

Magnetic Fe_3O_4 Nanoparticles as Efficient and Reusable Catalyst for the Green Synthesis of 2-Amino-4*H*-chromene in Aqueous Media

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A simple and efficient protocol for one-pot three-component coupling of aldehyde, malononitrile, and resorcinol in water using magnetically recoverable Fe_3O_4 nanoparticles at room temperature is reported. The high yields of products and short reaction time were attributed to the nanosize of about 18 nm in which the catalyst could act as a nanoreactor. This methodology is found to be fairly general and catalyst is easily separated by magnetic devices and can be reused without any apparent loss of activity for the reaction.

In recent years, being focused on green chemistry using environmentally benign reagents and conditions is one of the most fascinating developments in synthesis of widely used organic compounds. The use of water as a promising solvent for organic reactions has received considerable attention in the arena of organic synthesis owing to its green credentials,[1–3] and organic synthesis in aqueous media offering key advantages such as rate enhancement and insolubility of the final products, which facilitates their isolation by simple filtration.

Because of increasing environmental concerns, the development of clean synthetic procedures has become crucial and demanding research. In this sense, heterogeneous organic reactions have many advantages, such as ease of handling separation, recycling, and environmentally safe disposal.[4,5]

On the other hand magnetic nanoparticles (MNPs) have received a great deal of attention because of their potential biomedical applications in fields such as drug delivery,[6,7] magnetic resonance imaging,[8] biomolecular sensors,[9] bioseparation,[10] and magneto-thermal therapy.[11] Additionally, recent studies show that magnetic nanoparticles are excellent catalysts for organic reactions.[5,12–14] Additionally, the magnetic properties make possible the complete recovery of the catalyst by means of an external magnetic field. These advantages become even more attractive if such reactions can be conducted in aqueous media.

Multicomponent coupling reaction (MCR) is a powerful synthetic tool for the synthesis of biologically active compounds.[15–17] Heterocycles containing the chromene moiety show interesting features that make them attractive targets for MCRs. The 2-amino-chromenes are widely employed as pigments, cosmetics, potential agrochemicals, and represent an important class of chemical entities being the main constituents of many natural products.[18–20]

Among different types of chromene systems, 2-amino-4*H*-chromenes are of particular utility as they belong to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced anticoagulant, diuretic, spasmolitic, and antianaphylactic activities.[21–26] The current interest in 2-amino-4*H*-chromene derivatives arises from their potential application in the treatment of human inflammatory TNFα-mediated diseases, such as psoriatic arthritis and rheumatoid and in cancer therapy.[27–29] Many of the methods reported for the synthesis of these compounds[30–34] are associated with the use of hazardous organic solvents, long reaction time, use of toxic amine-based catalysts, and lack of general applicability. Along with other reaction parameters, the nature of the catalyst plays a significant role in determining yield, selectivity, and general applicability. Thus, development of an inexpensive, mild, general, and reusable catalyst for MCRs remains an issue of interest.

In this paper, we report convenient and facile multicomponent, one-pot synthesis of 2-amino-4*H*-chromene in water using nanosized magnetic Fe_3O_4 as efficient and eco-friendly heterogeneous catalyst (Scheme 1).

Experimental

Materials. Chemical reagents in high purity were purchased from the Merck Chemical Co. All materials were of commercial reagent grade.

Apparatus. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in DMSO-d_6 solutions and are reported as parts per million (ppm) downfield from tetramethylsilane as internal standard. The abbreviations used are: singlet (s), doublet (d), triplet (t), and multiplet (m). FT-IR spectra were obtained with potassium bromide pellets in the range 400–4000 cm^{-1} with a Perkin-Elmer 550 spectrometer. A mass spectrum was recorded with a QP-1100EX Shimadzu spectrometer. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer carried out on a Perkin-Elmer 240c analyzer. The UV–vis measurements were obtained with a GBC cintra 6 UV–vis spectrophotometer. Nanostructures were characterized using a Holland Philips Xpert, X-ray powder diffraction (XRD) diffractometer

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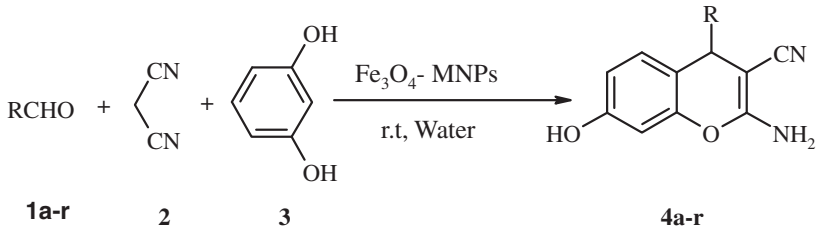


Scheme 1. Magnetic Fe_3O_4 nanoparticle catalyzed MCRs leading to 2-amino-4*H*-chromenes.

(Cu Kα, radiation, $\lambda = 0.154056$ nm), at a scanning speed of 2°/min from 10 to 100° (2θ). Scanning electron microscopy (SEM) was performed on a FEI Quanta 200 SEM operated at a 20 kV accelerating voltage. The samples for SEM were prepared by spreading a small drop containing nanoparticles onto a silicon wafer and being dried almost completely in air at room temperature for 2 h, and then were transferred onto SEM conductive tapes. Transmission electron microscopy (TEM) was performed with a Jeol JEM-2100UHR, operated at 200 kV.

Preparation of the Magnetic Fe_3O_4 Nanoparticles (MNPs). Fe_3O_4-MNPs were prepared using simple chemical coprecipitation described in the literature[35] with little modification. Typically, 20 mmol of $FeCl_3 \cdot 6H_2O$ and 10 mmol of $FeCl_2 \cdot 4H_2O$ were dissolved in 75 mL of distilled water in a three-necked bottom (250 mL) under Ar atmosphere for 1 h. Thereafter, under rapid mechanical stirring, 10 mL of NaOH (10 M) was added into the solution within 30 min with vigorous mechanical stirring and ultrasound treatment under continuous Ar atmosphere bubbling. After being rapidly stirred for 1 h, the resultant black dispersion was heated to 85 °C for 1 h. The black precipitate formed was isolated by magnetic decantation, exhaustively washed with double-distilled water until neutrality, and further washed twice with ethanol and dried at 60 °C in vacuum.

General Procedure for the Synthesis of 2-Amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene Derivatives. A mixture of resorcinol (1 mmol), aldehyde derivatives (1 mmol), malononitrile (1 mmol), H_2O (5 mL), and Fe_3O_4 nanoparticles (7 mol %) was stirred at room temperature for the appropriate time, as shown in Table 3. After completion of the reaction (TLC monitoring), the catalyst was separated by an external magnet and reused as such for the next experiment and the solvent was evaporated. The filtrate was concentrated to dryness, and the crude solid product was crystallized from EtOH to afford the pure 2-amino-3-cyano-7-hydroxy-4-substituted-4*H*-chromene derivatives (Table 3).

Spectral Data for New Compounds. 2-Amino-4-(3-chlorophenyl)-3-cyano-7-hydroxy-4*H*-chromene (4d): White solid; mp 106–108 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.739 (s, 1H, H-4), 6.382 (d, 1H, $J = 3$ Hz, H-Ar), 6.457 (dd, 1H, $J = 3$ Hz, $J = 9$ Hz, H-Ar), 6.591 (d, 1H, $J = 9$ Hz, H-Ar), 6.94 (s, 2H, NH_2), 7.04–7.305 (m, 4H, H-Ar), 9.731 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.32, 102.71, 112.96, 113.37, 113.66, 121.01, 128.23, 129.04, 129.75, 130.31, 130.38, 131.72, 145.79, 149.29, 157.69, 160.72; IR (KBr, cm^{-1}): 3423, 3338, 2192, 1656, 1582; Anal. Calcd for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38%. Found: C, 64.27; H, 3.65; N, 9.31%.

2-Amino-3-cyano-7-hydroxy-4-(3-hydroxyphenyl)-4*H*-chromene (4e): White solid; mp 215–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.490 (s, 1H, H-4), 6.391 (d, 1H, $J = 3$ Hz, H-Ar), 6.464 (dd, 1H, $J = 3$ Hz, $J = 9$ Hz, H-Ar), 6.521 (d, 1H, $J = 9$ Hz, H-Ar), 6.849 (s, 2H, NH_2), 6.539–7.085 (m, 4H, H-Ar), 9.335 (s, 1H, OH), 9.688 (s, 1H, 7-OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.04, 102.57, 112.79, 112.93, 114.38, 114.52, 121.19, 126.47, 128.89, 129.92, 130.39, 138.94, 149.22, 157.42, 158.42, 160.54; IR (KBr, cm^{-1}): 3415, 3336, 2188, 1651, 1586; Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.32; N, 9.99%. Found: C, 68.52; H, 4.26; N, 9.94%.

2-Amino-3-cyano-4-(2-fluorophenyl)-7-hydroxy-4*H*-chromene (4f): White solid; mp 218–221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.875 (s, 1H, H-4), 6.394 (d, 1H, $J = 3$ Hz, H-Ar), 6.464 (dd, 1H, $J = 3$ Hz, $J = 9$ Hz, H-Ar), 6.756 (d, 1H, $J = 9$ Hz, H-Ar), 6.918 (s, 2H, NH_2), 7.099–7.252 (m, 4H, H-Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.09, 102.59, 112.72, 112.97, 113.32, 114.64, 121.25, 125.87, 128.69, 130.93, 131.17, 138.74, 149.21, 158.02, 158.32, 160.44; IR (KBr, cm^{-1}): 3425, 3223, 2192, 1652, 1564; Anal. Calcd for $C_{16}H_{11}FN_2O_2$: C, 68.08; H, 3.93; N, 9.92%. Found: C, 68.02; H, 3.98; N, 9.88%.

2-Amino-3-cyano-7-hydroxy-4-(2-methoxyphenyl)-4*H*-chromene (4g): White solid; mp 222–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.772 (s, 3H, OMe), 4.971 (s, 1H, H-4), 6.370 (d, 1H, $J = 3$ Hz, H-Ar), 6.430 (dd, 1H, $J = 3$ Hz, $J = 10$ Hz, H-Ar), 6.808 (d, 1H, $J = 10$ Hz, H-Ar), 6.814 (s, 2H, NH_2), 6.816–7.171 (m, 4H, H-Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.42, 56.22, 102.41, 113.16, 113.32, 113.96, 121.12, 127.23, 128.34, 128.67, 130.43, 130.57, 138.68, 148.79, 157.39, 158.61, 160.42; IR (KBr, cm^{-1}): 3449, 3351, 2186, 1645, 1587; Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52%. Found: C, 69.31; H, 4.70; N, 9.58%.

2-Amino-4-(2,4-dichlorophenyl)-3-cyano-7-hydroxy-4*H*-chromene (4h): White solid; mp 256–258 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.121 (s, 1H, H-4), 6.397 (d, 1H, $J = 3$ Hz, H-Ar), 6.463 (dd, 1H, $J = 9$ Hz, $J = 3$ Hz, H-Ar), 6.696 (d, 1H, $J = 9$ Hz, H-Ar), 6.986 (s, 2H, NH_2), 7.193 (d, 1H, $J = 8$ Hz, H-Ar), 7.380 (dd, 1H, $J = 2$ Hz, $J = 8$ Hz, H-Ar), 7.571 (d, 1H, $J = 2$ Hz, H-Ar), 9.779 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.63, 102.72, 112.71, 112.91, 113.83, 113.97, 121.13, 121.63, 129.75, 129.95, 130.37, 142.04, 149.35, 155.62, 159.94, 160.69; IR (KBr, cm^{-1}): 3470, 3342, 2192, 1647, 1585; Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_2$: C, 57.68; H, 3.03; N, 8.41%. Found: C, 57.79; H, 3.08; N, 8.47%.

2-Amino-4-(2,6-dichlorophenyl)-3-cyano-7-hydroxy-4*H*-chromene (4i): White solid; mp 217–220 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.673 (s, 1H, H-4), 6.355 (d, 1H, $J = 3$ Hz,

H-Ar), 6.436 (dd, 1H, $J = 10$ Hz, $J = 3$ Hz, H-Ar), 6.555 (d, 1H, $J = 10$ Hz, H-Ar), 6.929 (s, 2H, NH_2), 7.271–7.535 (m, 3H, H-Ar), 9.735 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.42, 102.58, 112.91, 113.24, 113.54, 120.22, 120.93, 130.14, 130.25, 131.96, 146.32, 149.36, 157.79, 160.73; IR (KBr, cm^{-1}): 3465, 3336, 2191, 1648, 1588; Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_2$: C, 57.68; H, 3.03; N, 8.41%. Found: C, 57.64; H, 3.12; N, 8.48%.

2-Amino-3-cyano-7-hydroxy-4-(3,5-dimethoxyphenyl)-4*H*-chromene (4j): White solid; mp 191–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.672 (s, 6H, OMe), 4.517 (s, 1H, H-4), 6.282 (d, 1H, $J = 3$ Hz, H-Ar), 6.331 (dd, 1H, $J = 3$ Hz, $J = 9$ Hz, H-Ar), 6.458 (d, 1H, $J = 9$ Hz, H-Ar), 6.848 (s, 2H, NH_2), 6.97–7.28 (m, 3H, H-Ar), 9.735 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.62, 56.47, 102.77, 112.73, 113.82, 121.02, 128.64, 129.65, 130.22, 131.02, 143.06, 149.15, 156.63, 159.83, 160.72; IR (KBr, cm^{-1}): 3460, 3332, 2191, 1643, 1628; Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64%. Found: C, 66.57; H, 4.93; N, 8.59%.

2-Amino-3-cyano-7-hydroxy-4-(2-naphthyl)-4*H*-chromene (4k): White solid; mp 230–232 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.793 (s, 1H, H-4), 6.429 (d, 1H, $J = 3$ Hz, H-Ar), 6.444 (dd, 1H, $J = 3$ Hz, $J = 9$ Hz, H-Ar), 6.789 (d, 1H, $J = 9$ Hz, H-Ar), 6.935 (s, 2H, NH_2), 7.226–7.894 (m, 7H, H-Ar), 9.723 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 56.67, 102.59, 112.79, 113.27, 114.68, 114.95, 115.32, 116.21, 116.57, 121.14, 129.62, 129.83, 130.41, 131.36, 131.59, 143.11, 145.27, 146.79, 157.63, 160.67; IR (KBr, cm^{-1}): 3425, 3332, 2192, 1655, 1584; Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91%. Found: C, 76.36; H, 4.43; N, 8.86%.

2-Amino-3-cyano-4-(2-furyl)-7-hydroxy-4*H*-chromene (4l): White solid; mp 208–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.753 (s, 1H, H-4), 6.125 (d, 1H, $J = 2$ Hz, H-Ar), 6.332 (dd, 1H, $J = 2$ Hz, $J = 8$ Hz, H-Ar), 6.517 (d, 1H, $J = 8$ Hz, H-Ar), 6.949 (s, 2H, NH_2), 7.27–7.504 (m, 3H, H-furyl), 9.752 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.83, 102.81, 106.78, 110.31, 112.34, 112.93, 116.33, 120.97, 130.36, 149.55, 151.43, 155.57, 157.62, 161.33; IR (KBr, cm^{-1}): 3478, 3419, 2192, 1651, 1585; Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02%. Found: C, 66.07; H, 4.03; N, 11.06%.

2-Amino-3-cyano-7-hydroxy-4-(2-thienyl)-4*H*-chromene (4m): White solid; mp 228–231 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.968 (s, 1H, H-4), 6.374 (d, 1H, $J = 3$ Hz, H-Ar), 6.507 (d, 1H, $J = 3$ Hz, $J = 10$ Hz, H-Ar), 6.904 (d, 1H, $J = 10$ Hz, H-Ar), 6.914 (s, 2H, NH_2), 6.963–7.339 (m, 3H, H-thienyl), 9.746 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 53.87, 102.86, 106.94, 111.42, 112.39, 112.86, 116.53, 121.67, 130.97, 149.59, 153.49, 155.47, 157.69, 161.96; IR (KBr, cm^{-1}): 3459, 3421, 2192, 1652, 1588; Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36%. Found: C, 62.16; H, 3.69; N, 10.42%.

2-Amino-3-cyano-7-hydroxy-4-(5-methyl-2-furyl)-4*H*-chromene (4n): White solid; mp 179–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.149 (s, 3H, Me), 4.660 (s, 1H, H-4), 5.923 (d, 1H, $J = 2$ Hz, H-Ar), 5.981 (dd, 1H, $J = 2$ Hz, $J = 10$ Hz, H-Ar), 6.375 (d, 1H, $J = 10$ Hz, H-Ar), 6.536 (d, 1H, $J = 6$ Hz, H-furyl), 6.917 (s, 2H, NH_2), 6.938 (d, 1H, $J = 6$ Hz, H-furyl), 9.752 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.27, 53.86, 102.82, 106.74, 109.58, 110.32, 112.74, 120.96, 130.02, 146.79, 149.56, 151.40, 155.60, 157.82, 161.33; IR (KBr, cm^{-1}): 3437, 3333, 2189, 1649, 1586; Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44%. Found: C, 67.19; H, 4.48; N, 10.41%.

2-Amino-3-cyano-4-ethyl-7-hydroxy-4*H*-chromene (4o): Orange solid; mp 169–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.635 (t, 3H, $J = 6$ Hz, Me), 1.541 (qd, 2H, $J = 6$ Hz, $J = 8$ Hz, CH_2), 3.438 (t, 1H, $J = 8$ Hz, H-4), 6.326 (d, 1H, $J = 2$ Hz, H-Ar), 6.527 (dd, 1H, $J = 2$ Hz, $J = 10$ Hz, H-Ar), 6.710 (s, 2H, NH_2), 6.991 (d, 1H, $J = 2$ Hz, H-Ar), 9.607 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.62, 27.57, 43.76, 102.66, 107.94, 111.43, 112.26, 114.57, 121.69, 131.92, 156.58, 160.96; IR (KBr, cm^{-1}): 3460, 3332, 2193, 1650, 1625; Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95%. Found: C, 66.61; H, 5.52; N, 12.89%.

2-Amino-3-cyano-7-hydroxy-4-propyl-4*H*-chromene (4p): White solid; mp 160–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.778 (t, 3H, $J = 6$ Hz, Me), 1.011 (m, 2H, CH_3CH_2), 1.497 (m, 2H, CH_2CH), 3.358 (t, $J = 7$ Hz, 1H, H-4), 6.307 (d, 1H, $J = 2$ Hz, H-Ar), 6.503 (dd, 1H, $J = 2$ Hz, $J = 10$ Hz, H-Ar), 6.695 (s, 2H, NH_2), 6.959 (d, 1H, $J = 10$ Hz, H-Ar), 9.590 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.42, 26.65, 27.59, 43.78, 102.73, 107.93, 111.39, 112.27, 114.56, 121.65, 131.86, 156.58, 160.92; IR (KBr, cm^{-1}): 3466, 3338, 2193, 1648, 1620; Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17%. Found: C, 67.93; H, 6.18; N, 12.23%.

2-Amino-3-cyano-4-heptyl-7-hydroxy-4*H*-chromene (4q): White solid; mp 124–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.783 (t, $J = 6$ Hz, 3H, Me), 2.36 (m, 12H, $(CH_2)_6$), 3.358 (t, $J = 7$ Hz, 1H, H-4), 6.307 (d, 1H, $J = 2$ Hz, H-Ar), 6.503 (dd, 1H, $J = 2$ Hz, $J = 10$ Hz, H-Ar), 6.695 (s, 2H, NH_2), 6.959 (d, 1H, $J = 10$ Hz, H-Ar), 9.590 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.86, 24.69, 24.76, 26.42, 26.65, 26.88, 27.59, 43.78, 102.82, 107.94, 111.46, 112.23, 114.59, 121.67, 131.93, 156.69, 160.90; IR (KBr, cm^{-1}): 3482, 3328, 2197, 1647, 1589; Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78%. Found: C, 71.37; H, 7.76; N, 9.83%.

1,4-Bis(2-amino-3-cyano-7-hydroxy-4*H*-chromen-4-yl)-benzene (4r): Orange solid; mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.554 (s, 2H, H-4), 6.380 (d, 2H, $J = 3$ Hz, H-Ar), 6.455 (dd, 2H, $J = 3$ Hz, $J = 9$ Hz, H-Ar), 6.522 (d, 2H, $J = 9$ Hz, H-Ar), 6.826 (s, 4H, NH_2), 6.974–7.063 (m, 4H, H-Ar), 9.683 (s, 2H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 57.43, 102.62, 112.79, 112.82, 113.74, 113.92, 121.66, 128.85, 130.27, 144.02, 149.25, 159.93, 160.67; IR (KBr, cm^{-1}): 3427, 3330, 2191, 1650, 1588; Anal. Calcd for $C_{26}H_{18}N_4O_4$: C, 69.33; H, 4.02; N, 12.43%. Found: C, 69.39; H, 4.07; N, 12.49%.

Results and Discussion

In this paper, we describe a simple and high yielding protocol for the synthesis of 2-amino-4*H*-chromenes involving the three-component, one-pot condensation of aldehyde, malononitrile, and resorcinol using Fe_3O_4 nanoparticles as a novel and eco-friendly heterogeneous catalyst.

Characterization of the Prepared Fe_3O_4-MNPs. The magnetite nanoparticles of 18–20 nm were prepared by the well-known Massart's method[36] which consists of Fe(III) and

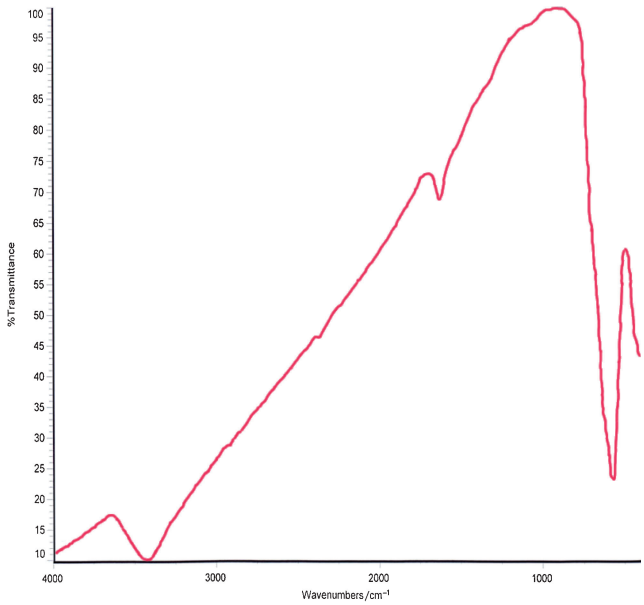


Figure 1. FT-IR spectrum of Fe_3O_4-MNPs.

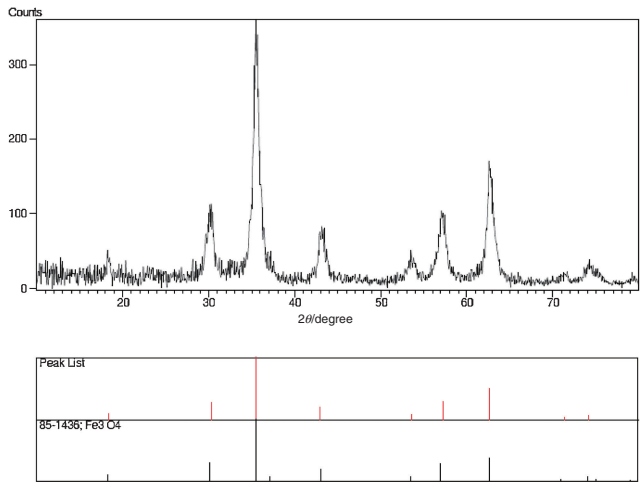


Figure 2. XRD pattern of Fe_3O_4-MNPs.

Fe(II) coprecipitation in alkaline solutions. Figure 1 shows the Fourier transform infrared (FTIR) spectrum of magnetic nanoparticles. The Fe–O stretching vibration near 580 cm^{-1}, O–H stretching vibration near 3432 cm^{-1}, and O–H deformed vibration near 1629 cm^{-1} were observed.[37]

Figure 2 presents the XRD pattern of the prepared MNPs. The position and relative intensities of all peaks confirm well with standard XRD pattern of Fe_3O_4 (JCPDS card No. 85-1436) indicating retention of the crystalline cubic spinel structure of MNPs. The XRD patterns of the particles show six characteristic peaks reveal a cubic iron oxide phrase ($2\theta =$ 18.35, 30.27, 35.53, 42.95, 53.60, 57.18, 62.69, 71.31, and 74.14°). These are related to their corresponding indices (110), (220), (311), (400), (331), (422), (511), (440), and (531) respectively. It is implied that the resultant nanoparticles are pure Fe_3O_4 with a spinel structure and that the grafting process did not induced any phase change of Fe_3O_4.[38]

The crystal size of MNPs can be determined from the XRD pattern by using Debye–Scherrer's equation.

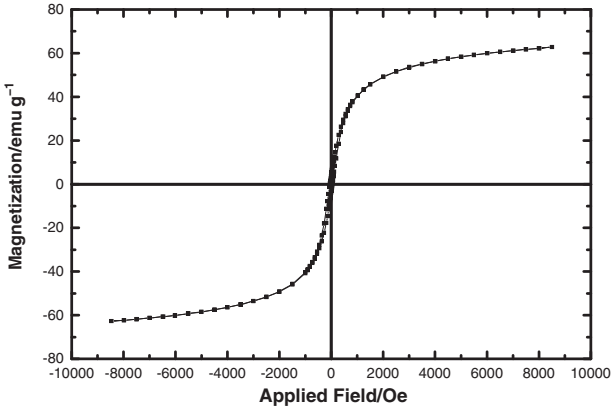


Figure 3. Magnetization curve for Fe_3O_4-MNPs at room temperature.

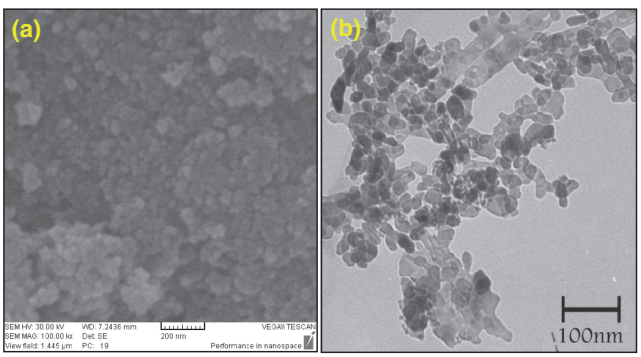


Figure 4. SEM (a) and TEM (b) images of MNPs.

$$D(hkl) = \frac{0.94\lambda}{\beta \cos\theta} \quad (1)$$

where $D(hkl)$ is the average crystalline diameter, 0.94 is the Scherrer's constant, λ is the X-ray wavelength, β is the half width of the XRD lines, and θ is the Bragg's angle in degrees. Here, the (311) peak of the highest intensity was picked out to evaluate the particle diameter of the nanoparticles. Size of MNPs were calculated to be 18 nm.

The magnetization curve for Fe_3O_4 nanoparticles is shown in Figure 3. Room-temperature specific magnetization (M) versus applied magnetic field (H) curve measurements of the sample indicate a saturation magnetization value (M_s) of 62.76 emu g^{-1}. We can also see that the magnetization curve follows a Langevin behavior over the applied magnetic field and the coercivity (H_C) could be ignored, which can be considered superparamagnetism.[39]

SEM and TEM images are shown in Figures 4a and 4b. The SEM image shows that magnetite nanoparticles have a mean diameter of about 18 nm and a nearly spherical shape in Figure 4a. The size and shape of synthesized nanoparticles are deduced from the TEM images in Figure 4b. The mean diameter of Fe_3O_4 nanoparticles is about 18–20 nm, which is consistent with SEM and XRD. Both images show the nanoparticles are well dispersed and uniform in shape and size.

Evaluation of the Catalytic Activity of MNPs through the Synthesis of 2-Amino-4*H*-chromene. In the preliminary stage of investigation we focused on systematic evaluation of different catalysts for the model reaction of benzaldehyde **1a**, malononitrile **2**, and resorcinol **3** at room temperature

in aqueous conditions. A wide variety of catalysts including $ZrCl_4$, VCl_3, $AlCl_3$, bulk Fe_3O_4, and Fe_3O_4-MNPs were employed to improve the yield for the specific synthesis of 2-amino-4*H*-chromene derivative. The results are presented in Table 1. Interestingly, when the reaction was carried out in the presence of 2 mol % Fe_3O_4-MNPs, it led to the desired product in 80% yield in 25 min (Table 1, Entry 6). The catalytic activity of Fe_3O_4-MNPs was evident when no product was obtained in the absence of the catalyst (Table 1, Entry 1).

Subsequent efforts were focused on optimizing conditions for formation of 2-amino-4*H*-chromene by using different amounts of Fe_3O_4-MNPs to determine their effects on the reaction (Table 2). As indicated, the best result was obtained with 7 mol % Fe_3O_4-MNPs. The reaction yield with increasing amount of Fe_3O_4-MNPs was not substantially increased.

The efficiency of water as solvent compared to various organic solvents was also examined (Table 3). In this study, it was found that water is a more efficient and superior solvent (Table 3, Entry 6) over other organic solvents (Table 3, Entries 1–5) with respect to reaction time and yield of the desired chromene.

Based on the above observations, we conducted the same reactions using various aldehydes **1a**–**1r**, malononitrile **2**, and resorcinol **3** in the presence of 7 mol % of Fe_3O_4-MNPs under optimal conditions. As expected, satisfactory results were observed, and the results are summarized in Table 4. Interestingly, a variety of aldehydes including acyclic, aromatic, and heteroaromatic aldehydes participated well in this reaction. It is noteworthy that methodology worked well for spatially hindered aldehydes (Table 4, Entries 6–11).

Encouraged by this achievement, the versatility of the reaction was explored further by extending the methodology to the synthesis of bis-4*H*-chromene. When *p*-phthalaldehyde was

Table 1. Influence of Different Catalysts for the Reaction of Benzaldehyde (**1a**), Malononitrile (**2**), and Resorcinol (**3**) at Room Temperature in Aqueous Medium

Entry	Catalyst[a)]	Time/min	Yield[b)]/%
1	None	150	—
2	$ZrCl_4$	70	55
3	VCl_3	50	68
4	$AlCl_3$	60	50
5	Fe_3O_4	50	60
6	Fe_3O_4-MNPs	25	80

a) Catalyst amount (2 mol %). b) Isolated yield of the pure compound.

Table 2. Optimizing the Reaction Conditions[a)]

Entry	Catalysts/mol %	Time/min	Yield[b)]/%
1	2	25	80
2	4	25	91
3	6	25	95
4	7	25	98
5	8	25	98

a) Malononitrile (1 mmol), benzaldehyde (1 mmol), and resorcinol (1 mmol) in H_2O (5 mL) was stirred at room temperature. b) Isolated yields.

Table 3. Solvent Screening for the Reaction between Malononitrile, Benzaldehyde, and Resorcinol[a)]

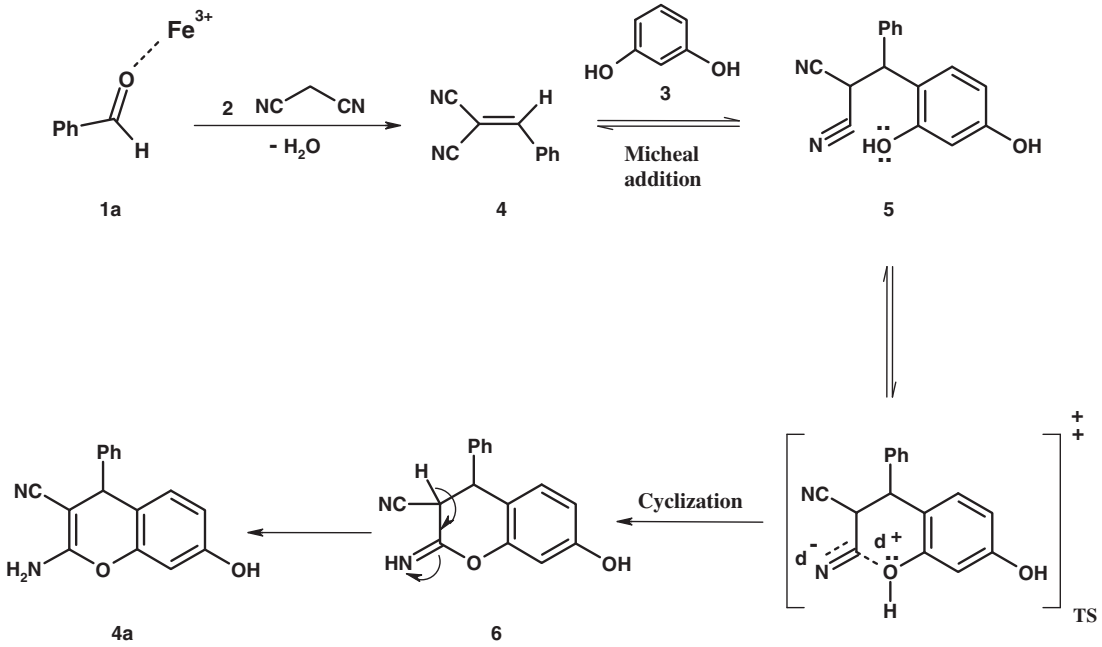
Entry	Solvent	Yield[b)]/%
1	Dichloromethane	30
2	Cyclohexane	15
3	Acetonitrile	42
4	EtOH	70
5	Acetone	70
6	Water	98
7	None	83

a) Fe_3O_4-MNPs (7 mol %), malononitrile (1 mmol), benzaldehyde (1 mmol), and resorcinol (1 mmol) in various solvents (5 mL) was stirred at room temperature. b) Isolated yields.

Table 4. Fe_3O_4-MNPs-Catalyzed Three-Component Condensations of Malononitrile, Aldehydes, and Resorcinol to Form 2-Amino-4*H*-chromenes

Entry	R	Product	Time/min	Yield[a)]/%	Mp/°C
1	C_6H_5	**4a**	25	98	234–237[d)]
2	4-MeC_6H_4	**4b**	28	95	183–186[d)]
3	4-MeOC_6H_4	**4c**	30	93	110–112[d)]
4	3-ClC_6H_4	**4d**	23	96	1106–109
5	3-HOC_6H_4	**4e**	30	97	2215–217
6	2-FC_6H_4	**4f**	25 (180)[b)]	97 (40)[c)]	2218–221
7	2-MeOC_6H_4	**4g**	35 (180)[b)]	95 (43)[c)]	2222–224
8	2,4-$Cl_2C_6H_3$	**4h**	20 (180)[b)]	95 (30)[c)]	2256–258
9	2,6-$Cl_2C_6H_3$	**4i**	20 (180)[b)]	95 (26)[c)]	217–220
10	3,5-$(MeO)_2C_6H_3$	**4j**	32 (180)[b)]	95 (25)[c)]	191–193
11	2-Naphthyl	**4k**	24 (180)[b)]	95 (43)[c)]	230–232
12	2-Furyl	**4l**	20	97	208–210
13	2-Thienyl	**4m**	20	95	228–231
14	5-Methyl-2-furyl	**4n**	22	96	179–181
15	Ethyl	**4o**	26	94	169–172
16	Propyl	**4p**	28	97	160–162
17	Hepthyl	**4q**	28	93	124–126
18	OHCC_6H_4	**4r**	25	98	>300

a) Isolated yields. b) Using commercial Fe_3O_4. c) Isolated yield using commercial Fe_3O_4. d) Ref. 40.



Scheme 2. A plausible mechanism for one-pot synthesis of 2-amino-4*H*-chromenes.

treated with two equiv of malononitrile and resorcinol under similar conditions, the reaction proceeded cleanly to give the corresponding bis-4*H*-chromene (**4r**) in 98% yield. The order of yield of aldehydes is aromatic > heteroaromatic > acyclic aldehydes. The activity of aldehydes with electron-withdrawing groups is higher than that with electron-donating groups. The position of substituent in the benzene rings of aldehyde influences this reaction. The activity of *o*-aldehyde is lower than *p*- and *m*-benzaldehyde.

A plausible mechanism explaining the aforementioned results and the selectivity is depicted in Scheme 2. The process represents a typical cascade of Knoevenagel condensation, Michael addition, and cyclization in the presence of Fe_3O_4-MNPs (Scheme 2). As can be seen in Scheme 2, magnetic Fe_3O_4 nanoparticles are Lewis acidic and so can activate the carbonyl group of aldehydes **1a** to decrease the energy of transition state for the nucleophilic attack of malononitrile. The reaction is thought to proceed through Knoevenagel condensation to form intermediate **4**. Subsequently Michael addition occurs to form intermediate **5**. The dipolar transition states **TS** occur resulting in generation intermediate of **6** in aqueous media as dipolar solvent that is converted to product **4a** via an intramolecular cyclization. Iron cations act as Lewis acid and play a significant role in increasing the electrophilic character of the aldehydes.

The reusability is one of the important properties of this catalyst. After the reaction was complete ethyl acetate was added, and the catalyst onto the magnetic stirring bar. The catalyst was then washed with ethyl acetate, air-dried and used directly with fresh substrates under identical conditions without further purification. It was shown that the catalyst could be reused for the next cycle without any appreciable loss of its activity. Similarly, reusability for sequential reaction was also carried out and catalyst was found to be reusable for five cycles (Figure 5). As observed in Figure 6 the XRD of the recovered

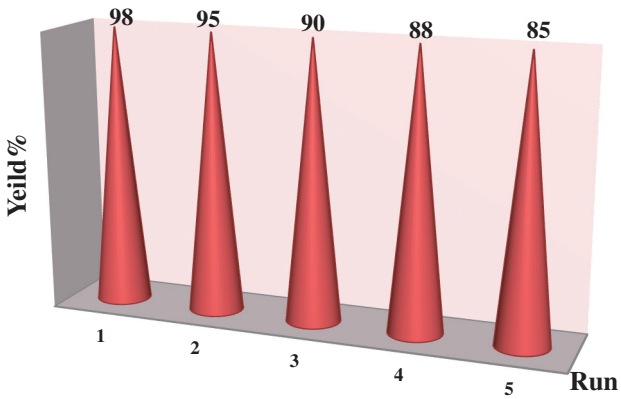


Figure 5. Recyclability of Fe_3O_4-MNPs (7 mol %) in the reaction of malononitrile (1 mmol), benzaldehyde (1 mmol), and resorcinol (1 mmol) in H_2O (5 mL) at room temperature.

nanocatalyst was indexed according to the magnetite phase (JCPDS card No. 79-0417), and so there is no considerable change in its magnetic phase. Thus, the magnetite nanocatalyst is stable during synthesis of 2-amino-4*H*-chromene in aqueous media.

In summary, we have been able to introduce an efficient and environmentally friendly approach for the synthesis of biologically active 2-amino-4*H*-chromenes by one-pot three-component condensation of aldehyde, malononitrile, and resorcinol in water using Fe_3O_4 nanoparticles at room temperature. This method offers several advantages including high yield, short reaction time, simple work-up procedure, and ease of separation by an external magnet.

Conclusion

In summary, we have developed an efficient method for the synthesis of 2-amino-4*H*-chromene derivatives by means of

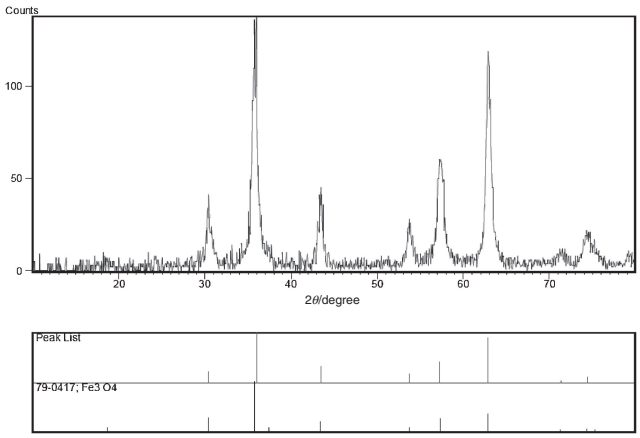


Figure 6. XRD pattern of recovered Fe_3O_4-MNPs after second recovery.

a three-component reaction between resorcinol, aldehyde, and malononitrile using a catalytic amount of Fe_3O_4-MNPs under neat conditions. This method offers several advantages including high yield, short reaction time, simple work-up procedure, easy of separation, and recyclability of the magnetic catalyst, as well as the ability to tolerate a wide variety of substitutions in the reagents.

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