Received: 5 February 2019 | Revised: 21 April 2019 | Accepted: 13 May 2019

DOI: 10.1002/aoc.5043

FULL PAPER

WILEY Applied Organometallic Chemistry

$Ag_3[PMo_{12}O_{40}]$: An efficient and green catalyst for the synthesis of highly functionalized pyran-annulated heterocycles via multicomponent reaction

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A facile, efficient and eco-friendly catalytic protocol was developed for the synthesis of medicinally important pyran-annulated heterocycles via multicomponent reaction (MCR). Cyclocondensation of differently substituted aromatic aldehydes, malononitrile/ethyl cyanoacetate and various β-dicarbonyl compounds in the presence of $Ag_3[PMo_{12}O_{40}]\cdot nH_2O$ as heterogeneous catalyst, in EtOH–H_2O, afforded diverse pyran-fused chromene analogues. The merits observed for this approach were it being conducted via MCR, using commercially available or easily accessible starting materials in the presence of a green and easily separable heterogeneous and reusable catalyst, and affording high yields of desired products in very short reaction times with high purity in one-pot fashion, thus providing a superior alternative approach for the synthesis of pyran-annulated heterocycles.

KEYWORDS

2-amino-4*H*-pyrans, $Ag_3[PMo_{12}O_{40}]$, heterogeneous catalysis, multicomponent reaction, one-pot synthesis, polyoxometalates

1 | INTRODUCTION

Nowadays, the design, preparation and use of efficient and environmentally friendly catalysts are important challenges in synthetic organic chemistry. Polyoxometalates (POMs), as anionic metal–oxygen nanoclusters, are considered as important inorganic catalysts for such purposes.[1]

Due to the multiple active sites, including protons, metal atoms and oxygen atoms, POMs have been used extensively as versatile catalysts in organic synthesis. In POMs, protons give Brønsted acid characters, thus promoting acid-catalysed reactions. Accepting this general idea, for choosing them as catalysts, attention should be focused on the metal ions of POM structures. Those metal ions that possess unoccupied orbitals are favourable since they can accept electrons thus gaining Lewis acid characters and as result the selected POMs possess higher acidic character which is beneficial for acid-catalysed reactions.[2] POM-acid-catalysed reactions have been well established over the years. Among them, Keggin-type POMs with the general formula $H_n[XM_{12}O_{40}]$ (X is the central heteroatom and M is the addenda atom) have attracted much attention.[3] They possess stable structures and strong acidity, which can be tuned by simply changing the polyanion chemical composition and the cationic moiety. Unhelpfully, pure bulk POMs have relatively small specific surface areas that hinder accessibility to active sites, thus affecting their catalytic activity. Moreover, their high solubility in many polar solvents favours them in the homogeneous phase. Although these homogeneous catalysts are remarkably efficient, their separation and recovery are difficult and as a result their reusability is uncertain.

Therefore, the development of methods for 'catalyst engineering' of POMs has been an important tendency in catalysis research and is still in much demand. If a certain POM acts as a heterogeneous catalyst which is separated easily, it can be recovered and reused several times with no significant change in its activity. Such qualities are among those of green chemistry principles.[4] One of the most promising approaches for the heterogenization of POMs is exchanging their protons with suitable metal cations.[5] POM salts with large metal ions are insoluble and possess high surface areas. When a reaction is conducted in the presence of certain heterogeneous POMs, and is possible in aqueous media, that reaction can be considered as doubly green.

Synthesis of 4*H*-pyran and its derivatives affords an important class of heterocycles both in academia and industry. They are present in the core of various naturally occurring compounds as well as showing photochromic properties.[6] They also show a broad range of biological activities such as antimicrobial,[7] anticancer,[8] antibacterial[9] and anti-allergic[10] activities. These compounds exhibit other remarkable pharmacological properties, being used in the treatment of Parkinson's disease,[11] Alzheimer's disease[11] and Huntington's disease, and furthermore they are found to be calcium channel antagonists[12] (Figure 1).

Coumarin-fused pyran-annulated 4*H*-chromenes, particularly dihydropyrano[3,2-*c*]chromene and chromeno [4,3-*b*]chromene derivatives, have attracted much attention of synthetic organic and medicinal chemists due to their exhibiting various biological properties as such as antitumour,[13] anticancer,[14] antimalaria,[15] anti-Alzheimer,[16] anti-HIV,[17] antibacterial,[18] anticoagulant[19] and anti-anaphylactic[20] activities. A selection of such biologically potent molecules is depicted in Figure 2.

Multicomponent reactions (MCRs) involve three or more reactants coming together in a one-pot fashion to afford desired target products containing significant elements of all the reactants used.[21] This approach permits molecular diversity in a one-vessel-fashion transformation.[22] MCRs provide fascinating heterocyclic systems, especially those that are applicable in combinatorial chemistry as powerful tools.[23] The advantages of MCRs are those such as atom-economy, eco-friendliness, direct reaction design and the opportunity of constructing desired targets by introducing several diverse chemicals in a single chemical operation.[24]

Nowadays, much attention has been focused on environmental control by using benign sources of energy and replacement of volatile environmentally harmful chemicals and biologically discordant common organic solvents.[25] Regarding environmental protection from chemical industry, water and aqueous media are green solvents for use in organic transformations due to the abundance of water, as well as it being non-flammable and non-hazardous.[26]

A literature survey revealed the biological significance of 2-amino-4*H*-chromenes having amino and nitrile moieties at the 2 and 3 positions, respectively (Figure 1).[9,27] Because they show such a broad scope of applications, the development of an efficient, green and economically feasible method for the formation of 2-amino-3-cyano-4*H*-chromenes as structural motifs is still in much demand. A literature survey showed several approaches for the construction of 2-amino-3-cyano-4*H*-chromenes, namely a one-pot, three-component condensation reaction between aldehyde, malononitrile and an enolizable C–H acid, like dimedone, barbituric acid, resorcinol, α-naphthol, β-naphthol, 2-hydroxy-1,4-naphthoquinone-4-hydroxycoumarin, Kojic acid, etc., and a Knoevenagel carba-Michael–Thorpe–Ziegler type cascade strategy.[28] Knoevenagel–Michael reactions can be efficiently performed employing basic catalysts, such as Et_3N, piperidine, K_2CO_3,[29] K_3PO_4,[30] $(NH_3)_2HPO_4$,[12] Mg–Al hydrotalcite,[31] DBU,[32] KF-Al_2O_3, chitosan,[33] basic ionic liquids,[34] hexamethylenetetramine[35] and electrogenerated bases.[36] Utilization of heteropolyacids[37] or Brønsted acids[38] has also been reported. Furthermore, 4-dimethylaminopyridine (DMAP), urea, imidazole, potassium phthalimide-*N*-oxyl, meglumine and ethylenediammonium diformate, as well as clinoptilolite, have been reported as effective catalysts for the preparation of 2-amino-4*H*-chromenes.[11,39] These approaches have their own merits and drawbacks. Thus, the introduction of a novel, green and reusable catalyst for the synthesis of medicinally significant 2-amino-4*H*-chromenes is very desirable.

$Ag_3[PMo_{12}O_{40}]$, in the category of hetero-POMs, is a type of magic acid consisting of a particular combination of Lewis acid and oxygen atoms with certain metal

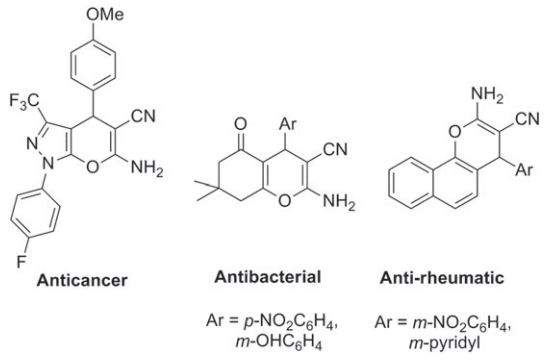


FIGURE 1 Some pharmacologically important 2-amino-4*H*-pyran derivatives

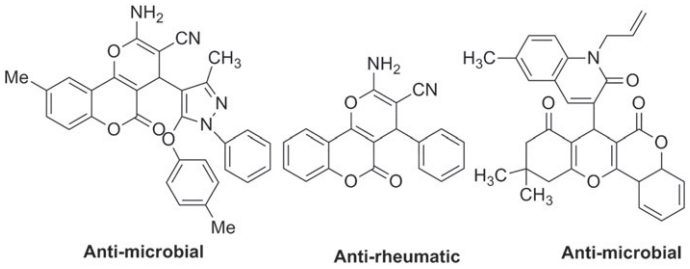


FIGURE 2 Various bioactive coumarin-fused 4*H*-chromenes

counterparts. This type of acid can be used as a reusable acid catalyst in many chemical transformations.

We are interested in heterocyclic chemistry,[39a,b,40] especially in the synthesis of heterocyclic systems via MCRs[39c–e,41] being performed under heterogeneous catalysis in water.[42] In the last few decades, our group has been engaged in research into heteropolyacids and their POM-catalysed reactions. The results of these efforts have been included in several review articles.[43] Based on the points mentioned above and in continuation of our interest in exploring green heterogeneous catalysts for organic transformations leading to heterocyclic systems, herein we report our successful attempt to apply a silver salt of Keggin-type polyoxomolybdate ($Ag_3[PMo_{12}O_{40}]]\cdot nH_2O$) as an efficient and reusable catalyst. This catalyst was used in the synthesis of 4*H*-pyrans via a one-pot three-component cyclocondensation reaction between aldehydes (**1**), malononitrile/ethyl cyanoacetate (**2**) and carbonyl compounds (**3**) possessing a reactive α-methylene group in aqueous media (Scheme 1).

2 | EXPERIMENTAL

2.1 | Materials

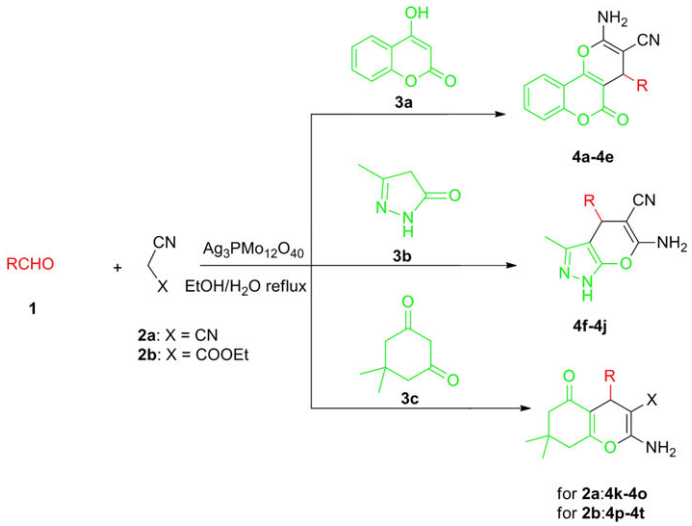
All chemicals used for synthesis and investigation of the catalytic activity of $Ag_3[PMo_{12}O_{40}]\cdot nH_2O$ were purchased from Merck and used as received. Melting points were measured with an Electrothermal 9200 apparatus. Fourier transform infrared (FT-IR) spectra were recorded with a Tensor 27 FT-IR spectrophotometer. All products were known and identified by comparison of their physical (melting points) and spectral (FT-IR spectra) data with those of authentic samples and found to be identical. $Ag_3[PMo_{12}O_{40}]\cdot nH_2O$ is not commercially available; thus, it was obtained by modification of an already reported procedure.[44]

2.2 | Preparation of catalyst

A solution of $AgNO_3$ (510 mg, 3 mmol) in 5 ml of water was added dropwise to a solution of $H_3[PMo_{12}O_{40}]$ (1.825 g, 1 mmol) in 5 ml of water under continuous stirring at room temperature. A yellow precipitate was immediately formed. The solid was filtered under reduced pressure, washed with ether and dried in a desiccator under vacuum.

2.3 | Characterization of catalyst

$Ag_3[PMo_{12}O_{40}]\cdot nH_2O$ was characterized using FT-IR spectroscopy and inductively coupled plasma (ICP) analysis. The FT-IR spectrum of this compound exhibits the



SCHEME 1 Synthesis of functionalized pyran-annulated heterocycles in the presence of Ag3[PMo12O40]

typical bands of the Keggin anions in the 700–1100 cm^{-1} region, the characteristic bands at 956, 901, 789 and 1063 cm^{-1} corresponding to ν(Mo—Od), ν(Mo—Ob—Mo), ν(Mo—Oc—Mo) and ν(P—O) of the $[PMo_{12}O_{40}]$ polyanions, respectively. In addition, a broad band at around 3400 cm^{-1} is indicative of the presence of molecules of water. The main element contents were determined using ICP analysis and hydrogen elemental analysis. $Ag_3[PMo_{12}O_{40}]\cdot 8H_2O$: calcd (wt%): Ag 14.1; P 1.3; Mo 50.3; H 0.70; found (wt%): Ag 14.2; P 1.3; Mo 51.1, H 0.67. The ratio of Ag:P:Mo atoms is equal to 3:1:12.

2.4 | Synthesis of 4*H*-pyrans: general procedure

A mixture of a suitable aldehyde (1 mmol), malononitrile /ethyl cyanoacetate (1 mmol) and 4-hydroxycoumarin/3-methyl-4*H*-pyrazole-5(4*H*)-one/dimedone (1 mmol) was refluxed in EtOH–H_2O (5 ml) in the presence of a catalytic amount of $Ag_3[PMo_{12}O_{40}]$ (0.05 g) for the required reaction time. The progress of the reaction was monitored by TLC (7:3 *n*-hexane–ethyl acetate). Upon completion of the reaction (indicated by TLC), the mixture was filtered off under reduced pressure. The filtrate was cooled to ambient temperature and the precipitated solid was separated by filtration under reduced pressure. The corresponding product was purified by crystallization from EtOH–H_2O to afford the corresponding product. The products were identified by comparison of their melting points as well as their FT-IR spectra (See Supporting information).

2.4.1 | Selected spectral data

1. 2-Amino-5-oxo-4-phenyl-4,5- dihydropyrano[3,2-*c*] chromene-3-carbonitrile (**4a**): FT-IR (KBr, ν_{max}, cm $^{-1}$): 3350, 3320, 2921, 2852, 2195, 1700, 1669, 1603, 1373, 1044, 759. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.9 (1H, d, J = 7.8 Hz), 7.7 (1H, t, J = 6.9 Hz), 7.4–7.5 (3H, m), 7.2–7.3 (5H, m), 4.5 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 159.5, 157.9, 153.4, 152.1, 143.3, 132.9, 128.5, 127.6, 127.1, 124.6, 122.4, 119.2, 116.5, 112.9, 104.0, 57.9, 36.9.[3b]
2. 2- Amino- 4-(4-chlorophenyl)- 5-oxo- 4,5-dihydropyrano-[3,2-*c*]chromene-3-carbonitrile (**4b**): FT-IR (KBr, ν_{max}, cm^{-1}): 3404, 2924, 2255, 2184, 2128, 1704, 1668, 1378, 1026, 1001, 763. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.9 (1H, d, J = 7.5 Hz), 7.7 (1H, t, J = 7.5 Hz), 7.4–7.5 (3H, m), 7.3–7.4 (4H, d, J = 8.4 Hz, 19.5 Hz), 4.5 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 160.0, 158.4, 154.0, 152.6, 142.8, 133.5, 132.2, 130.1, 128.9, 125.1, 123.0, 119.5, 117.0, 113.4, 103.9, 58.0, 36.8.[3b]
3. 2-Amino-4-(4-nitrophenyl)-3-cyano-4*H*,5*H* pyrano [3,2-*c*]chromene-5-one (**4c**): FT-IR (KBr, ν_{max}, cm $^{-1}$): 3482, 3432, 3371, 3335, 2195, 1718, 1673, 1607,1506, 1374, 1306. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.68 (1H, s), 7.47 (1H,d, J = 8.3 Hz), 7.52 (1H, t, J = 7.7 Hz), 7.57 (2H, br s, NH_2),7.60 (2H, d, J = 8.0 Hz), 7.74 (1H, t, J = 7.8 Hz), 7.91 (1H, d, J = 7.8 Hz), 8.18 (2H, d, J = 8.3 Hz).[54]
4. 2- Amino- 4-(4-methoxyphenyl)- 5-oxo -4,5-dihydropyrano-[3,2-*c*]chromene-3-carbonitrile (**4d**): FT-IR (KBr, ν_{max}, cm^{-1}): 3364, 3313, 3177, 2920, 2850, 2189, 1710, 1668, 1371, 1051, 766. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.9 (1H, d, J = 7.8 Hz), 7.7 (1H, t, J = 7.5 Hz), 7.4–7.5 (3H, m), 7.2–7.3 (1H, t, J = 8.4 Hz), 6.8 (1H, s), 6.8 (2H, s), 4.4 (1H, s), 3.7 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 159.5, 159.2, 157.9, 153.4, 152.1, 144.8, 132.9, 129.6, 124.6, 122.4, 119.7, 119.1, 116.5, 113.8, 112.9, 111.9, 103.8, 57.8, 54.9, 36.8.[3b]
5. 2-Amino-4-(pyridin-4-yl)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*] chromene-3-carbonitrile (**4e**): FT-IR (KBr, νmax, cm $^{-1}$): 3455, 2973, 2193, 1717, 1639, 1598, 1381, 1273. ^{1}H NMR (300 MHz, DMSO-d_6): 4.53 (s, 1H, CH), 7.33 (d, J = 6.0 Hz, 2H), 7.48–7.55 (m, 4H, NH_2), 7.75 (dt, J = 7.8,1.2 Hz, 1H); 7.92 (dd, J = 7.8,1.2 Hz, 1H); 8.52 (d, J = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 36.9, 56.9, 103.0, 113.4, 117.1, 119.4, 123.0, 123.4, 125.5, 133.6, 150.2, 152.2, 152.8, 154.6, 158.6, 160.1.[45]
6. 6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**4f**): FT-IR (KBr, ν_{max}, cm $^{-1}$): 3450, 3370, 2195, 1645, 1610, 1605, 1446. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.91 (s, 3H), 4.74 (s, 1H), 6.98 (s, 2H), 7.45–7.16 (m, 5H), 11.98 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6, δ, ppm): 11.5, 25.1, 70.8, 112.0, 126.2, 127.4, 130.1, 131, 140.2, 144.1 152.3, 160.5.[55]
7. 6- Amino- 3-methyl- 4-(4-chlorophenyl) -1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**4g**): FT-IR (KBr, ν_{max}, cm^{-1}): 3380, 3281, 2193, 1622, 1454. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.80 (s, 3H), 4.59 (s, 1H), 6.7 (s, 2H), 7.20 (d, 2H), 7.31 (d, 2H), 12.1 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6, δ. ppm): 11.5, 24.3, 70.2, 112, 126.8, 127.3, 130.2, 134.4, 141.3, 142, 153.5, 160.6.[55]
8. 6- Amino-3- methyl-4 -(4-nitrophenyl)-1, 4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**4h**): FT-IR (KBr, ν_{max}, cm^{-1}): 3439, 3378, 2180, 1651, 1597, 1516, 1456. ^{1}H NMR (300 MHz, DMSO-d_6, δ,

ppm): 1.98 (s, 3H), 4.71 (s, 1H), 6.94 (s, 2H), 7.49 (d, 2H), 8.14 (d, 2H), 11.65 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6, δ, ppm): 11.4, 23.5, 70.8, 112.8, 128, 129, 130.1, 135.5, 141.8, 150.2, 154.2, 160.8.[55]

9. 6- Amino- 3-methyl- 4-(4-methoxyphenyl) -1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**4i**): FT-IR (KBr, ν_{max}, cm^{-1}): 3480, 3259, 2181, 1610, 1442. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.78 (s, 3H), 3.85 (s, 3H), 4.60 (s, 1H), 6.88 (d, 2H), 6.89 (d, 2H), 7.20 (s, 2H), 12.08 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, δ, ppm): 10.1, 36.3, 55, 57.6, 107.7, 113.5, 114.3, 119, 136.8, 144.4, 156, 156.2, 160.5.[55]
10. 2-Amino-3-cyano-7,7-dimethyl-4- phenyl-5-oxo-5,6,7,8-tetra-4*H*-chromene (**4k**): FT-IR (KBr, ν_{max}, cm^{-1}): 733, 1027, 1065, 1125, 1264, 1385, 1444, 1515, 1592, 2198, 3324, 3471. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.30–7.10 (m, 5H), 5.85 (br, 2H, NH_2), 4.32 (s, 1H), 2.48 (br s, 2H), 2.25 (H-6a, J = 16.0 Hz), 2.15 (H-6b, J = 16.0 Hz), 1.10 (s, 3H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 195.1, 161.3, 157.7, 143.3, 127.6, 126.7, 126.0, 118.8, 113.0, 60.0, 49.9, 39.9, 35.0, 31.3, 28.1, 26.8.[56]
11. 2-Amino-3-cyano-7,7-dimethyl-4 -(4-chlorophenyl)-5-oxo-5,6,7,8-tetra-4*H*-chromene (**4l**): FT-IR (KBr, ν_{max}, cm^{-1}): 3380, 3323, 3183, 2959, 2188, 1675, 1635, 1603, 1365. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.30–7.10 (m, 4H), 6.30 (br s, 2H, NH_2), 4.28 (s, 1H), 2.46 (br s, 2H), 2.24 (H-6a, J = 16.0 Hz), 2.14 (H-6b, J = 16.0 Hz), 1.12 (s, 3H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 194.6, 161.1, 157.5, 141.9, 130.9, 127.9, 127.2, 118.4, 112.1, 58.1, 49.4, 38.9, 34.2, 30.9, 27.6, 26.3.[56]
12. 2-Amino-3-cyano-7,7-dimethyl-4- (4-nitrophenyl)-5-oxo-5,6,7,8-tetra-4*H*-chromene (**4m**): FT-IR (KBr, ν_{max}, cm^{-1}): 3314, 1043, 2191, 1514, 1603, 1112, 2971. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.14 (cd, 2H), 7.42 (cd, 2H), 6.50 (br s, 2H, NH_2), 4.48 (s, 1H), 2.52 (br s, 2H), 2.26 (H-6a, J = 16.0 Hz), 2.16 (H-6b, J = 16.0 Hz), 1.14 (s, 3H), 1.03 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm): 195.2, 162.1, 158.1, 150.9, 146.2, 128.1, 123.1, 118.1, 112.2, 58.5, 49.9, 40.1, 35.4, 31.6, 28.2, 27.0.[56]
13. 2-Amino-4- (4-methoxyphenyl)-7,7- dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4n**): FT-IR (KBr, ν_{max}, cm^{-1}): 3276, 3206, 3070, 2956, 2183, 1702, 1644, 1608, 1482, 1223. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.04–7.07 (d, 2H), 6.83 (s, 2H), 6.79–6.82 (d, 2H), 4.14 (s, 2H), 3.72 (s, 3H), 2.22 (d, 2H), 2.08 (d, 1H), 1.08 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO, δ, ppm): 196.1, 162.5, 158.8, 158.3, 137.2, 128.6, 120.2, 114.0.[57]
14. 2-Amino-5-oxo-4-(thiophen-2-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4o**): FT-IR (KBr, ν_{max}, cm^{-1}): 3363,3323, 3178, 2956, 2374, 2192, 1679, 1664, 1650, 1608,1409, 1359,1209, 1135, 1000, 709, 626, 536, 501. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 2.03 (m, 2H), 2.36 (m, 1H), 2.44 (m, 1H), 2.56 (m, 2H), 4.56 (s, 2H, NH), 4.8 (s, 1H), 6.89 (dd, J = 5.1 Hz, J = 1.2 Hz,1H), 6.98 (d, J = 3.2 Hz, 1H), 7.12 (d, J = 5.1 Hz, 1H).[51]
15. 2-Amino-3-ethylacetato-4-(phenyl)-7,7- dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran (**4p**): FT-IR (KBr, ν_{max}, cm^{-1}): 3423, 3265, 3020, 2980, 1667, 1614, 1520, 1462, 1378. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.01 (s, 3H), 1.08 (s, 3H), 1.24 (t, 3H), 2.16–2.25 (m, 2H), 2.34 (s, 2H), 4.24 (q, 2H), 4.37 (s, 1H), 5.52 (brs, 2H, D_2O exchangeable), 7.12–7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 19.12, 26.52, 27.65, 31.44, 35.56, 39.68, 50.15, 60.63, 71.47, 113.09, 126.42, 126.86, 127.03, 142.54, 156.68, 161.87, 172.42, 196.01.[58]
16. Ethyl-2-amino-4- (4-chlorophenyl)-7,7- dimethyl-5-oxo-5,6,7,8- tetrahydro-4*H*-chromene-3-carboxylate (**4q**): FT-IR (KBr, ν_{max}, cm^{-1}): 3480, 3327, 1688, 1660, 1525, 1206. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.96 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.17 (t, J = 7.32, 3H, CH_3), 2.17 and 2.25 (J = 16.04 Hz, 2H), 2.41 (s, 2H); 4.02–4.04 (m, 2H), 4.46 (s, 1H), 6.20 (s, br, 2H, NH_2), 7.15–7.20 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$, δ, ppm): 14.18, 27.31, 29.09, 32.21, 33.39, 40.58, 50.62, 59.74, 81.04, 116.33, 127.86, 129.62, 131.6, 144.38, 158.26, 161.46, 168.92, 196.40.[59]
17. Ethyl-2-amino-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo -5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**4r**): FT-IR (KBr, ν_{max}, cm^{-1}): 3471, 3335, 2996, 1685, 1654, 1508, 1341, 1204. ^{1}H NMR ($CDCl_3$, δ, ppm): 0.93 (3H, s), 1.07 (3H, s), 1.11 (3H, t, J = 7 Hz), 2.11 (1H, d, J = 16.3 Hz), 2.23 (1H, d, J = 16.3 Hz), 2.43 (2H, br s), 4.06 (2H, q, J = 7 Hz), 4.76 (1H, s), 6.32 (2H, br s, NH_2), 7.42 (2H, d, J = 8.7 Hz), 8.06 (2H, d, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, δ, ppm): 14.23, 27.29, 29.07, 32.25, 34.30, 40.61, 50.57, 59.87, 79.24, 115.52, 123.19, 129.24, 146.28, 153.56, 158.46, 162.08, 168.59, 196.32.[60]
18. Ethyl-2-amino-7,7- dimethyl-5-oxo-4-(*p*-tolyl)-5,6,7,8 -tetrahydro-4*H*-chromene-3-carboxylate (**4s**): FT-IR (KBr, ν_{max}, cm^{-1}): 3408, 3293, 2980, 1689, 1668, 1623, 1523, 1472, 1366. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 7.52 (s, 2H), 7.02–6.98 (m, 4H), 4.45 (s, 1H), 3.97–3.90 (m, 2H), 2.56–2.42 (m, 2H), 2.25 (d, 1H, J = 16.8 Hz), 2.20 (s, 3H), 2.04 (d, 1H, J = 16 Hz), 1.10 (t, 3H, J = 8 Hz), 1.03 (s, 3H),

0.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 195.7, 167.9, 161.9, 159.0, 143.3, 134.6, 128.2, 127.5, 115.6, 77.9, 58.7, 49.9, 32.7, 31.8, 28.6, 26.3, 20.5, 14.1.[61]

3 | RESULTS AND DISCUSSION

A literature survey revealed that the examination of the catalytic potency of $Ag_3[PMo_{12}O_{40}]$ in the promotion of organic transformations is very rare.[44b] The structure of the catalyst was well characterized using FT-IR spectroscopy and ICP analysis. Elemental analysis clearly demonstrated that all the protons of the parent Keggin acid were substituted by silver cations. By looking at the structure of the aforementioned neutral salt, it was expected to gain proton sites upon interaction with the reaction media by either the acidic dissociation of lattice water or the reduction of the metal cations.[62] Thus, $Ag_3[PMo_{12}O_{40}]\cdot nH_2O$ potentially possesses Lewis acidity originating from metal ions as electron pair accepters as well as Brønsted acidity which makes it an ideal candidate for acting as a catalyst in various organic transformations.

In continuation of our interest in the catalysed synthesis of heterocyclic compounds[42b]via MCRs,[39c] using heteropolyacids and their POMs as efficient catalysts[63] under green conditions,[64] we focused our attention on a Keggin-type heteropolyacid, $Ag_3[PMo_{12}O_{40}]\cdot nH_2O$. Compared with plentiful investigations on the catalytic activity of the salt of Keggin-type polyoxotungstate,[5b,65] the study of the catalytic effectiveness of salt of Keggin-type polyoxomolybdate has been largely overlooked.[42b] Thus, we thought it worthwhile to extend our research activities to the synthesis of various heteropolyacids and examine their catalytic activities in various organic transformations. Thus, we prepared $Ag_3[PMo_{12}O_{40}]$ and studied its catalytic activity as a green and effective catalyst in the synthesis of a heterocyclic system via MCR.

To this end, the reaction of benzaldehyde, malononitrile and 4-hydroxycoumarin expecting to afford the corresponding 4*H*-pyran was selected as a model reaction. Initially, the reaction was performed in the absence of any catalyst in water. In the absence of catalyst, the model reaction proceeded very slowly and in a long reaction time only a trace amount of the desired product was detected showing the necessity of the presence of the catalyst. The model reaction was performed in the presence of a catalytic amount of $Ag_3[PMo_{12}O_{40}]\cdot nH_2O$. The progress of the reaction was monitored by TLC (using 7:3 *n*-hexane–ethyl acetate as eluent). It was observed that the model reaction proceeded smoothly along with clean conversion of starting materials, resulting in the formation of the expected product. To secure the optimal reaction conditions, the solvent, amount of catalyst loading and temperature were varied in the three-component reaction involving benzaldehyde, 4-hydroxycoumarin and malononitrile as the model reaction. The results are summarized in Table 1. The influences of various polar and non-polar solvents such as H_2O, EtOH, EtOH–H_2O, dimethylformamide (DMF), CH_3CN and CH_2Cl_2, as well as solvent-free conditions, were investigated in the model reaction.

As evident from Table 1, when the model reaction was conducted in CH_2Cl_2, the expected product **4a** was obtained in only 52% yield (Table 1, entry 1). In DMF or CH_3CN, product **4a** was obtained in 45 and 40% yields, respectively (Table 1, entries 2 and 3). Furthermore, the model reaction in refluxing EtOH afforded the desired product in 83% yield (Table 1, entry 5). Then, water as the greenest solvent was examined which afforded the desired compound **4a** in 73% yield (Table 1, entry 6). When EtOH–H_2O (1:1) was used under reflux conditions, to our delight the desired target **4a** was obtained in 95% yield (Table 1, entry 7). Thus, EtOH–H_2O was selected as the solvent of choice.

In order to find the optimal reaction temperature, the model reaction was run in the presence of $Ag_3[PMo_{12}O_{40}]$ in EtOH–H_2O at ambient temperature which afforded a yield of only 40% (Table 1, entry 8). However, when the model reaction was performed in refluxing EtOH–H_2O the desired product was obtained in the highest yield (95%) (Table 1, entry 6).

As a final point, for finding the influence of the quantity of catalyst, the model reaction was performed in the absence of catalyst which was unsuccessful. (Table 1,

TABLE 1 Optimization of reaction conditions for synthesis of 4*H*-pyrans

Entry	Solvent	Temperature	Time (min)	Catalyst amount (g)	Yield (%)
1	CH_2Cl_2	Reflux	70	0.05	52
2	DMF	Reflux	80	0.05	45
3	CH_3CN	Reflux	70	0.05	40
4	EtOH	Reflux	80	0.05	83
5	H_2O	Reflux	70	0.05	73
6	EtOH/H_2O	Reflux	80	0.05	95
7	EtOH/H_2O	Reflux	60	0.05	87
8	EtOH/H_2O	Room temp.	80	0.05	40
9	EtOH/H_2O	Reflux	80	No catalyst	Trace
10	EtOH/H_2O	Reflux	80	0.01	35
11	EtOH/H_2O	Reflux	80	0.07	95

entry 9). In the presence of 0.01 g of $Ag_3[PMo_{12}O_{40}]$ the desired product was isolated in 35% yield indicating the requirement of the presence of the catalyst for the reaction to the progress to completion (Table 1, entry 10). Expectedly, the yield was increased from 35 to 95% on increasing the catalyst loading (from 0.01 to 0.05 g; Table 1, entries 6 and 10). Notably, further increasing the $Ag_3[PMo_{12}O_{40}]$ loading (from 0.05 to 0.07 g) resulted in no appreciable change in yield (Table 1, entry 11). Thus, 0.05 g of catalyst was found to be the optimal catalyst loading (Table 1, entry 6). The best result was obtained when the reaction was run in the presence of 0.05 g (mol%) of catalyst in refluxing EtOH–H_2O, in which the corresponding 4*H*-pyran (**4a**) was formed in 95% yield in 60 min (Table 1, entry 6).

Based on the optimal reaction conditions, the substrate scope and limitation of the synthesis of 4*H*-pyrans in the presence of 0.05 g of $Ag_3[PMo_{12}O_{40}]$ (as catalyst under reflux condition in EtOH–H_2O) were investigated. The generality of this approach was investigated using various heterocyclic aldehydes such as thiophene-2-carbaldehyde, pyridine-4-carbaldehyde and differently substituted benzaldehydes, bearing either electron-releasing or electron-withdrawing moieties in the *ortho*, *meta* and *para* positions, with malononitrile and either dimedone or 4-hydroxycoumarin or 3-methyl-4*H*-pyrazole-5(4*H*)-one under already secured optimal reaction conditions (Scheme 1). In all cases the corresponding 4*H*-pyran derivatives were obtained in good to excellent yields in relatively short times without detection of any by-products. The results are summarized in Table 2.

As can be seen, aldehydes containing electron-releasing groups such as 4-MeO and 4-Me as well as electron-withdrawing groups such as 3-NO_2 and 4-Cl

TABLE 2 Synthesis of 4*H*-pyrans in presence of $Ag_3[PMO_{12}O_{40}]\cdot nH_2O$ in water under reflux condition

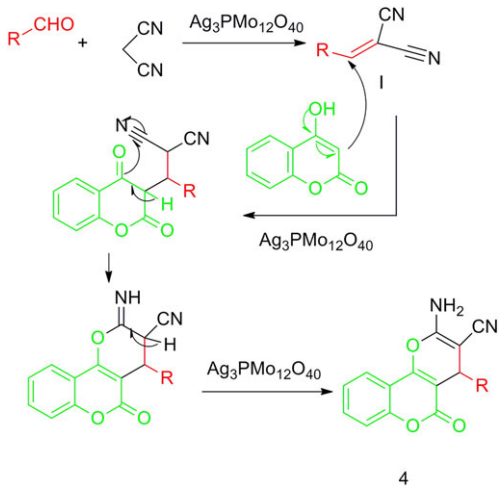
Entry	Aldehyde	Carbonyl compound (3)	Ethyl cyanoacetate/ malononitrile, X = CN/COOEt (2)	Product (4)	Yield (%)	Time (min)	M.p., found (°C)	M.p., lit. (°C)	Ref.
1	C_6H_5CHO	**3a**	**2a**	**4a**	95	60	257–259	256–257	[32,35,45,46]
2	4-Cl-C_6H_4CHO	**3a**	**2a**	**4b**	91	40	261–263	262–264	[32,35,45,46]
3	4-NO_2-C_6H_4CHO	**3a**	**2a**	**4c**	89	60	253–255	252–254	[32,35,45,46]
4	4-OCH_3-C_6H_4CHO	**3a**	**2a**	**4d**	87	80	236–238	238–240	[32,35,45,46]
5	Pyridine-4-carbaldehyde	**3a**	**2a**	**4e**	85	85	249–251	250–252	[45]
6	C_6H_5CHO	**3b**	**2a**	**4f**	95	70	244–246	244–246	[47]
7	4-Cl-C_6H_4CHO	**3b**	**2a**	**4g**	89	90	236–238	234–236	[47]
8	4-NO_2-C_6H_4CHO	**3b**	**2a**	**4h**	87	90	246–248	248–250	[47]
9	4-OCH_3-C_6H_4CHO	**3b**	**2a**	**4i**	95	110	210–212	210–212	[47]
10	Thiophene-2-carboxaldehyde	**3b**	**2a**	**4j**	87	110	189–191	190–191	[48]
11	C_6H_5CHO	**3c**	**2a**	**4k**	97	90	229–231	231–232	[49]
12	4-Cl-C_6H_4CHO	**3c**	**2a**	**4l**	92	110	214–215	217–219	[50]
13	4-NO_2-C_6H_4CHO	**3c**	**2a**	**4m**	93	130	179–181	180–183	[50]
14	4-OCH_3-C_6H_4CHO	**3c**	**2a**	**4n**	85	150	195–197	197–199	[50]
15	Thiophene-2-carbaldehyde	**3c**	**2a**	**4o**	85	125	212–213	210–212	[51]
16	C_6H_5CHO	**3c**	**2b**	**4p**	88	120	148–150	151–153	[52]
17	4-Cl-C_6H_4CHO	**3c**	**2b**	**4q**	90	100	153–156	153–154	[52]
18	4-NO_2-C_6H_4CHO	**3c**	**2b**	**4r**	95	110	153–154	154–156	[52]
19	4-CH_3-C_6H_4CHO	**3c**	**2b**	**4s**	93	100	149–151	151–152	[52]
20	Thiophene-2-carbaldehyde	**3c**	**2b**	**4t**	90	110	162–165	162–165	[53]

were fruitfully employed as substrates. The reaction of benzaldehyde, malononitrile and 4-hydroxycoumarin **3a** provided the desired product **4d** after 80 min in 87% yield (Table 2, entry 4). Aldehydes containing electron-donating groups containing 4-NO_2 or 4-OMe provided the desired products **4c** and **4d** in 89 and 87% yields, respectively (Table 2, entries 3 and 5). Moreover, aldehydes containing electron-withdrawing groups including 4-Cl and 3-NO_2 gave the corresponding products **4a** and **4b** in 95 and 91% yields, respectively (Table 2, entries 1 and 2). In the following, as mentioned above, for library validation, we examined 3-methyl-4*H*-pyrazole-5(4*H*)-one and dimedone instead of 4-hydroxycoumarin, which gave the corresponding products in good to excellent yields.

All products were known and identified by comparison of their physical (melting points) and spectral (FT-IR spectra) data with those of authentic samples which were found to be identical. The FT-IR spectrum of **4n** showed absorption bands related to NH_2 group at 3276 and 3206 cm^{-1}. CN and carbonyl groups showed absorption bands at 2183 and 1702 cm^{-1}. The ^1H NMR spectrum exhibited two singlet peaks at 0.97 and 1.08 ppm related to CH_3 groups. Two doublet peaks at 2.08 and 2.22 ppm corresponded to aliphatic hydrogens. The singlet peak at 3.72 ppm is related to methoxy group. The singlet peak at 6.83 ppm is related to 2H in NH_2. Also, the singlet peak at 4.14 ppm is related to H-4. The four aromatic protons appeared at 7.04–7.07 and 6.79–6.82 ppm as doublet peaks.[57]

To extend our study, we also prepared $Ag_3[PW_{12}O_{40}]$ in accordance with a method previously reported.[66] The catalytic activity of $Ag_3[PW_{12}O_{40}]$ was compared with that of $Ag_3[PMo_{12}O_{40}]$. The same model reaction was performed in the presence of $Ag_3[PW_{12}O_{40}]$ and $Ag_3[PMo_{12}O_{40}]$ as catalysts in water under reflux condition. The results are summarized in Table 3. The results indicated that the silver salt of dodecamolybdophosphate showed better catalytic activity in an acid-catalysed reaction compared with dodecatungstophosphate.

A probable mechanism for the $Ag_3[PMo_{12}O_{40}]$-catalysed transformations is shown in Scheme 2. Initially, the Knoevenagel coupling of aldehydes with malononitrile affords intermediate (I). Next, the subsequent 1,4-conjugate addition of 4-hydroxycoumarin to intermediate (I) followed by cyclization gives the desired products.[18,19,67]



SCHEME 2 Suggested probable mechanism for the of synthesis of 4H-pyrans

To reveal the advantages of this catalyst, its catalytic activity in the model reaction involving benzaldehyde, malononitrile and 4-hydroxycoumarin was compared with those of previously reported systems (Table 4). As evident from Table 4, the catalytic activity of $Ag_3PMo_{12}O_{40}$ was compared with other catalysts such as [DMAP-PEG_{1000}-DI L][BF_4],[68] nano-ZnO,[69] crown ether complex cation ionic liquids (CECILs),[70] ammonium acetate,[71] titanium dioxide nanowires,[72] nanomagnetic double-charged diazoniabicyclo[2.2.2]octane dichloride silica hybrid (Fe_3O_4@SiO_2/DABCO),[73] surfactant-modified bentonite (CTMAB-bentonite),[74] hexamethylenetetramine,[35] SiO_2/$H_3PW_{12}O_{40}$ nanohybrid,[75] $RuBr_2(PPh_3)_4$,[45] sodium malonate,[76] NaCl,[77] $(NH_4)_{42}[MoVI_{72}MoV_{60}O_{372}(CH_3COO)_{30}(H_2O)_{72}]$, a Keplerate-type giant-ball nanoporous isopolyoxomolybdate,[78] silica-supported molybdic acid,[79] $KNaC_4H_4O_6{\cdot}4H_2O$ (potassium sodium tartrate)[80] and polypyrrole/Fe_3O_4/CNT[81] that were previously used as catalysts in the same reaction. The results showed that compared to the other catalysts, our designed catalyst can catalyse the reaction in an appropriate manner. Moreover, it supplies the desired products in short reaction times. From the green chemistry point of view, the reusability of the catalyst and using water as the reaction medium render this catalyst green and eco-friendly. Notably, the importance of this work is introducing a catalyst with potential application for improving organic reactions and the synthesis of 4*H*-pyrans as a model organic transformation.

TABLE 3 Catalytic activity of $Ag_3[PW_{12}O_{40}]$ compared with that of $Ag_3[PMo_{12}O_{40}]$

Entry	R^1	Carbonyl compound (3)	Ethyl cyanoacetate/malononitrile, X = CN/COOEt (2)	Catalyst	Product (4)	Yield (%)	Time (min)
1	H	**3a**	**2a**	$Ag_3[PMo_{12}O_{40}]$	**4a**	95	60
2	H	**3a**	**2a**	$Ag_3[PW_{12}O_{40}]$	**4a**	40	180

TABLE 4 Comparison of catalytic activity of $Ag_3[PMO_{12}O_{40}]\cdot nH_2O$ with that of previously reported catalysts

Entry	Catalyst	Time	Catalyst amount	Temperature	Solvent	Yield (%)	Ref.
1	[DMAP-PEG_{1000}-DI L][BF_4]	30 min	0.2 mmol	Reflux	H_2O	92	[68]
2	Nano-ZnO	3 h	10 mol%	70°C	H_2O	87	[69]
3	Crown ether complex cation ionic liquids (CECILs)	15 min	30 mol%	Reflux	EtOH	90	[70]
4	Ammonium acetate	3 min	15 mol%, 0.15 mmol, 11.7 mg	Reflux	EtOH	94	[71]
5	Titanium dioxide nanowires	60 min	0.03 mmol (3 mol%	Reflux	EtOH–H_2O	90	[72]
6	Nanomagnetic double-charged diazoniabicyclo[2.2.2]octane dichloride silica hybrid (Fe_3O_4@SiO_2/DABCO)	35 min	0.05 g	80°C	H_2O	87	[73]
7	Surfactant-modified bentonite (CTMAB-bentonite)	6 min	0.03 g	70°C	H_2O–EtOH	89	[74]
8	Hexamethylenetetramine	15 min	10 mol%	Reflux	EtOH	92	[35]
9	$SiO_2/H_3PW_{12}O$	20 min	0.02 g	80°C	Solvent-free	94	[75]
10	$RuBr_2(PPh_3)_4$	30 min	5.0 mol%	Reflux	MeOH	80	[45]
11	Sodium malonate	20	10 mol%	70°C	H_2O	94	[76]
12	NaCl	20	5 mol%	Room temp.	H_2O–EtOH	91	[77]
13	$(NH_4)_{42}[Mo^{VI}_{72}Mo^{V}_{60}O_{372}(CH_3COO)_{30}(H_2O)_{72}]$, {$Mo_{132}$} a Keplerate-type giant-ball nanoporous isopolyoxomolybdate	12 min	0.07 g	Room temp.	H_2O–EtOH	92	[78]
14	Silica-supported molybdic acid	40 min	5 mol%	Reflux	H_2O–EtOH	94	[79]
15	$KNaC_4H_4O_6\cdot 4H_2O$ (potassium sodium tartrate)	30 min	10 mol%	40°C	H_2O–EtOH	85	[80]
16	Polypyrrole/Fe_3O_4/CNT	30 min	0.032 g	90°C	Solvent-free	89	[3]
17	$Ag_3[PMO_{12}O_{40}]\cdot nH_2O$	60 min	0.05 g	Reflux	Water	95	This work

To elucidate whether $Ag_3[PMo_{12}O_{40}]$ could really act as a heterogeneous catalyst and in view of the importance of reusability for large-scale applications, the reusability of $Ag_3[PMo_{12}O_{40}]$ was examined. The model reaction was performed in the presence of fresh catalyst; at the end of the reaction, it was separated, washed, dried and subjected to the next reaction run. The reusability of the catalyst was investigated for four successive reaction runs. The results in Figure 3 show that the catalyst could be recovered and reused for up to four reaction runs without appreciable loss in its catalytic activity.

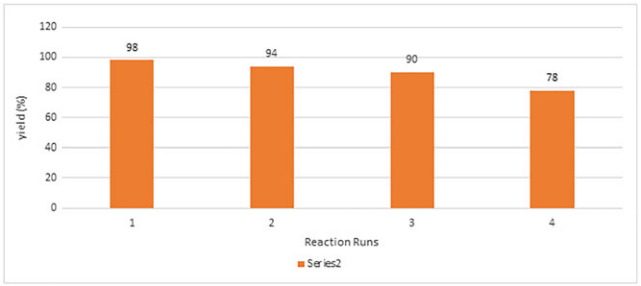


FIGURE 3 Recyclability of catalyst for the synthesis 4*H*-pyrans

4 | CONCLUSIONS

We have developed a highly effective and green strategy for a one-pot three-component synthesis of 4*H*-pyran derivatives as biologically potent compounds employing $Ag_3[PMo_{12}O_{40}]$ as an effective, green, heterogeneous, easily separable and recyclable catalyst in EtOH–H_2O. This strategy offers substantial improvements in reaction rates and yields. $Ag_3[PMo_{12}O_{40}]$ as a green catalyst in EtOH–H_2O can be recycled and used for several reaction runs with high efficiency. This catalyst was effectively employed for three-component reactions involving various 2-amino-4*H*-pyrans in a one-pot fashion. This strategy benefits from using EtOH–H_2O as solvent and that the catalyst can be reused several times giving high yields with a relatively short reaction times. These merits make this doubly green approach applicable for large-scale production.

ACKNOWLEDGMENTS

The authors appreciate partial financial supports from Alzahra University. MMH is also thankful to Iran National Science Foundation (INSF) for the individual given grant. MM is thankful to research council of Ferdowsi University of Mashhad, Mashhad, Iran.

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How to cite this article: Tamimi M, Heravi MM, Mirzaei M, Zadsirjan V, Lotfian N, Eshtiagh-Hosseini H. $Ag_3[PMo_{12}O_{40}]$: An efficient and green catalyst for the synthesis of highly functionalized pyran-annulated heterocycles via multicomponent reaction. *Appl Organometal Chem*. 2019;33:e5043. https://doi.org/10.1002/aoc.5043