Res Chem Intermed (2017) 43:1013–1029
DOI 10.1007/s11164-016-2680-y

Using magnetized water as a solvent for a green, catalyst-free, and efficient protocol for the synthesis of pyrano[2,3-*c*]pyrazoles and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines

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Received: 6 June 2016 / Accepted: 26 July 2016 / Published online: 10 August 2016

Abstract A facile, eco-friendly, and highly efficient one-pot four-component protocol is demonstrated for the synthesis of the pyrano[2,3-c]pyrazole and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidine derivatives using magnetized water as a new green solvent. Simplicity, short reaction time, high yield, easy work-up, and absence of hazardous organic solvents are the main advantages of this method.

Keywords Magnetized water · Catalyst-free · Pyrano[2,3-*c*]pyrazoles · Pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines

Introduction

Designing biologically active compounds is a challenging point of view in medicinal chemistry [1], and pyranopyrazoles have a critical role as biologically-ctive molecules [2]. Because of their biological importance, there has been a substantial interest in designing synthetic methods for the synthesis of pyranopyrazole derivatives in water [3–5]. On the other hand, pyranopyrimidine, which is a prominent member of the pyrimidine family, has acquired considerable attention because of its broad biological activities [6]. A more obvious effect is often noticed when a number of heterocyclic moieties occur in a specific molecule, because it can have the properties of all the moieties and improve the pharmacological activities. Important advances have recently been made to synthesize novel polycyclic heterocycles by combining unlike structurally-diverse motifs [7]. In this regard, we expected that it would be significant to combine the fused heterocycles in a

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molecular hybrid framework with both the pyranopyrazole and pyranopyrimidine moieties. Up to the present time, a few examples have been reported for the synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines. Heravi et al. [8] have developed a four-component reaction of hydrazines, ethyl acetoacetate, aldehydes, and barbituric acid in the presence of DABCO for the synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines in refluxing water. Zhang et al. [9] have reported a highly efficient protocol for the synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines using meglumine as a biodegradable and reusable catalyst. Also Khodabakhshi et al. [10] have investigated the synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines using nano-titanium dioxide.

Multi-component reactions (MCRs), which are one-pot reactions in which at least three different reagents merge through covalent bonds, have acquired significance in synthetic organic chemistry. MCRs permit the generation of a number of bonds in a single operation, and provide notable benefits such as operational simplicity, convergence, facile automation, extraction, reduction in the number of work-ups, and purification processes, and thus minimize waste generation, rendering the transformations green [11–13]. Thus, the design of noble MCRs with green methods has attracted much attention, in particular, in the areas of organic synthesis, drug discovery, and material science [14, 15].

Furthermore, MCRs performed in water offer more desirable environmental protections, and thus are regarded as clean and green reactions. The importance of green chemistry methods is continuously growing. Substitute processes aid to save resources, and can lower the costs. Replacement of the conventional solvents for water, which is available in large amounts and is safe for one's health, is an appealing fundamental approach along these lines [16]. Water is an interesting solvent. Biological processes are carried out in this medium. Some organic reactions are speeded up by water, while the others are inhibited in it. Hydrophobicity, hydrogen bonding, acidity, polarity, and entropy all have significant roles to play in the impact of water on the organic reactions mediated in its presence. The varying behavior of these properties can make water an appealing candidate as a solvent or co-solvent from an industrial viewpoint, even before its potential environmental advantages are taken into account. The reactivity and stereo-selectivity of these reactions conducted under aqueous conditions have been reported to increase [17]. However, most chemical reactions cannot be done in water, as a solvent, since they need the presence of reagents, catalysts, or energy. Therefore, if we can change the physical properties of water, its reactivity toward organic reagents will be altered. The change in the properties of water under the action of an applied magnetic field is just a typical case. Vermeiren [18] has patented that an applied magnetic field can affect the properties of water. It has been found that water gives rise to many phenomena when exposed to a magnetic field, even if the magnetic flux density is not high and the treatment time is short [19]. Water can be magnetized in the presence of an external magnetic field, and due to the magnetization many properties of water, such as density, penetration, specific heat, refractive index, electric dipole-moment, average cluster size in the bulk water, vaporization enthalpy, surface tension and viscosity, change compared with non-magnetic water [20–22].

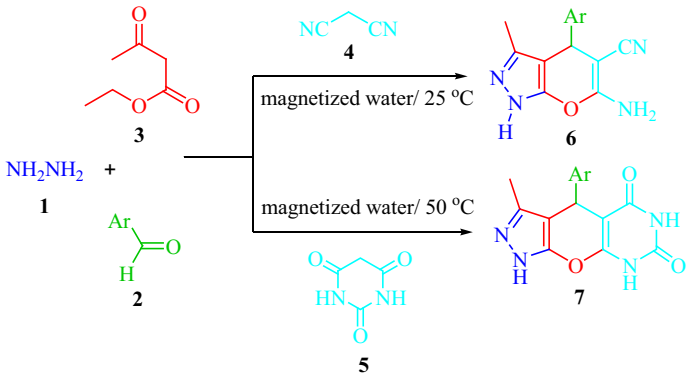
Based on the literature surveys carried out on magnetized water during the last few years, most researchers have been interested in the study of magnetic field effects on the properties of water [23, 24], especially the hydrogen bond distribution [25–27]. On the other hand, various researchers have studied the effects of magnetized water on the morphology of precipitated calcium carbonate [28], TiO_2-based varistors [29], synthesis of manganese oxide nano-crystals [30], crystallization, and salt precipitations [31]. However, there is no report on the use of magnetized water in organic reactions. Considering the above subjects, herein for the first time, we report a green and catalyst-free protocol for the synthesis of the biologically active pyrano[2,3-*c*]pyrazole and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidine derivatives using magnetized water as a solvent (Scheme 1).

Experimental

Reagents and solvents were purchased from Merck, Fluka or Aldrich. Melting points were determined using an electro-thermal C14500 apparatus. The reaction progress and the purity of compounds were monitored using TLC analytical silica gel plates (Merck 60 F250). All the known compounds were identified by comparison of their melting points and ^{1}H NMR data with those in the authentic samples. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectroscopies were run on a Bruker Avance DPX-250 FT-NMR spectrometer. The chemical shift values were given as δ values against tetramethylsilane as the internal standard, and the J values were given in Hz. Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer.

Preparation of magnetized water

Magnetized water was prepared using a static magnetic system of 6000 G [32] field strength with a flow rate of 500 mL s^{-1} at different magnetization times (Fig. 1).



Scheme 1 Four-component synthesis of pyrano[2,3-*c*]pyrazoles **6** and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines **7** in magnetized water

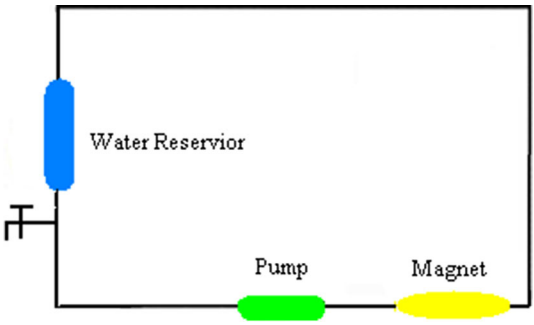


Fig. 1 Pilot for solvent magnetizing apparatus

As shown in Fig. 1, a centrifugal pump was used to circulate water in the system. Water was treated in the system for 10 min, and then 100 mL of this magnetized water was used in the current work.

General procedure for synthesis of dihydropyrano[2,3-*c*]pyrazoles (6a–x)

To a 10-mL round-bottomed flask equipped with a magnetic stirrer bar and containing magnetized water (4 mL, with magnetization time of 10 min), were added ethyl acetoacetate (1.0 mmol), hydrazine (1.0 mmol), an aldehyde (1.0 mmol), and malononitrile (1.0 mmol). The reaction mixture was stirred at room temperature, and monitored by thin layer chromatography (TLC) technique. After completion of the reaction, the precipitate thus formed was filtered and purified by recrystallization from ethanol to afford the desired product (Table 5).

General procedure for synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidine derivatives (7a–t)

To a 10-mL round-bottomed flask equipped with a magnetic stirrer bar and containing magnetized water (4 mL, with magnetization time of 10 min), were added ethyl acetoacetate (1.0 mmol), hydrazine hydrate (1.0 mmol), an aldehyde (1.0 mmol), and barbituric acid (1.0 mmol). The reaction mixture was stirred at 50 °C, and the reaction progress was monitored by TLC using chloroform as the eluent. After completion of the reaction, the precipitate formed was filtered and purified by recrystallization from ethanol to afford the desired product (Table 7).

*6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6a**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.82 (s, 3H, CH_3), 4.63 (s, 1H, CH), 6.90 (s, 2H, NH_2), 7.21–7.28 (m, 3H, Ph-H), 7.34–7.38 (m, 2H, Ph-H), 12.13 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.7, 36.1, 57.1, 97.6, 120.7, 126.7, 127.4, 128.4, 135.5, 144.4, 154.7, 160.8; Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21; found: C, 66.85; H, 4.90; N, 22.03.

*6-Amino-3-methyl-4-(4-N,N-dimethylamino-phenyl)-1,4-dihydropyano[2,3-c]pyrazole-5-carbonitrile (**6f**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80 (s, 3H, CH_3), 2.87 (s, 6H, NCH_3), 4.46 (s, 1H, CH), 6.66 (d, 2H, *J* 8.4 Hz, Ar-H), 6.77 (s, 2H, NH_2), 6.97 (d, 2H, *J* 8.4 Hz, Ar-H), 12.05 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.2, 35.8, 58.4, 98.6, 112.7, 121.4, 128.4, 132.5, 135.7, 135.9, 149.7, 155.2, 160.9; Anal. Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71; found: C, 64.90; H 5.71; N 23.87.

*6-Amino-3-methyl-4-(2-chlorophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6h**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H, CH_3), 5.16 (s, 1H, CH), 7.03 (s, 2H, NH_2), 7.26–7.28 (m, 1H, Ar-H), 7.33–7.43 (m, 2H, Ar-H), 7.50 (dd, 1H, *J* 6.9, 0.9 Hz, Ar-H), 12.21 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.8, 34.1, 56.3, 96.8, 120.3, 127.7, 128.5, 129.4, 130.6, 131.9, 135.3, 140.8, 154.9, 162.2; Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54; found: C, 58.46; H, 3.79; N, 19.73.

*6-Amino-3-methyl-4-(2,3,4-trimethoxy-phenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6p**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80 (s, 3H,CH_3), 3.68 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.74 (s, 1H, CH), 6.75–6.79 (m, 2H, Ar-H), 12.01 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.9, 31.0, 56.1, 57.3, 60.6, 61.3, 98.4, 121.5, 123.8, 130.1, 135.5, 141.9, 151.5, 152.5, 155.4, 161.4; Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37; found: C, 59.84; H, 5.21; N, 16.54.

*6-Amino-3-methyl-4-(4-hydroxy-,3,5-dimethoxy-phenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5q**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H, CH_3), 3.81 (s, 6H, OCH_3), 4.52 (s, 1H, CH), 6.42 (s, 2H, NH_2), 6.84 (s, 2H, Ar-H), 8.28 (s, 1H, OH), 12.08 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.8, 36.2, 55.9, 57.3, 97.6, 104.8, 120.8, 134.3, 134.4, 135.6, 147.7, 147.8, 154.6, 160.7; Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06; found: C, 58.35; H, 4.80; N 17.25.

*6-Amino-3-methyl-4-(furan-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6r**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.98 (s, 3H, CH_3), 4.78 (s, 1H, CH), 6.18 (d, 1H, *J* 3.0 Hz, furan-H), 6.37–6.39 (m, 1H, furan-H), 6.96 (s, 2H, NH_2), 7.54 (t, 1H, *J* 0.9 Hz, furan-H), 12.17 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.0, 30.2, 54.4, 95.5, 106.1, 110.7, 121.0, 136.1, 136.3, 142.7, 155.2, 156.1, 161.9; Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13; found: C, 59.70; H, 4.24; N, 23.32.

*6-Amino-3-methyl-4-(2-chloroquinolin-3-yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**6u**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.79 (s, 3H, CH_3), 5.21 (s, 1H, CH), 7.11 (s, 2H, NH_2), 7.63–7.68 (m, 1H, quinolin-H), 7.79–7.84 (m, 1H, quinolin-H), 7.95 (d, 1H, *J* 8.4 Hz, quinolin-H), 8.08 (d, 1H, *J* 8.4 Hz, quinolin-H), 8.40 (s, 1H, quinolin-H), 12.21 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.1, 34.1, 56.3, 96.5, 120.9, 127.7, 127.9, 128.4, 131.3, 135.8, 136.0, 140.0, 146.6, 149.6, 155.5, 161.9; Anal. Calcd for $C_{17}H_{12}ClN_5O$: C, 60.45; H, 3.58; N, 20.73; found: C, 60.66; H, 3.69; N, 20.90.

*4-(4-Hydroxyphenyl)-3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7 (1H,4H)-dione (**7b**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H, CH_3), 5.30 (s, 1H, CH), 6.58 (d, 2H, *J* 8.4 Hz, Ar-H), 6.87 (d, 2H, *J* 8.4 Hz, Ar-H), 9.94 (s, 2H, NH); Anal. Calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94; found: C, 57.88; H, 3.96; N, 17.78.

*4-(4-Methoxyphenyl)-3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7 (1H,4H)-dione (**7d**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 5.37 (s, 1H, CH), 6.77 (d, 2H, *J* 8.4 Hz, Ar-H), 6.95 (d, 2H, *J* 8.4 Hz, Ar-H), 10.15 (s, 2H, NH); Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17; found: C, 59.05; H, 4.23; N, 17.33.

*4-(4-N,N-dimethylaminophenyl)-3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d] pyrimidine-5,7(1H,4H)-dione (**7f**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3H, CH_3), 2.83 (s, 6H, NCH_3), 5.35 (s, 1H, CH), 6.85 (d, 2H, *J* 8.1 Hz, Ar-H), 7.65 (d, 2H, *J* 8.1 Hz, Ar-H), 10.14 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.9, 30.1, 44.6, 95.5, 109.2, 111.4, 111.7, 127.8, 130.1, 139.7, 143.5, 154.7, 162.4; Anal. Calcd for $C_{17}H_{17}N_5O_3$: C, 60.17; H, 5.05; N, 20.64; found: C, 60.36; H, 5.14; N, 20.82.

*4-(2,6-Dichlorophenyl)-3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7 (1H,4H)-dione (**7j**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.09 (s, 3H, CH_3), 5.29 (s, 1H, CH), 7.45–7.47 (m, 1H, Ar-H), 7.49–7.53 (m, 2H, Ar-H), 10.23 (s, 2H, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 11.1, 30.3, 88.8, 127.8, 129.0, 129.2, 131.3, 132.0, 134.1, 151.6, 152.4, 156.6, 160.8; Anal. Calcd for $C_{15}H_{10}Cl_2N_4O_3$: C, 49.34; H, 2.76; N, 15.34; found: C, 49.55; H, 2.63; N, 15.50.

*4-(4-Bromophenyl)-3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7 (1H,4H)-dione (**7k**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3H, CH_3), 5.37 (s, 1H, CH), 7.0 (d, 2H, *J* 8.4 Hz, Ar-H), 7.39 (d, 2H, *J* 8.4 Hz, Ar-H), 10.14 (s, 2H, NH); Anal. Calcd for $C_{15}H_{11}BrN_4O_3$: C, 48.02; H, 2.96; N, 14.93; found: C, 48.19; H, 2.88; N, 15.09.

*4-(4-Nitrophenyl)-3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (**7n**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24 (s, 3H, CH_3), 5.48 (s, 1H, CH), 7.30 (d, 2H, *J* 8.4 Hz, Ar-H), 8.10 (d, 2H, *J* 8.4 Hz, Ar-H): 11.50 (s, 2H, NH); Anal. Calcd for $C_{15}H_{11}N_5O_5$: C, 52.79; H, 3.25; N, 20.52; found: C, 52.98; H, 3.33; N, 20.68.

*1,4-Bis(3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione) benzene (**7o**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3H, CH_3), 5.42 (s, 1H, CH), 6.93 (s, 2H, Ar-H), 11.51 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.9, 30.8, 96.0, 105.4, 126.1, 127.1, 128.1, 139.0, 143.7, 145.6, 159.2, 161.1; Anal. Calcd for $C_{24}H_{18}N_8O_6$: C, 56.03; H, 3.53; N, 21.78; found: C, 56.24; H, 3.63; N, 21.56.

*4-(3,5-Dimethoxy-4-hydroxyphenyl)-3-methyl-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d] pyrimidine-5,7(1H,4H)-di one (**7q**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (s, 3H, CH_3), 3.82 (s, 6H, OCH_3), 5.34 (s, 1H, CH), 6.32 (s, 2H, Ar-H), 7.16 (s, 1H, OH), 10.18 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.0, 55.9, 91.4, 105.7, 124.2, 132.7, 133.7, 143.3, 147.4, 148.0, 150.5, 156.2, 160.67; Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05; found: C, 54.65; H, 4.25; N, 15.22.

*3-Methyl-4-(furan-2-yl)-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (**7r**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.01 (s, 3H, CH_3), 4.99 (s, 1H, CH), 7.21 (t, 1H, *J* 7.2 Hz, furan-H), 7.37 (d, 1H, *J* 8.1 Hz, furan-H), 7.69–7.75 (m, 1H, furan-H), 11.21 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.0, 27.7, 79.3, 102.2, 105.9, 110.1, 133.0, 138.8, 140.9, 155.7, 160.5, 163.8; Anal. Calcd for $C_{13}H_{10}N_4O_4$: C, 54.55; H, 3.52; N, 19.57; found: C, 54.73; H, 3.60; N, 19.75.

*3-Methyl-4-(2-chloroquinoline-3-yl)-6,8-dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (**7t**)*

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H, CH_3), 5.19 (s, 1H, CH), 7.49-7.58 (m, 1H, quinolin-H), 7.69–7.96 (m, 3H, quinolin-H), 8.04 (s, 1H, quinolin-H), 10.85 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 9.9, 26.7, 105.5, 125.1, 126.3, 127.2,

130.9, 131.1, 138.6, 139.3, 144.7, 149.7, 153.6, 154.1, 159.0, 163.0; Anal. Calcd for $C_{18}H_{12}ClN_5O_3$: C, 56.63; H, 3.17; N, 18.34; found: C, 56.80; H, 3.26; N, 18.16.

Results and discussion

Choosing a suitable reaction medium is very important in a successful organic synthesis. In this work, the four-component reaction of ethyl acetoacetate (1.0 mmol), hydrazine hydrate (1.0 mmol), malononitrile (1.0 mmol), and benzaldehyde (1.0 mmol) was taken initially as a model reaction for the synthesis of 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile **6a** at 25 °C in different solvents and in the absence of any catalyst (Table 1). The target product was not formed in non-polar solvents (Table 1, entries 1 and 2), and even methanol and ethanol, as polar protic solvents, were unable to produce the desired product 6a in an acceptable yield (Table 1, entries 5 and 6). It was found that water is a suitable solvent with respect to reaction yield (Table 1, entry 7). This effect can be ascribed to the existence of powerful hydrogen bond interactions at the organic phase-water interface, which stabilizes the reaction intermediate [33]. According to the results obtained in the Table 1, we tried to optimize the reaction conditions using magnetized water, which could help to reduce the reaction time and improve the yield of the target product.

Magnetized water was prepared using a static magnetic system of 6000 G field strength with a flow rate of 500 mL s^{-1} at different magnetization times (Fig. 1). As shown in Fig. 1, the equipment was connected from one end to a liquid pump and from the other end to the pipelines of a water reservoir. The water had to flow through a static magnetic gap and come back to the water reservoir. Therefore, the water could pass through the field for many times in a closed cycle.

Doubly distilled water, which was deionized by a Millipore Q-Plus 185 system, was used in the experiments. After magnetizing water, the elementary constituents of the resulting magnetized water were measured. The Ca, Si, Na, K, and nitrate contents of magnetized water were 0.01, 0.005, 0.007, 0.002, and 1 mg L^{-1}, respectively. Therefore, there were no metallic and magnetic elements present in the magnetized water.

Meanwhile, we measured the changes in the values for pH, viscosity, refractive index, dielectric constant, and electric conductivity of magnetized water relative to

Table 1 Synthesis of compound **6a** in different solvents

Entry	Solvent	Yield (%)[a]
1	Benzene	–
2	Toluene	–
3	CH_3CN	5
4	THF	5
5	MeOH	10
6	EtOH	10
7	H_2O	30

Reaction conditions: hydrazine hydrate **1** (1.0 mmol), ethyl acetoacetate **3** (1 mmol), benzaldehyde **2a** (1.0 mmol), malononitrile **4** (1.0 mmol), solvent (3 mL), 25 °C for 4 h

[a] Isolated yield

those for normal water (Table 2). As shown in Table 2, the magnetic field applied decreased the values for pH and viscosity of water, and increased the values for refraction index, dielectric constant, and electric conductivity of it after magnetization. Pang et al. [23] have reported the measurement of the electromagnetic properties of magnetized water. They have found that the applied magnetic field increases the values for refraction index, dielectric constant, and electric conductivity of water. According to the mechanism and theory of magnetization of water proposed by Pang, the macroscopic properties of magnetized water are due to the variations in the microscopic structure of water, for example, the distribution of molecules and electrons, displacement and polarization of molecules and atoms, and dipole moments of the transitional and vibrational states of molecules, under the action of an applied magnetic field. In Pang's theory, the increase in the dielectric constant and electric conductivity of water under the influence of an external magnetic field is due to the increase in the shift speed of the charged particles, for example, hydronium and OH^- ions from one water molecule of to another under the action of an external magnetic field. Obviously, the greater the shift speed, the stronger is the magnetic field, and the longer is the magnetization time. This directly results in an increase in the electric conductivity of magnetized water.

Then, the above model reaction was carried out in different magnetized waters. As indicated in Table 3 (entries 1–3), the magnetization time seems to play an important role in achieving a high-yield product **6a**. With increase in the water magnetization time from 5 to 15 min, the pH value for the magnetized water decreased, and the reaction product **6a** was obtained in a shorter time and with more yield. The best product yield was found to be in the water magnetized in 10 min, and for a reaction time of 10 min (Table 3, entry 2). Increasing the reaction time did not improve the product yield (Table 3, entry 4). Further optimization studies revealed that the magnetized water volume did not have a pivotal effect on the outcome of the reaction (Table 2, entries 5–8). Although satisfactory yields were obtained with several magnetized water volumes tested, it turned out that the reactions proceeded with higher yields in 4 mL of magnetized water (Table 3, entry 2). Also, the above four-component reaction was carried out in an aqueous solution of pH 5.5 to establish the real efficacy of magnetized water. As shown in Table 3, only a low product yield was obtained even after the reaction time was prolonged to 2 h (Table 3, entry 9).

Table 2 Comparison between some properties of doubly distilled water and those for magnetized water

Entry	Physicochemical properties	Doubly distilled water	Magnetized water
1	pH	6.9	5.5
2	Viscosity (μ Pa s)	965.42 ± 1.20	995.63 ± 4.40
3	Refractive index	1.3310	1.3320
4	Electric dipole-moment (Debye)	1.85	>1.85
5	Electric conductivity (S $m^{-1)}$	0.1×10^{-6}	0.2×10^{-6}

Conditions: Magnetization time (10 min), temperature (25 °C)

Table 3 Optimization of the reaction conditions for the synthesis of pyrano[2,3-*c*]pyrazole **6a**

Entry	Solvent (mL)	Magnetization time (min)	pH	Reaction time (min)	Yield (%)[a]
1	Magnetized water (4)	5	6.0	15	85
2	Magnetized water (4)	10	5.5	10	97
3	Magnetized water (4)	15	5.5	7	97
4	Magnetized water (4)	10	5.5	15	96
5	Magnetized water (2)	10	5.5	10	94
6	Magnetized water (3)	10	5.5	10	96
7	Magnetized water (5)	10	5.5	10	92
8	Magnetized water (6)	10	5.5	10	92
9	Distilled water (4)	–	5.5	120	35

Reaction conditions: ethyl acetoacetate (1.0 mmol), hydrazine hydrate (1.0 mmol), benzaldehyde (1.0 mmol), and malononitrile (1.0 mmol), at 25 °C

[a] Isolated yield

Some experiments have shown that when the magnetic exposure is stopped, the magnetic effect of the magnetized water left behind does not disappear immediately, and can be maintained for a very long period of time. This phenomenon is called the memory effect of magnetized water [34, 35]. According to Pang and Deng [36] the memory effect for magnetized water increases with increase in the applied magnetic field. Coey and Cass [37] have reported that the memory of a magnetic treatment can be maintained for up to 200 h. Thus we examined the memory effect, i.e., how long the water magnetization effect remains after completion of the magnetic exposure. We carried out the model reaction in magnetized water at different times after completion of the magnetic exposure. After a magnetic exposure of 10 min, magnetized water was left standing for different time periods, and the reaction yields were tabulated in Table 4. As shown in Table 4, the product yield decreases gradually with increasing time and becomes finally the same as that of pure water after 8 h. We found that water kept its magnetization property for up to 4 h, and a reaction performed in water magnetized for some time was as satisfactory as that performed in a freshly-magnetized water, with high yield.

Table 4 Synthesis of pyrano[2,3-*c*]pyrazole **6a** at different times after water magnetization

Entry	Time after completion of magnetic exposure (h)	Yield (%)[a]
1	0 (freshly-magnetized water)	97
2	2	97
3	4	90
4	6	70
5	8	40

With these results in hand, we focused on the general applicability of the developed one-pot protocol by screening a number of aldehydes with different substituents (Table 5). A broad scope of different aldehydes was tested, and pyrano[2,3-*c*]pyrazoles were obtained in good to excellent yields. The nature of the functional group present on the aromatic ring of the aldehyde used exerted a slight influence on the reaction time. Furthermore, the steric effects of the substituents at the ortho positions of the aromatic aldehydes had no obvious impact on the reaction yield (Table 5, entries 1–17). Notably, the heteroaryl aldehydes such as furan-2-carbaldehyde, thiophene-2-carbaldehyde, pyridine-4-carbaldehyde, and 2-chloro quinolone-3-carbaldehyde were also well-tolerated to afford their corresponding products in high isolated yields (Table 5, entries 18–21). It is pertinent to note that aliphatic aldehydes were not found to be appropriate starting materials in many

Table 5 Synthesis of pyrano[2,3-*c*]pyrazoles **6**

Entry	Ar	Product	Time (min)	Yield (%)[a]	MP (°C) (lit.) [ref.]
1	Ph	**6a**	10	98	240–242 (242–244) [38]
2	2-OH-C_6H_4	**6b**	12	87	210–212 (208–210) [3]
3	4-Me-C_6H_4	**6c**	12	93	197–199 (197–198) [39]
4	4-MeO-C_6H_4	**6d**	15	95	211–213 (210–212) [40]
5	2-MeO-C_6H_4	**6e**	15	90	248–250 (249–250) [38]
6	4-Me_2N-C_6H_4	**6f**	20	87	217–219 (219–220) [40]
7	4-Cl-C_6H_4	**6g**	20	92	232–234 (234–235) [38]
8	2-Cl-C_6H_4	**6h**	20	88	244–246 (245–246) [38]
9	2,4-$Cl_2C_6H_3$	**6i**	15	90	227–229 (229–230) [38]
10	2,6-$Cl_2C_6H_3$	**6j**	20	88	189–191 (188–190) [41]
11	4-Br-C_6H_4	**6k**	10	90	246–248 (249–250) [40]
12	2-NO_2-C_6H_4	**6l**	15	86	241–242 (243–244) [38]
13	3-NO_2-C_6H_4	**6m**	10	87	230–232 (232–233) [40]
14	4-NO_2-C_6H_4	**6n**	10	95	249–250 (248–249) [38]
15[b]	4-CHO-C_6H_4	**6o**	15	94	238–240 (240–242) [42]
16	2,3,4-$(OMe)_3$-C_6H_2	**6p**	10	90	224–225 (223–225) [40]
17	3,5-$(OMe)_2$-4-OH-C_6H_2	**6q**	20	88	210–212
18	2′-Furanyl	**6r**	10	94	228–230 (230–232) [40]
19	2′-thiophenyl	**6s**	15	97	222–224 (224–226) [40]
20	4′-Pyridinyl	**6t**	10	96	215–217 (216–217) [40]
21	2-Chloro quinolone-3-yl	**6u**	10	92	235–237
22	CH_3–	**6v**	20	86	155–157 (155–158) [43]
23	$(CH_3)_2CH$–	**6w**	25	90	163–165 (166–168) [44]
24	$(CH_3)_2CHCH_2$–	**6x**	20	93	184–186 (186–188) [45]

Reaction conditions: Hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), malononitrile (1.0 mmol), aldehyde (1.0 mmol), and magnetized water (4 mL), magnetization time (10 min) at 25 °C

[a] Isolated yield

[b] Disubstituted product

reported procedures due to the formation of unwanted by-products via various side-reactions such as the aldol condensation and Cannizzaro reaction. Fortunately, the magnetized water-catalyzed transformations were not found to be limited to the aliphatic aldehydes, and gave the pyranopyrazole products in high yields (Table 5, entries 22–24).

The excellent efficiency of magnetized water, as a promoting medium, in the synthesis of pyrano[2,3-*c*]pyrazoles motivated us to explore their efficacy for the synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidine derivatives. In order to optimize the reaction conditions, the reaction of ethyl acetoacetate (1.0 mmol), hydrazine hydrate (1.0 mmol), benzaldehyde (1.0 mmol), and barbituric acid (1.0 mmol) was chosen as a model reaction in water and magnetized water in order to establish the effectiveness of magnetized water at various temperatures, and the results obtained are tabulated in Table 6 (Scheme 1). As shown in Table 6, only a low yield of product **7a** was formed in water and an aqueous solution with pH 5.5 at 50 °C (Table 6, entries 1 and 2). Then we tried to optimize the reaction conditions with different magnetized water. As indicated in Table 6 (entries 3–5), with increase in the time of water magnetization from 5 to 15 min, the reaction product **7a** was obtained in a shorter time and with more yield. The best product yield was found to be in water magnetized in 10 min, and for a reaction time of 10 min at 50 °C (Table 6, entry 4). It was found that at 25 °C, the reaction proceeded slowly, giving a low product yield (Table 6, entry 6). The increase in the reaction temperature up to 50 °C did not improve the yield (Table 6, entry 7). In addition, to demonstrate the efficiency and practicability of this method in the synthesis of these types of molecules, the model reaction was carried out in a scale of 50 mmol. As expected, the desired product could be obtained with 97 % yield in 10 min (Table 6, entry 8).

Using the optimized reaction condition, several pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidine derivatives were prepared (Table 7). As it is evident in this table, all reactions proceeded efficiently, and the desired products were produced in high to

Table 6 The synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidine **7a** under various conditions

Entry	Solvent	Magnetization time (min)	pH	Temp. (°C)	Reaction time (min)	Yield (%)[a]
1	Distilled water	–	6.9	50	120	25
2	Distilled water	–	5.5	50	120	30
3	Magnetized water	5	6.0	50	20	84
4	Magnetized water	10	5.5	50	10	96
5	Magnetized water	15	5.5	50	10	96
6	Magnetized water	10	5.5	25	40	57
7	Magnetized water	10	5.5	70	10	96
8[b]	Magnetized water	10	5.5	50	10	97

Reaction conditions: Ethyl acetoacetate (1.0 mmol), hydrazine hydrate (1.0 mmol), benzaldehyde (1.0 mmol), barbituric acid (1.0 mmol), and solvent (5 ml)

[a] Isolated yield

[b] 50 mmol scale

Table 7 Synthesis of pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines **7**

Entry	Ar	Product	Time (min)	Yield (%)[a]	MP (°C) (lit.) [ref.]
1	Ph	**7a**	5	98	217–219 (218–220) [9]
2	4-OH-C_6H_4	**7b**	5	92	264–266 (263–265) [10]
3	4-Me-C_6H_4	**7c**	10	90	201–203 (200–201) [9]
4	4-MeO-C_6H_4	**7d**	5	92	226–228 (228–230) [10]
5	2-MeO-C_6H_4	**7e**	10	97	231–233 (230–231) [9]
6	4-Me_2N-C_6H_4	**7f**	12	87	258–260 (260–262) [10]
7	4-Cl-C_6H_4	**7g**	5	94	220–222 (222–223) [9]
8	2-Cl-C_6H_4	**7h**	10	90	224–226 (223–225) [9]
9	2,4-$Cl_2C_6H_3$	**7i**	10	94	234–236 (233–234) [9]
10	2,6-$Cl_2C_6H_3$	**7j**	12	92	194–196
11	4-Br-C_6H_4	**7k**	10	88	209–211 (211–212) [9]
12	2-NO_2-C_6H_4	**7l**	8	92	208–210 (208–209) [9]
13	3-NO_2-C_6H_4	**7m**	5	94	264–266 (266–267) [9]
14	4-NO_2-C_6H_4	**7n**	5	97	233–235 (233–234) [9]
15[b]	4-CHO-C_6H_4	**7o**	17	92	165–167
16	2,3,4-$(OMe)_3$-C_6H_2	**7p**	15	85	195–197 (193–194) [9]
17	3,5-$(OMe)_2$-4-OH-C_6H_2	**7q**	20	86	240–242
18	2′-Furanyl	**7r**	15	92	173–175 (176–177) [9]
19	2′-Pyridinyl	**7s**	15	88	246–248 (247–248) [9]
20	2-Chloro quinolone-3yl	**7t**	5	93	271-273

Reaction conditions: Hydrazine hydrate (1.0 mmol), ethylacetoacetate (1.0 mmol), aldehyde (1.0 mmol), barbituric acid (1.0 mmol), and magnetized water (5 mL), magnetization time (10 min), at 50 °C

[a] Isolated yield

[b] Disubstituted product

excellent yields in relatively short reaction times without formation of any by-product. The reactions proceeded rapidly for aromatic aldehydes with the electron-withdrawing or electron-donating groups at different positions of the ring (Table 7, entries 1–17), and heteroaryl aldehydes (Table 7, entries 18–20), and the desired products were isolated in excellent yields without any side product formation in short reaction times.

Interestingly, all the starting materials were soluble in magnetized water so that at the beginning of the reaction, a solution that looked nearly transparent was observed. All the products obtained were found to be insoluble in magnetized water, and with the reaction progress, they sedimented slowly in the reaction mixture (Fig. 2).

A comparative study of the reaction conditions for the synthesis of pyrano[2,3-*c*]pyrazoles (Table 8, entries 1–7) and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines (Table 8, entries 8–11) using the methods given in Table 8 and reported in the present article demonstrate that the present protocol is indeed superior to several of the other protocols. As shown in Table 8, most of the listed methodologies suffer

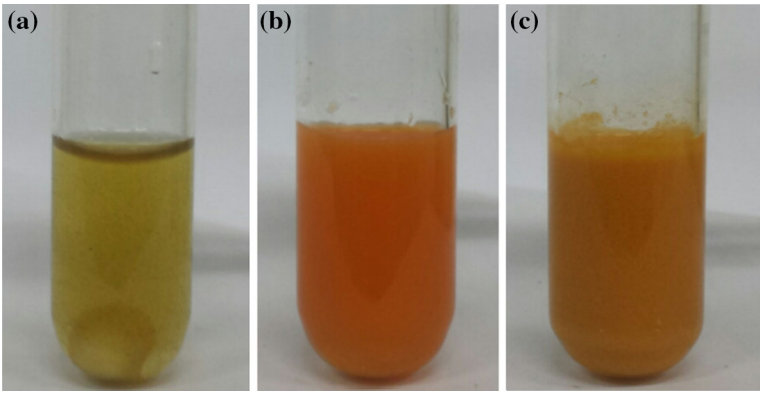


Fig. 2 Progress of the reaction between ethyl acetoacetate, hydrazine hydrate, 4-nitrobenzaldehyde, and barbituric acid in magnetized water without any catalysts (**a** beginning of the reaction, **b** after 10 min of reaction at 50 °C, **c** the end of the reaction)

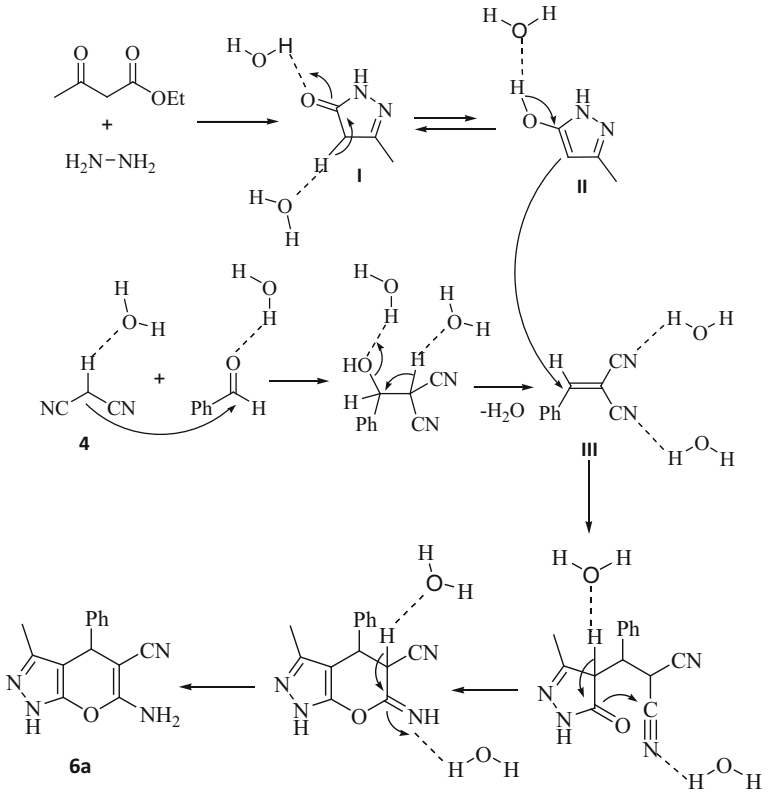
Table 8 Comparison of reaction conditions of magnetized water with the most recent reported catalyst for the synthesis of pyrano[2,3-*c*]pyrazoles and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines

Entry	Catalyst (mol%)	Product	Conditions	Time (min)	Yield (%) [ref.]
1	β-Cyclodextrin (10)	**6a**	H_2O/80 °C	15	92 [3]
2	Cetyltrimethyl ammonium chloride (30)	**6a**	H_2O/90 °C	24	92 [4]
3	Cocamidopropyl betaine (0.02)	**6a**	H_2O/60 °C	4	90 [43]
4	Imidazole (50)	**6a**	H_2O/80 °C	20	89 [46]
5	Meglumine (10)	**6a**	H_2O/rt	15	30 [38]
6	Piperidine (5)	**6a**	H_2O/rt	5	94 [47]
7	Present work (no catalyst)	**6a**	Magnetized water/ 25 °C	7	97
8	DABCO (20)	**7a**	H_2O/reflux	20	99 [8]
9	Meglimine (10)	**7a**	H_2O/rt	15	95 [9]
10	Nano-titanium dioxide (10)	**7a**	H_2O/reflux	60	55 [10]
11	Present work (no catalyst)	**7a**	Magnetized water/ 50 °C	5	96

from some limitations such as the prolonged reaction times, elevated temperatures, and use of catalysts.

The plausible mechanism for the synthesis of pyrano[2,3-c]pyrazole **6a** from ethyl acetoacetate, hydrazine, benzaldehyde, and malononitrile in magnetized water is shown in Scheme 2.

Pyrazolone **I** was formed by the condensation of ethyl acetoacetate and hydrazine, and was converted to its corresponding enolate form **II** in the presence of magnetized water. Magnetized water plays a major role in its promoting activity for the formation of phenylidenemalononitrile **III**, which is readily prepared in situ by



Scheme 2 Plausible mechanism for synthesis of pyrano[2,3 *c*]pyrazole **6a**

the Knoevenagel condensation of benzaldehyde **2a** with the highly active CH acidic malononitrile **4**. Finally, the Michael-type addition of 3-methyl-1*H*-pyrazol-5(4*H*)-one **II** to phenylidenemalononitrile **III** followed by cyclization and tautomerization yielded pyrano[2,3-*c*]pyrazole **6a**.

Conclusion

In conclusion, we reported a highly efficient, catalyst-free, and green method for the one-pot four-component synthesis of pyrano[2,3-*c*]pyrazole and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidine derivatives using magnetized water as an inexpensive new solvent. The merits for the presented methodology are its efficiency, generality, green solvent, wide scope of substrates, high yield, short reaction time, cleaner reaction profile, and simple work-up procedure, which make it a useful and attractive process for the synthesis of pyranopyrazoles and pyrano[4′,3′:5,6]pyrazolo [2,3-*d*]pyrimidines. We would like to state that this method involves an environmentally-friendly procedure, and that it is the first

reported procedure for the organic synthesis in magnetized water. Moreover, the presented method can be used in a large scale synthesis.

Acknowledgments We gratefully acknowledge the financial support of the Research Council of the Shahrood University of Technology.

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