs with spherical and oval shape, with average particle size ranging from 10 to 35 nm. Monodispersity might be due to capping of *Radix Puerariae* extract and sonication effect.

2.2.3. EDX analysis

The morphology studies and EDX of Ag NPs synthesized with *Radix Puerariae* extract were analyzed on the instrument (JAM-6700F Jeol Ltd.). The SEM samples of Ag NPs were prepared by dropping a small amount of Centrifuged Ag NPs solution on a silicon wafer and drying it at room temperature. The EDX analysis of Ag NPs synthesized with *Radix Puerariae* extract is shown in Fig. 3. The EDX spectrum shows a strong peak at 3 keV, corresponding to Ag as, reported by Rokade et al. [11] The peak for the silicon is due to the substrate used for sample preparation. The EDX spectrum confirms the formation of Ag NPs synthesized with *Radix Puerariae* extract.

Table 2
Synthesis of pyrimido[1,2-*b*]indazole derivatives[a].



Entry	R_1	R_2	Product	Time (h)	Yield (%)[b]	M.p (°C)
1	2-$OCH_3C_6H_4$	H	**4a**	1	96	142–144
2	3-$OCH_3C_6H_4$	H	**4b**	1	93	138–140
3	4-$OCH_3C_6H_4$	H	**4c**	1	92	202–204
4	4-$OC_2H_5C_6H_4$	H	**4d**	1	95	147–149
5	4-$C(CH_3)_2C_6H_4$	H	**4e**	1	90	130–132
6	2-$OCH_3C_6H_4$	4-CH_3	**4f**	1	91	164–166
7	3-$OCH_3C_6H_4$	4-CH_3	**4g**	1	90	158–160
8	4-$OCH_3C_6H_4$	4-CH_3	**4h**	1	89	185–187
9	4-$C(CH_3)_2C_6H_4$	4-CH_3	**4i**	1	92	142–144
10	2,5-$CH_3C_6H_3$	H	**4j**	1	88	152–154
11	2,5-$CH_3C_6H_3$	4-CH_3	**4k**	1	89	157–159
12	2-Cl-6-FC_6H_3	H	**4l**	1	87	191–193
13	4-ClC_6H_4	H	**4m**	1.2	92	205–207
14	4-ClC_6H_4	4-CH_3	**4n**	1.2	91	193–195
15	4-FC_6H_4	H	**4o**	1.2	90	182–184
16	3-ClC_6H_4	H	**4p**	1	89	172–174
17	4-BrC_6H_4	4-CH_3	**4q**	1	88	172–174
18	3-FC_6H_4	H	**4r**	1	87	196–198
19	2-FC_6H_4	H	**4s**	1	88	177–179
20	4-BrC_6H_4	H	**4t**	1	89	210–212
21	2-ClC_6H_4	H	**4u**	1	90	168–170
22	3-BrC_6H_4	H	**4v**	1	88	181–183
23	4-CNC_6H_4	H	**4w**	1	92	246–248
24	4-CNC_6H_4	H	**4x**	1	93	240–242
25		4-CH_3	**4y**	1.2	88	198–200
26		H	**4z**	1.2	89	188–190
27		H	**4ab**	1.1	86	202–204
28		H	**4ac**	1.2	84	184–186
29		H	**4ad**	1.2	76	178–180
30	Benzaldehyde	H	**4ae**	1	92	148–150
31	3,4,5-$OCH_3C_6H_2$	H	**4af**	1	89	230–232

The structures of the products synthesized in the current study were determined using ^{1}HNMR, and ^{13}C NMR spectroscopies, and HRMS analysis.
[a] Reaction conditions: 3-aminoindazoles (1, 1 mmol), 2-methoxy-benzaldehyde (2, 1 mmol), (3, 1 mmol) and ethynylbenzene(3, 1 mmol), Ag NPs (0.5 mol%), solvent-free, 80 °C.
[b] Isolated yields.

2.2.4. X-ray diffraction analysis

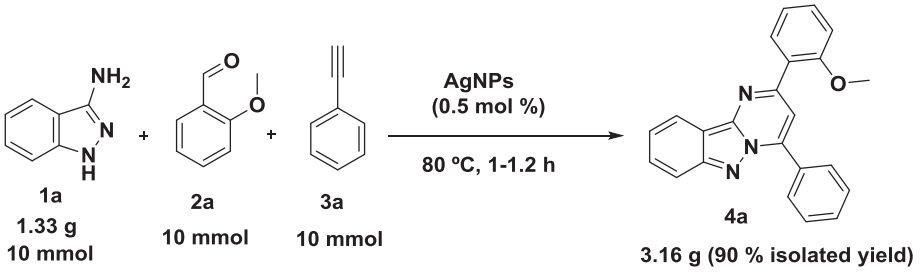
The Crystalline phase of Ag NPs synthesized with *Radix Puerariae* extract was analyzed by X-ray diffraction. The sample of Ag NPs synthesized with *Radix Puerariae* extract was prepared by drying Ag NPs overnight at room temperature. The XRD pattern of Ag NPs synthesized with *Radix Puerariae* extract is shown in Fig. 4. To confirm the UV–Vis analysis and EDX analysis XRD study was done. The XRD pattern contains clear peaks at 38.2°, 44.20°, 64.36° and 77.30° which can be indexed to 〈111〉, 〈200〉, 〈220〉, and 〈311〉 respectively confirming crystalline Ag NPs.

2.2.5. Dynamic Light Scattering (DLS) and zeta potential

The hydrodynamic diameter and stability of Ag NPs was analyzed on the DLS. The Ag NPs synthesized with *Radix Puerariae* extract were filtered through a membrane filter (0.2 μm) in order to remove any dust particle. Dynamic Light Scattering analysis of Ag NPs synthesized with *Radix Puerariae* extract is shown in (Supporting information) Fig. 5 (a) From DLS analysis the average particle size of Ag NPs was determined to be 25 nm, which is in accordance with TEM results. (b) shows the Zeta potential values of Ag NPs synthesized with *Radix Puerariae* extract. The Zeta potential analysis determines the stability of Ag NPs, the zeta potential values higher than − 30 mV and less than + 30 mV are considered to be stable Ag NPs. The zeta potential values of Ag NPs

synthesized with *Radix Puerariae* extract were − 31.9 mV, which indicate the Ag NPs are highly stable.

2.4. Gram scale preparation of the compound (**4a**)



2.3. Catalytic activity of Ag NPs for 'one-pot' A^3 coupling reaction

Multicomponent reactions provide a very versatile and efficient method to construct desired molecules. The effect of Ag NPs on their catalytic activity for the A^3-coupling reaction was investigated using 3-aminoindazoles (1, 1 mmol), 2-methoxybenzaldehyde (2, 1 mmol) and ethynylbenzene (3, 1 mmol). Initially, we examined the effect of various solvents on the model reaction with 0.5 mol% of Ag NPs catalyst under reflux condition. Among all the solvents tested ACN, toluene, EtOH, THF, dioxane, H_2O, and DMF, it was found that the rate of reactions was slower and resulted in moderate yields of **4a** in even after prolonged reaction times (Table 1, entries 1–7). To our delight, when the reaction was carried out under solvent-free condition, furnished the desired product **4a** in 96% yield at 80 °C in 1 h. (Table 1, entry 8). Further increment in the catalyst loading was not found to be effective (Table 1 entries, 9 and 10). Similarly, increasing the temperature and time of the reaction did not show improvement in the yield (Table 1, entries 12 and 13). To confirm the catalytic activity of the Ag NPs catalyst, a comparison study was conducted with various copper catalysts under solvent-free conditions at 80 °C and observed low catalytic properties (Table 1, entries 14–16). From all these establishments we were satisfied to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed to afford the desired product **4a** in 96% yield using Ag NPs under solvent-free conditions.

Having established the optimized reaction conditions, the scope and generality of this protocol were explored and representative results are summarized in Table 2. To our delight, we found this transformation to be very general for a wide range of aldehydes which provided easy access to substituted pyrimido[1,2-*b*]indazole derivatives (**4a-4af**). It was found that electronic effect of the substrate had no significant impact on the overall yields of the products. For example, aromatic aldehydes carrying electron-donating and withdrawing substituents, could react efficiently to give the corresponding products without significant difference. Moreover, when the aromatic ring was replaced by a hindered naphthyl group, the desired product was obtained in 84% yield. Subsequently, the heteroaromatic thiophene-2-carboxaldehyde and furan-2- carboxaldehyde also well tolerated. We were delighted to find that the aliphatic aldehydes such as cyclohexanecarbaldehyde, also afforded the desired product with good yields. We also employed two different alkyne substrates, such as 1-ethynylbenzene and 1-ethynyl-4-methylbenzene, produced pyrimido[1,2-*b*]indazole in good to excellent yields. However, aliphatic alkynes such as n-hexyne and n-pentyne, did not afford the desired products. Therefore, the present protocol has general applicability, accommodating a variety of substitution patterns.

2.5. Recycling efficiency of Ag NPs catalyst

.Finally, we investigated the recovery and reusability of the catalytic system in the model reaction. After completion of the reaction, the reaction mixture was cooled to room temperature and ethyl acetate was added. The reaction mixture was centrifuged at 10000 rpm for 25 min. Then separated Ag NPs was recovered and washed with triple distilled water for several times and centrifuged at 13500 rpm for 30 min. (three times). It was found that the catalytic system could be reused up to three consecutive runs. Furthermore, no significant change was observed in textural properties as is clear in TEM of the recycled catalyst. (Fig. 6 in Supporting information). In addition, no detectable aggregation was observed in the recovered Ag NPs. However, lower yield was found with recycled Ag NPs, it may be due to handling loss during work-up in subsequent cycles.

3. Conclusion

In conclusion, we have developed a simple and green approach towards the development of a new method for the synthesis of silver nanoparticles (Ag NPs). The resulting Ag NPs showed enhanced catalytic activity for the synthesis of biologically important pyrimido[1,2-*b*] indazole via one-pot, three-component reaction. The promising points of this methodology are simplicity in the catalyst preparation from inexpensive materials, an easy work-up procedure for reactions, shorter reaction times, higher reaction rates, reusability of catalyst and the potential for a variety of desirable products being synthesized.

Appendix A. Supplementary data

All Compounds NMR spectra were provided as Supplementary data. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.catcom.2017.06.006.

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