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Mild preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives with magnetic Fe_3O_4 nanoparticles coated by (3-aminopropyl)-triethoxysilane as catalyst under ambient and solvent-free conditions

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Abstract An efficient, one-pot quantitative procedure for preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives from four-component condensation reaction of hydrazine monohydrate, phthalic anhydride, malononitrile or ethyl cyanoacetate, and aromatic aldehydes in the presence of magnetic Fe_3O_4 nanoparticles coated by (3-aminopropyl)-triethoxysilane as catalyst under mild, ambient, and solvent-free conditions is described. Simple procedure, high yield, short reaction time, and environmentally benign method are advantages of this protocol. The magnetic Fe_3O_4 nanoparticles coated by (3-aminopropyl)-triethoxysilane can be recovered and reused several times without loss of activity.

Keywords Magnetic properties · Four-component reaction · Ambient conditions · Solvent-free · Heterogeneous catalyst

Introduction

Multicomponent reactions (MCRs) have proven to be a valuable asset in organic and medicinal chemistry [1–7]. Such protocols can be used for drug design and drug discovery because of their simplicity, efficiency, and high selectivity [8, 9]. MCRs can reduce the number of steps and present advantages such as low energy consumption and little to no waste production, leading to desired environmentally friendly processes. Synthesis of bioactive and complex molecules should be facile, fast, and efficient with minimal workup in this methodology [6, 10].

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically

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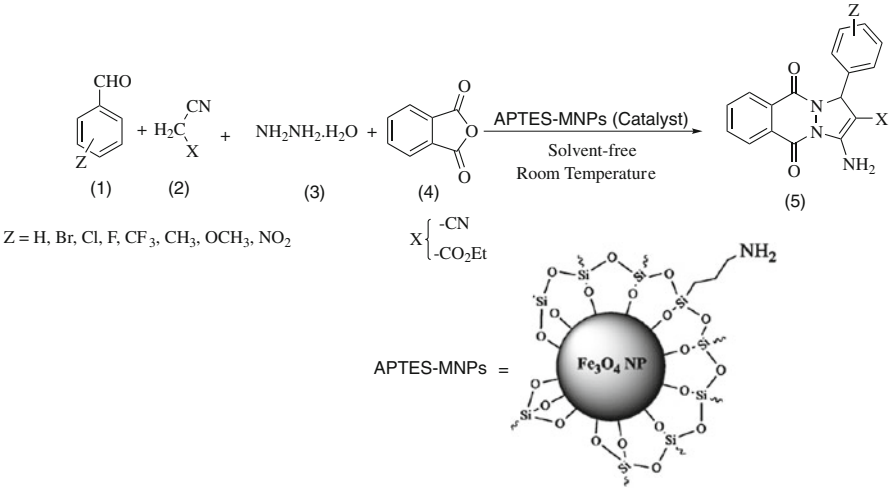
active pharmacological compounds [11–14] and drug molecules such as celecoxib and pyrazofurine [15]. Pyrazolo[1,2-*b*]phthalazine-dione derivatives have been reported to have anti-inflammatory, analgesic, antihypoxic, anticonvulsant, cardiotonic, vasorelaxant, antipyretic, antihyperglycemic, antibacterial, and antiviral activities [16–18].

In continuation of our research on multicomponent reactions [19–21], herein we describe the preparation of functionalized 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives from four-component condensation reaction of hydrazine monohydrate, phthalic anhydride, malononitrile or ethyl cyanoacetate, and aromatic aldehydes in the presence of magnetic Fe_3O_4 nanoparticles coated by (3-aminopropyl)-triethoxysilane (APTES-MNPs) as catalyst under ambient and solvent-free conditions (Scheme 1).

Surface-functionalized iron oxide magnetic nanoparticles (MNPs) are a kind of novel functional material which has been widely used in biotechnology and catalysis. The presence of many hydroxyl groups on the surface of the MNPs leads to reaction with 3-aminopropyltriethyloxysilane and formation of Si–O bonds which support terminal $–NH_2$ functional groups on the shell of the Fe_3O_4 core [22]. Such surface modification provides Fe_3O_4 nanoparticles coated by (3-aminopropyl)-triethoxysilane with basic character as catalyst. Due to the high magnetization of the Fe_3O_4 core in the catalyst, it can be satisfactorily recovered by a simple external magnet and could then be recycled and reused, which is important for green organic synthesis. The Brønsted basic ($–NH_2$) functionalized Fe_3O_4 core plays a crucial catalytic role in the described transformation. APTES-MNPs core–shell nanoparticles can be readily harvested upon applying an external magnetic field, providing this protocol with an easy and simple workup.



Scheme 1 Synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives

Experimental

Chemicals and materials

All reagents were purchased from Merck and Aldrich and used without further purification. APTES-MNPs was prepared according to the literature [22]. All yields refer to isolated products after purification. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance DPX 300 MHz instrument. The spectra were measured in dimethyl sulfoxide (DMSO)-d_6 relative to tetramethylsilane (TMS, 0 ppm). Infrared (IR) spectra were recorded on a JASCO FT–IR 460 plus spectrophotometer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica-gel Poly Gram SIL G/UV 254 plates.

General procedure for synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones under solvent-free and ambient conditions

Hydrazine monohydrate (10 mmol) and phthalic anhydride (10 mmol) were mixed at 100 °C until a white solid phthalhydrazide was formed (10 min). Then, arylaldehydes (10 mmol), malononitrile or ethyl cyanoacetate (10 mmol), and APTES-MNPs (10 mol%) as catalyst were stirred under ambient and solvent-free conditions for the specific time. After completion of the reaction, the mixture was diluted with dichloromethane and the catalyst was separated by an external magnet to check for reusability. The solution containing the product was evaporated to give a yellow solid. The solid was recrystallized with ethanol to give a pure yellow solid. All of the desired product(s) were characterized by comparison of their physical data with those of known compounds.

Spectroscopic data of new products are given below

3-Amino-1-(2,6-dichlorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5n**): yellow powder; m.p. = 268–270 °C IR (KBr): ν_{max} = 3,398, 3,304, 2,200, 1,683, 1,595 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 6.89 (1H, *s*, CH), 7.09–7.11 (3H, *m*, Ar), 7.42–8.26 (6H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 61.2, 62.6, 116.5, 122.4, 126.7, 127.5, 128.1, 128.2, 129.5, 129.8, 131.2, 132.7, 133.9, 135.0, 141.6, 151.3, 153.2, 156.7 ppm; MS (EI, 70 eV) *m*/*z* (%) = 384 (M^+, 17), 367 (18), 239 (100), 240 (74), 130 (14), 104 (25), 76 (19); Anal. Calcd. for $C_{18}H_{10}Cl_2N_4O_2$: C, 56.12; H, 2.62; N, 14.54 %. Found C, 56.13; H, 2.58; N, 14.56 %.

3-Amino-1-(2,4-dichlorophenyl)-5,10-dioxo-5,10-dihydro-1*H*pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5o**): yellow powder; m.p. = 228–230 °C; IR (KBr): ν_{max} = 3,411, 3,374, 2,204, 1,675, 1,602 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 6.44 (1H, *s*, CH), 7.41–8.88 (9H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.8, 59.2, 60.0, 115.5, 120.5, 126.6, 127.3, 128.0, 128.2, 128.8, 129.1, 132.2, 133.5, 133.8, 134.7, 151.2, 153.5, 156.6 ppm; MS (EI, 70 eV) *m*/*z* (%) = 384 (M^+, 16), 367 (16), 349 (12), 239 (100), 162 (24), 104 (27), 76 (16);

Anal. Calcd. for $C_{18}H_{10}Cl_2N_4O_2$: C, 56.12; H, 2.62; N, 14.54 %. Found C, 56.17; H, 2.58; N, 14.50 %.

3-Amino-1-(2,3-dichlorophenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5p**): yellow powder; m.p. = 265–268 °C; IR (KBr): ν_{max} = 3,415, 3,372, 2,211, 1,686, 1,660 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 6.52 (1H, *s*, CH), 7.35–8.27 (9H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 61.3, 62.7, 116.5, 122.3, 126.7, 127.3, 128.0, 128.2, 129.5, 129.9, 131.1, 131.7, 133.9, 135.0, 141.7, 151.3, 153.2, 156.6 ppm; MS (EI, 70 eV) *m*/*z* (%) = 384 (M^+, 17), 349 (12), 240 (80), 239 (100), 162 (0), 104 (31), 76 (21); Anal. Calcd. for $C_{18}H_{10}Cl_2N_4O_2$: C, 56.12; H, 2.62; N, 14.54 %. Found C, 56.17; H, 2.59; N, 14.52 %.

3-Amino-1-(2-methoxyphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5q**): yellow powder; m.p. = 248–251 °C IR (KBr): ν_{max} = 3,383, 3,255, 2,201, 1,681, 1,560 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 3.73 (3H, *s*, OCH_3), 6.34 (1H, *s*, CH), 6.90 (1H, *t*, *J* = 7.18 Hz), 7.03 (1H, *d*, *J* = 7.91 Hz, Ar), 7.29 (2H, *t*, *J* = 7.72 Hz, Ar), 7.97–8.27 (6H, *m*, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 55.8, 58.9, 60.6, 111.6, 115.9, 120.6, 125.8, 126.6, 127.2, 127.3, 128.5,128.6, 129.3, 133.7, 134.6, 150.9, 153.2, 155.5, 155.6 ppm; MS (EI, 70 eV) *m*/*z* (%) = 346 (M^+, 20), 329 (72), 315 (13), 239 (100), 240 (16), 162 (9), 104 (13); Anal. Calcd. for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18 %. Found C, 65.87; H, 4.11; N, 16.21 %.

3-Amino-1-(3-methoxyphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5r**): yellow powder; m.p. = 258–260 °C; IR (KBr): ν_{max} = 3,422, 3,362, 2,192, 1,680, 1,654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 3.62 (3H, *s*, CH_3), 6.08 (1H, *s*, CH), 6.87–7.23 (4H, *m*, Ar), 7.94–8.36 (6H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 61.3, 62.7, 116.5, 122.3, 126.5, 127.1, 127.7, 129.0, 129.5, 129.9, 131.1, 131.7, 134.2, 135.0, 141.7, 151.2, 153.5, 154.2, 157.2; MS (EI, 70 eV) *m*/*z* (%) = 346 (M^+, 70), 329 (56), 240 (83), 239 (100), 184 (19), 104 (17); Anal. Calcd. for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18 %. Found C, 65.84; H, 4.11; N, 16.14 %.

3-Amino-1-(2,4,6-trimethoxyphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5s**): yellow powder: m.p. = 257–260 °C IR (KBr): ν_{max} = 3,416, 3,328, 2,190, 1,635, 1,575 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 3.65 (3H, *s*, OCH_3), 3.74 (6H, *s*, OCH_3), 6.05 (1H, *s*, CH), 6.76 (2H, *s*, Ar), 7.97 (2H, *s*, NH_2), 8.05 (3H, *s*, Ar), 8.25 (1H, *s*, Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.0, 59.9, 61.2, 63.3, 104.2, 110.6, 116.1, 120.4, 125.6, 126.6, 127.2, 128.7, 128.9, 133.6, 134.0, 134.5, 137.2, 150.5, 152.9, 153.8, 156.7 ppm; MS (EI, 70 eV) *m*/*z* (%) = 406 (M^+, 28), 389 (32), 244 (50), 239 (100), 229 (32), 162 (18), 104 (14); Anal. Calcd. for $C_{21}H_{18}N_4O_5$: C, 62.06; H, 4.46; N, 13.79 %. Found C, 62.02; H, 4.42; N, 13.75 %.

3-Amino-1-(2,5-dimethoxyphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]-phthalazine-2-carbonitrile (**5t**): yellow powder; m.p. = 257–260 °C IR (KBr): ν_{max} = 3,420, 3,348, 2,180, 1,681, 1,595 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 3.66 (3H, *s*, OCH_3), 3.67 (3H, *s*, OCH_3), 6.29 (1H, *s*, CH), 6.82–6.98 (3H, *m*, Ar), 7.95–8.28 (6H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.4, 56.3, 59.0, 60.4, 112.9, 113.3, 113.8, 116.0, 126.6, 127.0, 127.2, 128.5,

128.7, 133.6, 134.6, 150.6, 151.0, 153.3, 153.4, 156.6 ppm; MS (EI, 70 eV) *m/z* (%) = 376 (M^+, 23), 359 (43), 345 (25), 329 (24), 239 (100), 214 (29), 199 (39); Anal. Calcd. for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89 %. Found C, 63.78; H, 4.24; N, 14.84 %.

3-Amino-1-(2-methylphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5u**): yellow powder; m.p. = 248–250 °C, IR (KBr): ν_{max} = 3,366, 3,302, 2,210, 1,661, 1,601 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.45 (3H, *s*, CH_3), 6.30 (1H, *s*, CH), 7.25–7.30 (4H, *m*, Ar), 7.95–8.24 (6H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.65, 61.0, 62.4, 122.0, 126.7 127.1, 127.7, 128.0, 128.2, 128.5, 128.7, 130.4, 133.7, 134.7, 135.2, 136.5,153.5, 154.2, 156.6 ppm; MS (EI, 70 eV) *m/z* (%) = 330 (M^+, 70), 315 (14), 240 (56), 239 (100), 184 (10), 169 (8), 104 (10); Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96 %. Found C, 69.04; H, 4.31; N, 16.92 %.

3-Amino-1-(4-trifluoromethylphenyl)-5,10-dioxo-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile (**5v**): yellow powder; m.p. = 268–270 °C, IR (KBr): ν_{max} = 3,359, 3,284, 2,195, 1,659, 1,594 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 6.24 (1H, *s*, CH), 7.7 (4H, *s*, Ar), 7.97–8.26 (6H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 55.8, 60.3, 60.6, 111.6, 115.8, 120.6, 125.4, 126.6, 127.2, 127.6, 128.2, 128.4, 128.9, 133.8, 134.6, 143.1, 150.8, 153.7, 156.6 ppm; MS (EI, 70 eV) *m/z* (%) = 384 (M^+, 25), 367 (34), 240 (70), 239 (100), 104 (30), 76 (19), 57 (2); Anal. Calcd. for $C_{19}H_{11}F_3N_4O_2$: C, 59.38; H, 2.88; N, 14.58 %. Found C, 59.35; H, 2.84; N, 14.52 %.

Ethyl 3-amino-5,10-dihydro-1-(2,6-dichlorophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**5w**): yellow powder; m.p. = 260–262 °C, IR (KBr): ν_{max} = 3,446, 3,332, 1,707, 1,659, 1,645 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 0.96 (3H, *t*, *J* = 6.7 Hz, CH_3), 3.91 (2H, *q*, *J* = 6.5 Hz, OCH_2), 6.52 (1H, *s* CH), 7.22–8.27 (9H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.9, 55.8, 58.6, 63.3, 80.2, 124.2, 126.7, 127.2, 127.3, 128.0, 128.1, 128.8, 129.5, 131.3, 133.8, 134.7, 150.3, 153.1, 156.7, 163.8 ppm; MS (EI, 70 eV) *m/z* (%) = 431 (M^+, 8), 286 (100), 258 (45), 240 (93), 239 (60), 173 (12), 104 (15); Anal. Calcd. For $C_{20}H_{15}Cl_2N_3O_4$: C, 55.57; H, 3.50; N, 9.72 %. Found C, 55.60; H, 3.52; N, 9.74 %.

Ethyl 3-amino-5,10-dihydro-1-(2,4-dichlorophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**5x**): yellow powder; m.p. = 228–230 °C, IR (KBr): ν_{max} = 3,452, 3,340, 1,700, 1,660, 1,620 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 0.95 (3H, *t*, *J* = 6.7 Hz, CH_3), 3.91 (2H, *q*, *J* = 6.6 Hz, OCH_2), 6.42 (1H, *s*, CH), 7.62–8.28 (9H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.0, 58.7, 62.7, 81.0, 120.1, 124.8, 126.6, 127.2, 127.3, 128.4, 128.7, 128.8, 132.6, 133.7, 134.7, 143.2, 148.9, 153.02, 156.7, 163.8 ppm; MS (EI, 70 eV) *m/z* (%) = 431 (M^+, 11), 286 (100), 258 (44), 241 (14), 240 (91), 173 (11), 104 (14); Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O_4$: C, 55.57; H, 3.50; N, 9.72 %. Found C, 55.60; H, 3.52; N, 9.64 %.

Ethyl 3-amino-5,10-dihydro-1-(2,3-dichlorophenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**5y**): yellow powder; m.p. = 260–263 °C IR (KBr): ν_{max} = 3,446, 3,333, 1,707, 1,647, 1,629 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 0.95 (3H, *t*, *J* = 6.8 Hz, CH_3), 3.90 (2H, *q*, *J* = 6.7 Hz, OCH_2),

6.51 (1H, *s* CH), 7.21–8.26 (9H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.9, 55.6, 58.6, 63.4, 80.2, 124.2, 126.6, 127.2, 128.0, 128.1, 128.4, 128.7, 129.5, 131.3, 133.7, 134.7, 150.2, 153.0, 156.7, 163.8$ ppm; MS (EI, 70 eV) *m*/*z* (%) = 431 (M^+, 7), 286 (100), 258 (39), 240 (94), 239 (73), 173 (11), 104 (15); Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O_4$: C, 55.57; H, 3.50; N, 9.72 %. Found C, 55.63; H, 3.52; N, 9.74 %.

Ethyl 3-amino-5,10-dihydro-1-(2-methoxyphenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**5z**): yellow powder; m.p. = 205–208 °C IR (KBr): $\nu_{max} = 3{,}444, 3{,}329, 1{,}700, 1{,}660, 1{,}622\ cm^{-1}$; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 0.98$ (3H, *t*, $J = 8.9$ Hz, CH_3), 3.62 (3H, *s*, CH_3), 3.90 (2H, *q*, $J = 9.0$ Hz, OCH_2), 6.27(1H, *s*, CH), 7.16–8.28 (10H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 14.0, 55.7, 58.4, 62.4, 80.7, 111.4, 120.0, 126.6, 126.8, 127.2, 128.4, 128.6, 128.8, 131.1, 133.5, 134.6, 150.2, 152.6, 156.5, 156.9, 164.1$ ppm; MS (EI, 70 eV) *m*/*z* (%) = 393 (M^+, 20), 376 (33), 320 (34), 286 (100), 258 (33), 240 (79), 104 (17); Anal. Calcd. for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68 %. Found C, 64.18; H, 4.84; N, 10.70 %.

Ethyl 3-amino-5,10-dihydro-1-(4-trifluoromethylphenyl)-5,10-dioxo-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carboxylate (**5aa**): yellow powder; m.p. = 222–225 °C; IR (KBr): $\nu_{max} = 3{,}430, 3{,}325, 1{,}692, 1{,}661, 1{,}625\ cm^{-1}$; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.01$ (3H, *t*, $J = 7.1$ Hz, CH_3), 3.96 (2H, *q*, $J = 7.0$ Hz, CH_2), 6.1 (1H, *s*, CH), 7.62–8.28 (10H, *m*, Ar and NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 14.1, 58.7, 62.7, 81.0, 124.8, 126.6, 127.2, 127.8, 128.2, 128.6, 128.8, 132.6, 133.6, 134.6, 143.2, 144.4, 149.8, 153.2, 156.3, 156.8, 163.8$ ppm; MS (EI, 70 eV) *m*/*z* (%) = 431 (M^+, 14), 286 (100), 258 (52), 240 (91), 173 (11), 104 (14), 76 (8); Anal. Calcd. for $C_{21}H_{16}F_3N_3O_4$: C, 58.47; H, 3.74; N, 9.74 %. Found C, 58.44; H, 3.78; N, 9.70 %.

Results and discussion

First, to optimize conditions, the solvent-free reaction of hydrazine monohydrate, phthalic anhydride, 4-chlorobenzaldehyde, and malononitrile in the presence of different amount of APTES-MNPs as catalyst under ambient and solvent-free conditions was selected as a model. The reaction was carried out with different amounts of APTES-MNPs as catalyst (5, 10, 15 mol%) (Table 1). As shown in Table 1, 10 mol% of APTES-MNPs as catalyst afforded 3-amino-5,10-dioxo-1-(4-chlorophenyl)-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile in 15 min with 93 % yield (Table 1).

Next, using these optimized reaction conditions, the scope and efficiency of these procedures were explored for synthesis of a wide variety of substituted 1*H*-pyrazolo[1,2-*b*]phthalazines in the presence of APTES-MNPs. Interestingly, a variety of aromatic aldehydes including *ortho*-, *meta*-, and *para*-substituted aryl aldehyde participated well in this reaction and gave the corresponding products in good to excellent yield (Table 2). As seen from Table 2, both aromatic aldehydes carrying electron-donating or electron-withdrawing substituent act well under these

Table 1 Optimization of amount of APTES-MNPs as catalyst in four-component synthesis of 3-amino-5,10-dioxo-1-(4-chlorophenyl)-5,10-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile from reaction of phthalic anhydride, hydrazine monohydrate, malononitrile, and 4-chlorobenzaldehyde under solvent-free and ambient conditions

Entry	Catalyst (mol%)	Time (min)	Yield (%)[a]
1	5	18	81
2	10	15	93
3	15	14	93

[a] Yields refer to isolated pure product

Table 2 Four-component synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives from the reaction of phthalic anhydride, hydrazine, malononitrile or ethyl cyanoacetate, and aldehydes in the presence of APTES-MNPs as catalyst

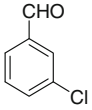
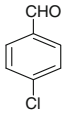
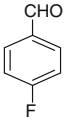
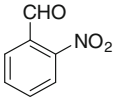
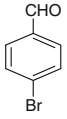
Entry	Aldehyde	X	Product	Time (min)	Yield (%)	Melting point Report. m.p (°C)/Lit. m.p (°C) [Ref]
1		CN	**5a**	19	92	274–276/(276–278) [23]
2		CN	**5b**	15	93	258–259/(259–261) [23]
3		CN	**5c**	16	90	267–268/(266–267) [24]
4		CN	**5d**	15	93	272–273/(270–272) [23]
5		CN	**5e**	17	89	266–267/(263–265) [24]
6		CN	**5f**	14	91	266–267/(265–266) [24]
7		CN	**5g**	15	92	263–265/(265–267) [24]

Table 2 continued

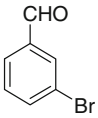
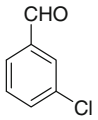
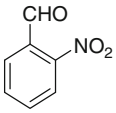
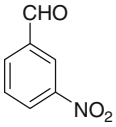
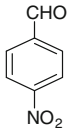
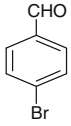
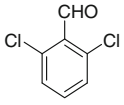
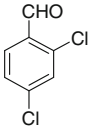
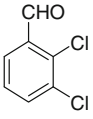
Entry	Aldehyde	X	Product	Time (min)	Yield (%)	Melting point Report. m.p (°C)/Lit. m.p (°C) [Ref]
8		CN	**5h**	16	89	271–273/(270–272) [24]
9		COOEt	**5i**	23	88	211–212/(211–213) [24]
10		COOEt	**5j**	21	89	235–236/(235–237) [24]
11		COOEt	**5k**	22	91	238–239/(239–240) [23]
12		COOEt	**5l**	21	89	242–244/(241–243) [23]
13		COOEt	**5m**	22	90	206–207/(205–206) [24]
14		CN	**5n**	14	92	269–271 The product prepared for the first time
15		CN	**5o**	15	91	228–229 The product prepared for the first time
16		CN	**5p**	16	93	267–268 The product prepared for the first time

Table 2 continued

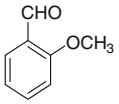
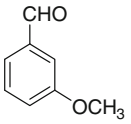
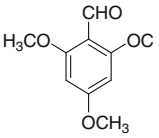
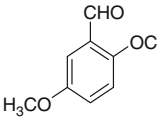
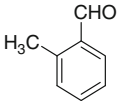
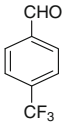
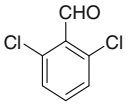
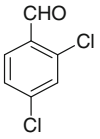
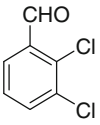
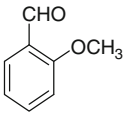
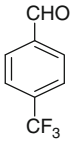
Entry	Aldehyde	X	Product	Time (min)	Yield (%)	Melting point Report. m.p (°C)/Lit. m.p (°C) [Ref]
17		CN	**5q**	14	90	248–250 The product prepared for the first time
18		CN	**5r**	16	92	259–261 The product prepared for the first time
19		CN	**5s**	17	91	258–259 The product prepared for the first time
20		CN	**5t**	16	93	259–260 The product prepared for the first time
21		CN	**5u**	16	92	248–251 The product prepared for the first time
22		CN	**5v**	16	90	265–267 The product prepared for the first time
23		COOEt	**5w**	22	89	262–264 The product prepared for the first time
24		COOEt	**5x**	21	88	230–232 The product prepared for the first time
25		COOEt	**5y**	23	89	262–263 The product prepared for the first time

Table 2 continued

Entry	Aldehyde	X	Product	Time (min)	Yield (%)	Melting point Report. m.p (°C)/Lit. m.p (°C) [Ref]
26		COOEt	**5z**	22	90	206–208 The product prepared for the first time
27		COOEt	**5aa**	22	89	220–221 The product prepared for the first time
28	*n*-Heptanal	CN	–	10 h	Trace	–

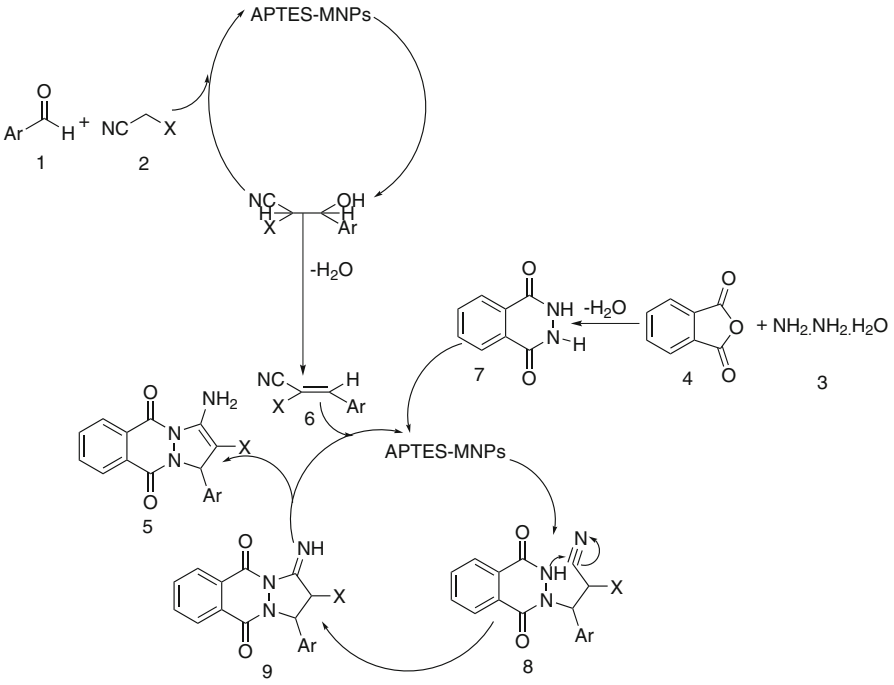
[a] Yields refer to the isolated pure products. The desired pure products were characterized by comparison of their physical data (melting points, IR, ^{1}H and ^{13}C NMR) with those of known compounds

reaction conditions. In addition, malononitrile acts well in comparison with ethyl cyanoacetate in the mentioned reaction. Furthermore, we examined aliphatic aldehyde such as *n*-heptanal instead of benzaldehydes in the reaction. All starting materials in the reaction were almost intact with formation of only trace product without any side-products after 10 h (Table 2, entry 28). Our observation is confirmed with other catalysts reported in the literature [23–25].

According to the literature survey [23], the suggested mechanism for the formation of the products using APTES-MNPs is shown in Scheme 2. First the standard Knoevenagel condensation product of arylaldehydes (**1**) with malononitrile (**2**) in the presence of the basic APTES-MNPs as catalyst was afforded, benzylidenemalononitrile (**6**). Then, condensation of hydrazine monohydrate (**3**) with phthalic anhydride (**4**) via dehydration afforded phthalhydrazide (**7**). The second cycle involves 1,4-conjugated addition of the phthalhydrazide to benzylidenemalononitrile (**6**) in the basic catalytic media, followed by cyclization and tautomerism, affording the corresponding product (**5**) (Scheme 2).

We also investigated recycling of the APTES-MNPs as catalyst under solvent-free conditions using the model reaction of hydrazine monohydrate, phthalic anhydride, 4-chlorobenzaldehyde, and malononitrile (Table 2, entry 4). After completion of the reaction, the reaction mixture was dissolved in dichloromethane. Then, APTES-MNPs as catalyst were separated by an external magnet for subsequent experiments to check their reusability under similar reaction conditions. The results showed that APTES-MNPs are a stable catalyst in reaction media and can be reused several times without significant loss of catalytic activity (Fig. 1).

To show the accessibility of the present work (4-CRs) in comparison with results reported in the literature such as for *p*-toluenesulfonic acid (*p*-TSA) as catalyst [23], triethylamine (0.02 g, 20 mol%) as catalyst under ultrasound conditions at



Scheme 2 Suggested mechanism for the formation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

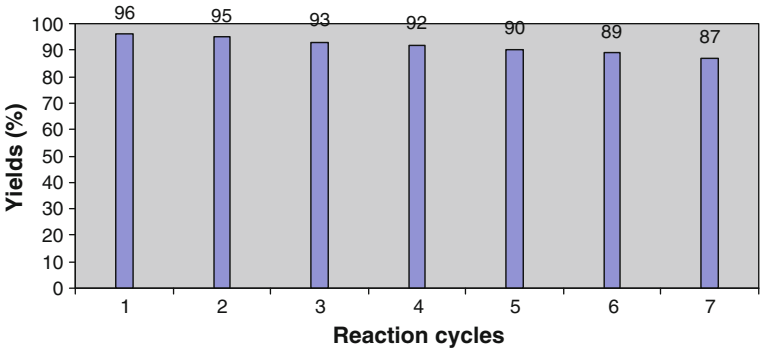


Fig. 1 Recycling of APTES-MNPs as catalyst

frequency of 50 kHz and output power of 350 W [24], 1-butyl-3-methylimidazolium hydroxide ([Bmim]OH) [25], and triethylamine (360 mol%) [26], we summarize some of the results for the preparation of 1*H*-pyrazolo[1,2-*b*]phthalazines in Table 3. The results show that APTES-MNPs are the most efficient catalyst with respect to reaction time and in terms of yield.

Table 3 Comparison of the results for APTES-MNPs with [Bmim]OH, Et_3N, and *p*-TSA for synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

Entry	Catalyst	Conditions	Time (min)	Yield (%) [Ref]
1	*p*-TSA (30 mol%)	[Bmim]Br/100 °C	180	94 [23]
2	Et_3N (20 mol%)	EtOH/50 °C/ultrasound	60	90 [24]
3	[Bmim]OH (20 mol%)	MW, 100 W, 45 °C	4	96 [25]
4	Triethylamine (360 mol%)	DMF (20 ml), refluxed	180	72 [26]
5	APTES-MNPs (10 mol%)	Solvent-free, room temperature	15	93 (present work)

Conclusions

In this research, APTES-MNPs were used for mild preparation of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives under solvent-free and ambient conditions for the first time. The attractive features of this protocol are the simple procedure, cleaner reaction, and use of recyclable nanocatalyst. Satisfactory yields of products and easy workup make this a useful protocol for green synthesis of this class of compounds.

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