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Ag/SiO$_2$ as a recyclable catalyst for the facile green synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-ones

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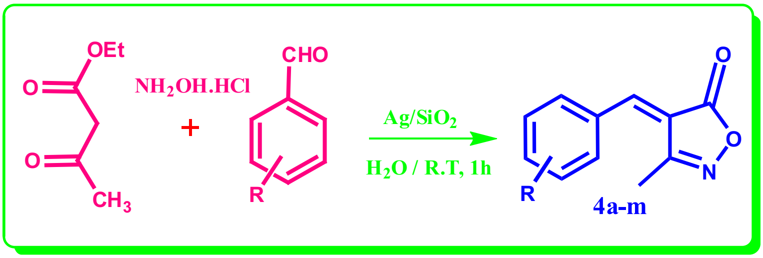
Abstract An efficient and facile green method for synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one (**4a-m**) via room temperature reaction of hydroxylamine, ethylacetoacetate and substituted aromatic aldehydes is designed, using Ag/SiO$_2$ as catalyst with water as solvent. This protocol offers several advantages, such as it being a benign, energy conserving and eco-friendly reaction with products obtained in excellent yields (88–93 %). The reaction requires relatively short reaction times (< 1 h), a simple workup procedure with good atom efficiency and easily recoverable catalyst. The heterogeneous catalyst, Ag/SiO$_2$, was fully characterized and is reusable without loss of activity for up to seven cycles with marginal activity loss.

Graphical Abstract



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Introduction

In recent years, multicomponent reactions (MCR) have captivated researchers due to a number of green principles, including facile operation, and being environmental friendly and economical. MCRs allow three or more compounds to react together, providing products in high yields without having to isolate intermediates. This is an attractive option [1–3], thus making MCRs an important tool in the synthesis of heterocyclic molecules with combinatorial, medicinal and agricultural chemistry applications [3–5]. The other advantages of these reactions include high bond-forming efficiency, cost effectiveness, energy saving and simple workup procedures [6, 7].

Interest in the use of heterogeneous catalysts in organic syntheses has increased due to improved selectivity, facile separation, reusability and low cost [8, 9]. Metal oxides have emerged as candidates for such a role due to their proven record as catalysts, supports, and as ion-exchangers. Mixed metallic oxides with both acidic and basic sites can be generated by calcination at about 700 K. The calcined composites have moderate surface areas and can accelerate various condensation reactions. Relative to conventional linear syntheses, these eco-friendly protocols also have benefits, such as long catalytic life, thermal stability, cost effectiveness, atom economy and scope to modify the surface properties [10].

Silica (SiO_2), which is an acidic functional material in pure form, is one of the widely used inorganic supports in the catalytic systems [11, 12] used in the activation and stabilization of several metals [13, 14]. The crystalline structure of SiO_2 has been documented as one of the key factors for the justification of the structure–activity relationships of metal-based catalysts [15]. In organic synthesis, silica as support for various metal oxide catalysts allows the design of a varied distribution of its Lewis and Brønsted acidic and basic sites [16–19] on the surface, facilitating its use as catalyst for specific applications.

Isoxazoles are an important class of heterocyclic compounds; they are predominant in nature and display fascinating biological and pharmaceutical properties [20, 21]. Isoxazole is considered a major scaffold compound in the discovery of combinatorial synthesis and protein kinase inhibitors, playing a crucial role in the development of chemotherapeutic agents [22, 23]. Many isoxazole derivatives exhibit antibacterial [24], antifungal [25], antitumor [26], antioxidant [27], antiprotozoal [28], antiviral [29], anti-tubercular [30], anti-inflammatory [31] and anti-HIV [32] activities. Several procedures have been reported in the literature for the synthesis of isoxazole derivatives and their analogues. A Literature survey shows that many catalyzed methods were reported for the synthesis of various isoxazole derivatives. To mention a few, such protocols employed sodium saccharin [33], ultrasonic irradiation [34], sodium silicate [35], sodium benzoate [36], pyridine [37, 38], DABCO [39], CH_3COONa/UV [40], sodium ascorbate [41], sodium tetraborate [42], sodium sulfide [43], pyridine/UV [44], and boric acid [45] as catalysts. Many of these methods have some limitations and drawbacks, such as use of toxic reagents, strong acidic or basic conditions, costly reagents and catalysts, strict reaction conditions, tedious steps, and low product yields and/or long reaction times, which restrict their scope in practical applications. Therefore, a novel protocol with good and inexpensive catalyst demanding short reaction times is sought after.

In continuation of our interest in the environmental friendly protocols for the various syntheses of heterocyclic derivatives with better yields [46–49], we herein report the one-pot reaction of ethylacetoacetate, hydroxyl amine and substituted aldehydes in the presence of a catalyst Ag/SiO_2 for the synthesis of isoxazole derivatives in excellent yields.

Experimental

Catalyst characterization

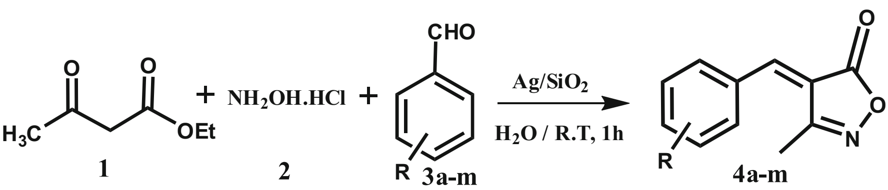
Micromeritics Tristar-II porosity and surface area analyzer was used to determine the values of surface area, pore size and pore volume of the catalyst material. The catalyst sample was degassed overnight using N_2 flow at 200 °C. The BJH adsorption–desorption curves were generated at −196 °C and were used to assess the catalyst's particulate properties. Employing a Bruker D8 Advance instrument (Cu K radiation source with a wave length of 1.5406 Å), the X-ray diffraction data related to the structural phases of the catalyst were acquired. Using a Jeol JEM-1010 electron microscope and JEOL JSM-6100 microscope, transmission electron microscopy (TEM) and scanning electron microscope (SEM) analysis data were recorded. iTEM software was used analyze the TEM data and images. Employing the X-ray analyzer (energy-dispersive), EDX-analysis on the SEM images was conducted. To confirm the elemental composition catalyst materials, an inductively coupled plasma optical emission spectrometer (ICP-OES) (Optima 5300 DV) was used.

Preparation of catalyst

The wet impregnation method was used for the synthesis of catalyst material, Ag/SiO_2. An appropriate amount of silver nitrate hydrate $AgNO_3{\cdot}9H_2O$, Aldrich (99.9 %) was dissolved in double distilled water (50.0 ml), which was added to silica (3.0 g) with continuous stirring with a magnetic stirrer at room temperature for 12 h. Then the resulting slurry was dried in an oven at 110–130 °C for 12 h and calcined in the presence of air at 450 °C for 3 h to acquire the 5 % w/w catalyst [50, 51].

General procedure for the synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives

To equimolar ratios of hydroxylamine (1.1 mmol), ethylacetoacetate (1 mmol) and aldehyde (1 mmol) dissolved in water (10 ml) at room temperature (RT) using Ag/SiO_2 (30 mg) as catalyst. The reaction mixture was stirred continuously for 1 h at RT, (Scheme 1) using a magnetic stirrer. The progress of the reaction was



Scheme 1 Synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives

monitored by thin-layer chromatography (TLC). The reaction mixture was then filtered, and the filtrate was subsequently extracted with ethyl acetate and evaporated under reduced pressure to obtain the crude product. Further, the crude product was purified with a 4:6 ratio of EtOAc:Hexane mobile solvent to afford pure products (**4a-m**). The recovered catalyst was subjected to washing with ethanol, dried, and could be reused for up to seven cycles.

*3-Methyl-4-(4-hydroxyphenyl)methylene-isoxazole-5(4H)-one (**4a**)* Yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.24$ (s, 3H, CH$_3$), 6.94 (d, $J = 8.80$ Hz, 2H, ArH), 7.78 (s, 1H, =CH), 8.44 (d, $J = 8.84$ Hz, 2H, ArH), 10.85 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.24, 113.83, 116.12, 124.53, 137.44, 151.51, 162.24, 163.82, 168.78; IR (KBr, cm^{-1}): 3232, 2363, 1734, 1559, 1358, 1297, 1179, 669; HRMS of $[C_{11}H_9NO_3–H]^+$ (*m*/*z*): 202.0503; Calcd.: 202.0504.

*3-Methyl-4-(4-methoxyphenyl)methylene-isoxazole-5(4H)-one (**4b**)* Yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.25$ (s, 3H, CH$_3$), 3.89 (s, 3H, OCH$_3$), 7.14 (d, $J = 8.96$ Hz, 2H, ArH), 7.85 (s, 1H, =CH), 8.51 (d, $J = 8.96$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.24, 55.80, 114.63, 115.19, 125.76, 136.86, 151.19, 132.23, 164.21, 168.57; IR (KBr, cm^{-1}): 3446, 2362, 1734, 1594, 1269, 1176, 668; HRMS of $[C_{12}H_{11}NO_3 + Na]^+$ (*m*/*z*): 240.0641; Calcd.: 240.0637.

*3-Methyl-4-phenyl-methylene-isoxazole-5(4H)-one (**4c**)* Light yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.29$ (s, 3H, CH$_3$), 7.56–7.67 (m, 3H, ArH), 7.96 (s, 1H, =CH), 8.40 (d, $J = 7.40$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.25, 118.32, 128.84, 132.40, 133.51, 133.86, 151.62, 162.18, 167.78; IR (KBr, cm^{-1}): 3446, 2362, 1739, 1561, 1341, 1284, 1140, 685; HRMS of $[C_{11}H_{10}NO_2 + Na]^+$ (*m*/*z*): 211.0618; Calcd.: 211.0609.

*3-Methyl-4-(4-dimethylaminophenyl)methylene-isoxazole-5(4H)-one (**4d**)* Red solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.20$ (s, 3H, CH$_3$), 3.33 (s, 6H, N(CH$_3$)$_2$), 6.85 (d, $J = 9.16$ Hz, 2H, ArH), 7.60 (s, 1H, =CH), 8.45 (d, $J = 8.80$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.27, 108.98, 111.59, 120.95, 137.52, 150.44, 154.32, 162.08, 169.79; IR (KBr, cm^{-1}): 3432, 2362, 1709, 1582, 1380, 1202, 1161, 668; HRMS of $[C_{13}H_{14}N_2O_2 + Na]^+$ (*m*/*z*): 253.0953; Calcd.: 253.0953.

Anal. calcd. for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; Found: C 67.83, H 6.10, N 12.14.

*3-Methyl-4-(anthracen-9-yl)methylene-isoxazole-5(4H)-one (**4e**)* Brown solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.57$ (s, 3H, CH$_3$), 7.72–776 (m, 3H, ArH), 8.07–8.09 (m, 3H, ArH), 8.79 (d, $J = 8.74$ Hz, 3H, ArH), 8.86 (s, 1H, CH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.46, 123.44, 125.05, 125.39, 125.73, 125.81, 127.05, 127.43, 128.72, 148.35, 158.68, 161.09, 166.22, 168.25, 168.78; IR (KBr, cm^{-1}): 3431, 2360, 1752, 1352, 1292, 1182, 668; HRMS of $[C_{19}H_{13}NO_2 + Na]^+$ (*m/z*): 310.0848; Calcd.: 310.0844.

*3-Methyl-4-(2,5-dihydroxyphenyl)methylene-isoxazole-5(4H)-one (**4f**)* Yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.23$ (s, 3H, CH$_3$), 6.85 (d, $J = 8.88$ Hz, 1H, ArH), 6.97–7.00 (m, 1H, ArH), 8.02 (s, 1H, =CH), 8.23 (d, $J = 8.78$ Hz, 1H, ArH), 9.18 (s, 1H, OH), 10.38 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.16, 115.67, 116.45, 116.78, 119.69, 125.56, 144.98, 149.32, 153.36, 162.17, 168.23; IR (KBr, cm^{-1}): 3308, 2361, 1751, 1602, 1368, 1273, 1170, 668; HRMS of $[C_{11}H_9NO_4–H]^+$ (*m/z*): 218.0453; Calcd.: 218.0453.

*3-Methyl-4-(3,4-dihydroxyphenyl)methylene-isoxazole-5(4H)-one (**4g**)* Yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.19$ (s, 3H, CH$_3$), 6.42 (s, 2H, ArH), 7.96 (s, 1H, =CH), 8.97 (d, $J = 8.81$ Hz, 1H, ArH), 9.90 (s, 1H, OH), 11.06 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.17, 101.69, 109.02, 110.57, 113.01, 135.14, 143.94, 162.22, 163.10, 166.63, 169.40; IR (KBr, cm^{-1}): 3487, 2363, 1734, 1589, 1391, 1258, 1212, 761.

*3-Methyl-4-(3-hydroxyphenyl)methylene-isoxazole-5(4H)-one (**4h**)* Light yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.27$ (s, 3H, CH$_3$), 7.06 (d, $J = 7.46$ Hz, 1H, ArH), 7.37 (t, $J = 7.90$ Hz, 1H, ArH), 7.78 (d, $J = 7.88$ Hz, 1H, ArH), 7.85 (s, 1H, =CH), 7.92 (s, 1H, ArH), 9.90 (s, 1H, OH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.25, 118.48, 119.38, 121.34, 125.25, 129.80, 133.57, 151.98, 157.35, 162.21, 167.71; IR (KBr, cm^{-1}): 3432, 2356, 1739, 1575, 1347, 1288, 1113, 668; HRMS of $[C_{11}H_9NO_3–H]^+$ (*m/z*): 202.0512; Calcd.: 202.0504.

*3-Methyl-4-(2,3-dimethoxyphenyl)methylene-isoxazole-5(4H)-one (**4i**)* Light yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.29$ (s, 3H, CH$_3$), 3.86 (s, 6H, 2OMe), 7.06 (d, $J = 7.82$ Hz, 1H, ArH), 7.36 (d, $J = 7.64$ Hz, 1H, ArH),7.99 (s, 1H, =CH), 8.22 (d, $J = 9.08$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.13, 56.00, 61.67, 118.83, 119.26, 123.34, 123.70, 125.63, 145.12, 149.85, 152.15, 162.02, 167.47; IR (KBr, cm^{-1}): 3432, 2362, 1698, 1524, 1268, 1125, 668.

*3-Methyl-4-(2,5-dimethoxyphenyl)methylene-isoxazole-5(4H)-one (**4j**)* Orange solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.25$ (s, 3H, CH$_3$), 3.75 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.12–7.27 (m, 2H, ArH), 8.01 (s, 1H, =CH), 8.41 (d, $J = 8.04$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$): δ 11.12, 55.50, 56.50, 112.84, 115.78, 117.79, 120.79, 123.23, 144.21, 152.26, 154.43, 162.02, 168.01; IR (KBr, cm^{-1}): 3430, 2362, 1730, 1596, 1237, 1045, 668; HRMS of $[C_{13}H_{13}NO_4 + Na]^+$ (*m/z*): 270.0742; Calcd.: 270.0742.

*3-Methyl-4-(2,4,6-trimethoxyphenyl)methylene-isoxazole-5(4H)-one (**4k**)* Yellow solid: ^{1}H NMR (400 MHz, DMSO-d$_6$) $\delta = 2.22$ (s, 3H, CH$_3$), 3.76 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.25 (s, 1H, ArH), 6.35 (s, 1H, ArH), 7.72 (s, 1H, =CH), 8.11 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.16, 55.76, 55.99, 56.07, 90.68, 90.96, 104.25, 117.47, 141.08, 142.33, 159.16, 160.02, 160.98, 165.58; IR (KBr, cm^{-1}): 3431, 2364, 1751, 1602, 1330, 1207, 1157, 668.

*3-Methyl-4-(2,4-dimethylphenyl)methylene-isoxazole-5(4H)-one (**4l**)* Cream solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.29 (s, 3H, CH_3), 2.34 (s, 3H, $ArCH_3$), 2.45 (s, 3H, $ArCH_3$), 7.14 (d, J = 8.04 Hz, 1H, ArH), 7.19 (s, 1H, ArH), 8.00 (s, 1H, =CH), 8.34 (d, J = 8.84 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.16, 19.45, 21.28, 117.86, 126.46, 127.91, 131.32, 131.52, 141.04, 144.23, 149.26, 162.03, 167.76; IR (KBr, cm^{-1}): 3449, 2372, 1770, 1599, 1383, 1097, 658; HRMS of $[C_{13}H_{14}NO_2 + H]^+$ (m/z): 216.1032; Calcd.: 216.1025.

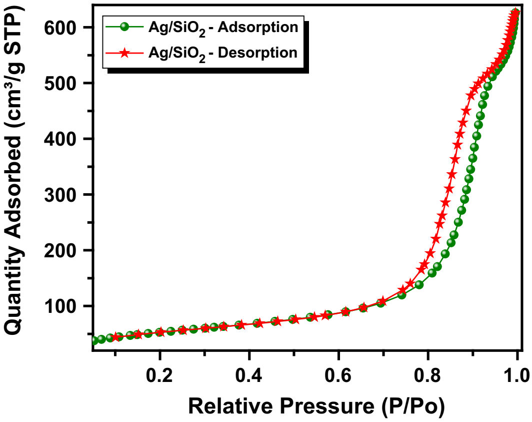
*3-Methyl-4-(4-ethylphenyl)methylene-isoxazole-5(4H)-one (**4m**)* White solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.20 (t, J = 8.12 Hz, 3H, $CH_2\underline{CH_3}$), 2.27 (s, 3H, CH_3), 2.70 (q, J = 7.57 Hz, 2H, $\underline{CH_2}CH_3$), 7.43 (d, J = 8.28, 2H, ArH), 7.91 (s, 1H, =CH), 8.36 (d, J = 8.20, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.23, 14.84, 28.44, 117.62, 126.38, 128.38, 130.25, 131.79, 133.99, 151.09, 151.60, 162.20, 168.03; IR (KBr, cm^{-1}): 3446, 2368, 1740, 1594, 1344, 1257, 1103, 668; HRMS of $[C_{13}H_{14}NO_2 + H]^+$ (m/z): 216.1035; Calcd.: 216.1025.

Results and discussion

BET surface area (BET) and elemental (ICP) analysis

The texture of the prepared catalysts was determined by physisorption analysis. The N_2 adsorption–desorption isotherms showed a type-IV adsorption isotherm, demonstrating the mesoporous nature of the catalysts (Fig. 1). The prepared catalyst showed a surface area of 189 $m^2\ g^{-1}$ with a pore volume of 0.994 cc g^{-1}. The large surface area was obtained for the catalyst sample with high pore volumes

Fig. 1 N_2 adsorption and desorption spectra of Ag/SiO_2 catalyst



due to the narrow pore size distribution of catalyst. The ICP analysis results showed the presence of a nominal amount of Ag in the catalyst (4.94 wt%).

TEM analysis

The TEM micrograph reveals more structural information of the catalyst. Figure 2 shows a distinctive TEM image of Ag loaded on silica catalyst, from which it can be seen that the Ag nanoparticles showed a sphere-shape with an average size of 13 nm, and are highly dispersed and homogeneously distributed on the silica support with strong interaction between the AgNPs and silica supports.

SEM analysis

Figure 3 shows an illustrative SEM morphologies micrograph of the sample Ag on silica. A lot of large white elliptical irregular shapes are perceived from the low magnification SEM image of Ag/SiO_2. This micrograph reveals that the aggregative state of the silica important particles is with silver. While a homogeneous distribution of Ag and silica on the catalyst is specified by the EDS analysis, elemental analysis by ICP-OES confirmed the elemental composition in the catalyst material (Fig. 4). Furthermore, the morphology of the catalyst, as per the SEM images, noticeably points to the crystallinity and homogeneity of the sample.

Powder X-ray diffractogram (XRD) analysis

XRD patterns of the calcined Ag/SiO_2 catalyst are shown in Fig. 5. All of the PXRD diffraction patterns can be indexed to fcc silver. The calcined 2 % Ag on SiO_2 sample showed diffraction peaks at 38.1°, 44.3°, 64.4° and 77.4°, corresponding to

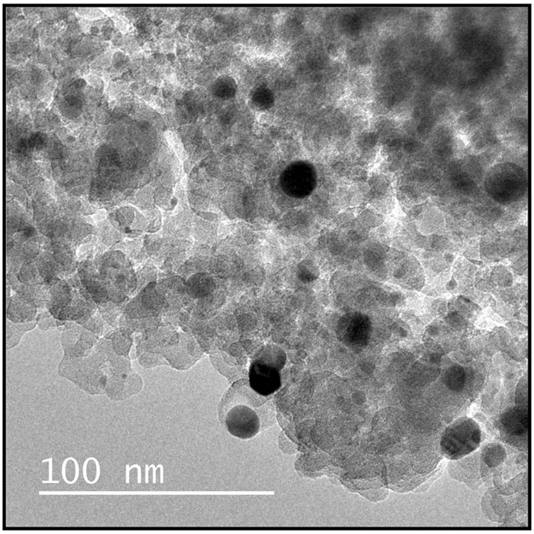


Fig. 2 TEM micrograph of Ag/SiO_2 catalyst

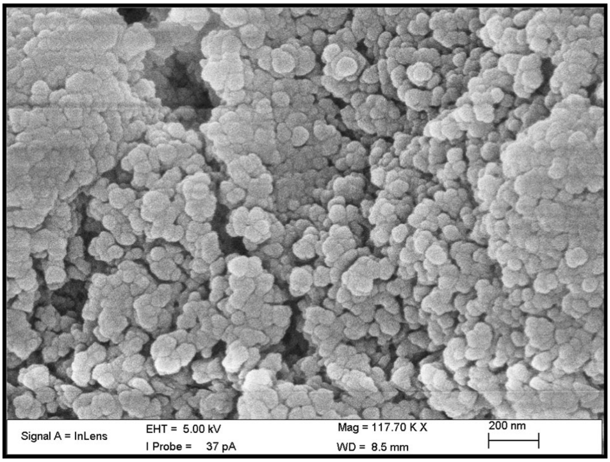


Fig. 3 SEM micrograph of Ag/SiO_2 catalyst

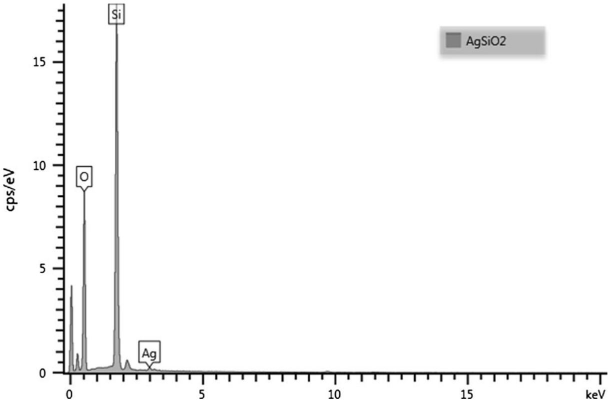


Fig. 4 SEM-EDX spectra of Ag/SiO_2 catalyst

the (1 1 1), (2 0 0), (2 2 0) and (3 1 1) lattice planes of hexagonal Ag_2O (JCPDS # 72-2108) and cubic Ag_2O_3 (JCPDS # 72-0607), respectively. Important peaks in the silver XRD spectra agree with the JCPDS-PDF # 00-004-0783 files, and the two broad peaks centered at 12.1° and 22.1° were due to the amorphous silica support.

Optimization procedure

At the start of the investigations, the impact of availability of catalyst material and solvents was examined. With ethyl acetoacetate, aromatic aldehyde, hydroxyl amine hydrochloride and water as solvent and with no catalyst, there was no reaction at RT, even after 24 h under reflux conditions, (Table 1, entries 1, 2). The same reaction was tried in ethanol in the absence of any catalyst at RT for 12 h, and failed

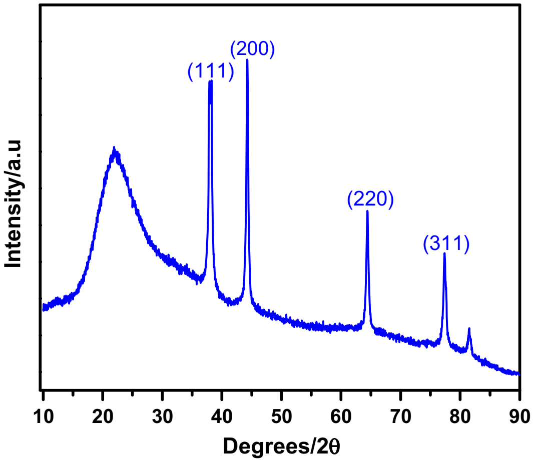


Fig. 5 XRD spectrum of Ag/SiO$_2$ catalyst

to achieve any desired product (Table 1, entries 3, 4). The scope of the various types of catalysts and use of NaOH and K_2CO_3 as a basic catalyst in aqueous media provided no yield at RT (Table 1, entry 5, 6). The reaction was performed under reflux conditions in ethanol, using pyridine and Na_2S as basic catalysts, which gave improved yields (Table 1, entry 7, 8). The use of ionic liquid (Bmim)BF_4 on the product yield was investigated, but yields were very low under reflux conditions (Table 1, entry 9). Use of pure heterogeneous acidic catalysts such as SiO_2, Al_2O_3, Fe_2O_3, and CeO_2 at RT in aqueous media showed no reaction progress or yield (Table 1, entries 10–13). The reaction performed with $AgNO_3$ as catalyst gave 18 % yield (Table 1, entry 14). When Ag loaded on SiO_2 was used as catalyst, a reaction occurred with an impressive 93 % yield of isoxazole derivative at RT after 1 h reaction time (Table 1, entry 15). The efficacy of this catalytic system was further tested by comparing it with two other silica-supported catalysts under otherwise similar conditions. Use of $HClO_4$–SiO_2 and $FeCl_3$/SiO_2 gave lower product yields and took 4–6 h for completion of the reaction (Table 1, entry 16, 17). Furthermore, the reaction using Ag/SiO_2 as catalyst under solvent free conditions gave a small yield, even after prolonged reaction time (Table 1, entry 18).

Accepting that Ag/SiO_2 as catalyst and water as solvent are ideal means for the reaction, the effect of amount of catalyst on the yield and reaction time was further investigated. Performing the reaction with $>$ 30 mg of catalyst had no significant improvement on the yield or reaction time. However, the decrease in the amount of the catalyst used to 20 and 10 mg affected the product yield by reducing it to 70 and 63 %, respectively (Table 1, entries 19–23). Therefore, 30 mg of Ag/SiO_2 at RT with water as solvent is assumed as the optimal condition for the model reaction, giving a conversion of 93 % in 1 h.

A perusal of the experimental results and the effect of various polar and non-polar solvents on the three-component reaction clearly indicate that water as solvent plays a vital role in facilitating the reaction (Table 1). Noticeably, under otherwise similar conditions, the Ag/SiO_2 catalyzed reaction in the presence of comparatively

Table 1 Optimization condition for the synthesis of isoxazole by Ag/SiO_2 catalyst[a]

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%)[b]
1	No catalyst	H_2O	RT	24	–
2	No catalyst	H_2O	Reflux	24	–
3	No catalyst	EtOH	RT	12	–
4	No catalyst	EtOH	Reflux	12	–
5	NaOH	H_2O	RT	12	–
6	K_2CO_3	H_2O	RT	12	–
7	Na_2S	EtOH	Reflux	2.5	61
8	Pyridine	EtOH	Reflux	5	42
9	$(Bmim)BF_4$	EtOH	Reflux	3	23
10	SiO_2	H_2O	RT	12	–
11	Al_2O_3	H_2O	RT	12	–
12	Fe_2O_3	H_2O	RT	12	–
13	CeO_2	H_2O	RT	12	–
14	$AgNO_3$	H_2O	RT	12	18
15	Ag/SiO_2	H_2O	RT	1	93
16	$HClO_4/SiO_2$	H_2O	RT	3	58
17	$FeCl_3/SiO_2$	H_2O	RT	3.5	37
18	Ag/SiO_2	–	RT	12	43
19	Ag/SiO_2 (10 mg)	H_2O	RT	3	85
20	Ag/SiO_2 (20 mg)	H_2O	RT	2	89
21	Ag/SiO_2 (30 mg)	H_2O	RT	1	93
22	Ag/SiO_2 (40 mg)	H_2O	RT	1	93
23	Ag/SiO_2 (50 mg)	H_2O	RT	1.5	91
24	Ag/SiO_2	CH_3CN	RT	3	29
25	Ag/SiO_2	DMF	RT	2.5	32
26	Ag/SiO_2	n-Hexane	RT	8	13
27	Ag/SiO_2	1,4-Dioxane	RT	6	24
28	Ag/SiO_2	EtOH	RT	1.5	78
29	Ag/SiO_2	MeOH	RT	2	72

–, No reaction

[a] All products were characterized by IR, ^{1}HNMR, ^{13}C NMR and HRMS spectral analysis

[b] Isolated yields

less polar solvents like CH_3CN, DMF, n-hexane and 1,4-dioxane gave insignificant yields (Table 1 entries 24–27). The efficiency of methanol and ethanol relative to water was also investigated. Although comparable yields were observed (Table 1, entries 28, 29), water had a marginal advantage, thus proving to be the best medium for the reaction. A highly polar solvent that dissipates heat faster may provide optimum conditions for formation of intermediates, and their conversion to final products on the catalyst surface.

Employing the optimized reaction conditions, the strength of the protocol was evaluated for the synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives from various aromatic aldehydes. The Ag/SiO_2 heterogeneous catalyst proved to catalyze the facile one-pot synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives with good to excellent yields. All the reaction products with other details are depicted in Table 2. Interestingly, the substrates used and reaction yields obtained show that the reaction using several electron-withdrawing and electron donating substrates in ortho, meta and para positions of the aromatic ring have also contributed positively to obtaining the desired isoxazole derivatives in good to excellent yields (Table 2). A reaction scheme is proposed based on the chemistry of the reacting substrates and observed selectivity towards the product (Fig. 6). At first, the nucleophilic attack of hydroxylamine hydrochloride at the carbonyl carbon of the compound **1** afforded the intermediate compound oxime. When the intermediate lost one hydrogen atom, the methylene group would convert to be the active carbon anion. Then, the aldehyde carbonyl group was attacked by carbon anion and a subsequent Knoevenagel reaction occurred. After losing one ethanol molecule, ring-closing was brought to the corresponding products. All the resultant products were characterized and structures were confirmed by FTIR, ^1H NMR, ^{13}C NMR and HRMS spectral analysis (Electronic Supplementary Information).

Table 2 Synthesis of isoxazole derivatives catalyzed by Ag/SiO_2 catalyst

Entry	*R*	Product	Yield (%)	Mp °C	Lit Mp °C
1	4-OH	**4a**	92	214–215	214–216 [32]
2	4-OMe	**4b**	90	173–174	174–175 [32]
3	H	**4c**	93	141–142	141–143 [35]
4	$4\text{-}N(Me)_2$	**4d**	92	227–228	226–228 [35]
5	Anthracenyl	**4e**	90	219–221	–
6	$2,5\text{-}(OH)_2$	**4f**	89	187–188	–
7	$3,4\text{-}(OH)_2$	**4g**	90	212–213	–
8	3-OH	**4h**	92	164–166	–
9	$2,3\text{-}(OMe)_2$	**4i**	90	210–211	–
10	$2,5\text{-}(OMe)_2$	**4j**	89	178–179	–
11	$2,4,6\text{-}(OMe)_3$	**4k**	88	232–233	–
12	$2,4\text{-}(Me)_2$	**4l**	92	193–195	–
13	4-Et	**4m**	91	201–203	–

–, New compounds/no literature available

[a] Reaction conditions: hydroxylamine (1.1 mmol), ethylacetoacetate (1.0 mmol), aromatic aldehyde (1.0 mmol) and water (10 ml), RT

[b] All synthesized compounds are identified and their structures were confirmed with IR, ^1H NMR, ^{13}C NMR and HRMS spectral data and melting points, as compared with literature values

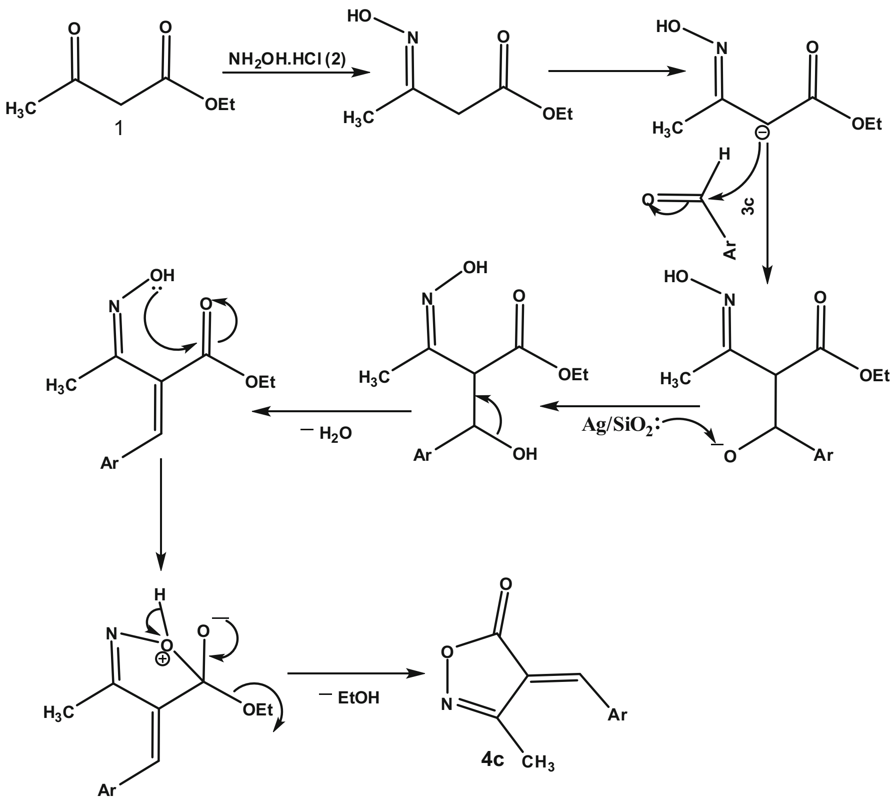


Fig. 6 Proposed reaction mechanism

Reusability of catalyst

In one of the photochemical methods, using CH_3COONa catalyst, visible light and aqueous ethanol solvent conditions [40], the obtained yield was only 56–68 % in 20 min; furthermore, in this method the catalyst was not recyclable. The main attraction of the use of heterogeneous catalysts is reusability. Experiments were performed to investigate the recyclable phenomenon of the heterogeneous catalyst in the title reaction. The catalyst was recovered after filtration, washed with EtOH and dried under reduced pressure after the completion of reaction. The recovered catalyst was reused for seven consecutive runs following a similar recovery procedure, and observed loss of activity was minimal (Fig. 7). No significant loss was observed in the first four cycles. The marginal loss in catalytic activity noticed after the 4th run can be attributed to the probable organic contaminations, trivial alterations and loss of catalyst material in the recovery process under the examined conditions.

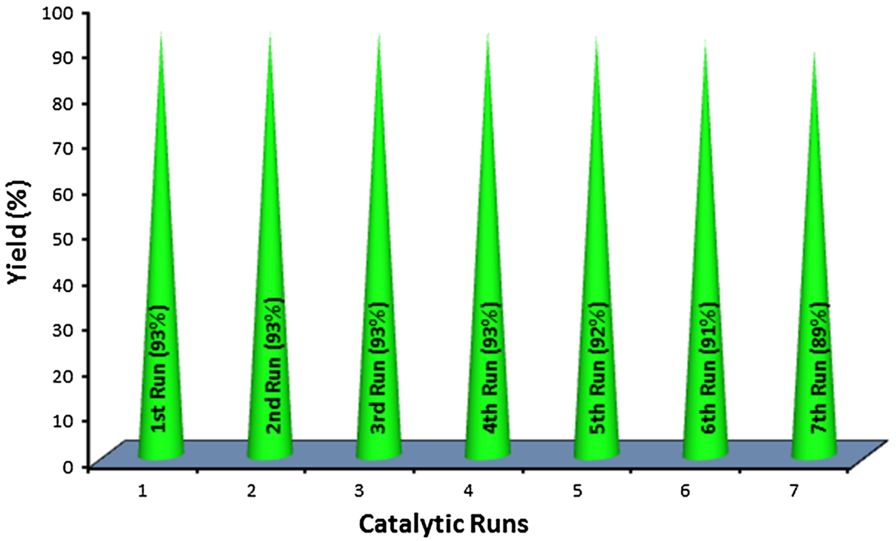


Fig. 7 Recyclability of Ag/SiO$_2$ catalyst

Conclusion

We have described a green, simple, efficient and environmentally benign one-pot multicomponent protocol for the synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4*H*)-one derivatives with good to excellent yields. The new heterogeneous catalyst, Ag/SiO$_2$ is simple, highly efficient and recyclable for the MCR protocol at RT. The main advantages of this approach are green solvent, cheap materials, easy workup, non-hazardous and environment friendly reaction conditions, recyclable catalyst, excellent yields, and short reaction times.

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