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Ultrasonic-accelerated rapid protocol for the improved synthesis of pyrazoles

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Abstract:

A simple, catalyst-free, green synthetic protocol is described for the one-pot synthesis of pyrazoles *via* multicomponent reaction of aromatic aldehydes, hydrazine monohydrate and ethyl acetoacetate and malononitrile/ammonium acetate in water under ultrasound irradiation. This protocol avoids traditional chromatography and purification steps and it affords highly selective conversion with no byproducts.

***Keywords*:** Ultrasound, multicomponent reaction (MCR), one-pot synthesis, pyrazole derivatives, water as solvent.

1. Introduction

Development of simple and eco-friendly procedures for synthesis of compounds with biological interest is the driving force for the discovery and design of new bioactive compounds. Multicomponent reactions (MCRs) are gaining importance and are in high demand in modern organic synthesis. It is particularly true in case of heterocycles [1] as those reactions facilitate formation of several bonds in one unit operation [2, 3]. In the recent years, ultrasound irradiation has gained recognition as a clean and advantageous approach in organic synthesis [4]. The sonochemical phenomenon is the result of the interaction of suitable field of acoustic waves with potentially reacting chemical system. This phenomenon occurs through acoustic cavitation. The phenomenon of cavitation in an irradiated solution may be expressed as a sequential process of involving the bubble formation, its growth and breakdown. Cavitation phenomenon develops high temperature and pressure in the micro environment which creates turbulence and facilitates the mass transfer in the neighborhood. Compared to conventional heating which provides

thermal energy in the macro system, ultra sonification reduces reaction times, improves yields and minimizes side product formation by providing the activation energy in micro environment [5]. As this technology involves energy conservation and minimal waste generation, it is widely accepted as a green chemistry approach [6]. Furthermore, this technique can be applied to a variety of organic syntheses accomplishing better yields, under mild reaction conditions and shorter reaction times [7].

Countless biologically and pharmacologically important compounds constitute pyrazoles and their derivatives [8]. A number of pyrazole containing compounds such as Celebrex, Viagra and Acomplia have been successfully commercialized [9]. Pyrazoles have also found applications in the agrochemical industry as ultraviolet stabilizers and energetic materials and in the field of photoprotectors [10]. Owing to the attractive pharmacological properties of pyrazoles, new methodologies for the design of different pyrazoles have attracted the attention of the researchers. Several methods are available in literature for one-pot synthesis of pyrazoles derivatives in presence or absence of catalysts [11]. Certain protocols reported to use catalysts such as triethyamine [12], hydrotalcite [13], L-proline in [bmim]BF_4 [14] and using water as a solvent in catalyst-free condition [15], to mention a few. While Dabiri *et al.* [16] have reported the synthesis of tetrahydropyrazolopyridine derivatives using ethanol as solvent; Zhao *et al.* [17] have synthesized tetrahydropyrazolopyridine derivatives using a pre-formed pyrazolone and ethanol as solvent under refluxing conditions. Many of the reported methods suffer some drawbacks, like high temperature requirements, prolonged reaction times, toxic solvents and/or expensive reagents. Some of the protocols have limitations of low yields or undesired product formation due to poor selectivity of the process. Hence, there is definite longing for less expensive and catalyst free protocols. Thus, the greater demand for better and efficient protocols materials has accentuated the need to develop novel, value-added, eco-compatible and green routes motivated the present work.

2. Materials and methods

2.1. Apparatus and analysis

All chemicals used were reagent grade and were used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 ^{o}C at 400 MHz and 100 MHz

(Bruker Avance) instrument respectively, using TMS as internal standard. Chemical shifts are given in parts per million (ppm). The FT-IR spectroscopy of samples was carried out on a Perkin Elmer Perkin Elmer Precisely 100 FT-IR spectrometer in the 400-4000 cm^{-1} region. The HRMS were recorded on a waters micromass LCT premier mass spectrometer using electrospray ionization in the positive or negative mode. The ultrasonic assisted reactions are carried out in a ''Spectralab model UMC 20 Ultrsonic cleaner" with a frequency of 40 kHz and a nominal power 250 W. Melting points were recorded on a hot stage melting point apparatus Ernst Leitz Wetzlar, Germany and were uncorrected. All the reactions and the purity of products were monitored using thin layer chromatography (TLC) on aluminum-backed plates coated with Merck Kieselgel 60 F254 silica gel, visualizing the spots under ultraviolet light and iodine chamber.

2.2. General procedure for the synthesis tetrahydropyrazolopyridine under silent conditions

A mixture of hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2.0 mmol) in H_2O (15 mL) was magnetically stirred for 30 min at room temperature (25°C) followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture was heated at 70°C for appropriate time as shown in Table 2. After the starting material was completely consumed, the reaction mixture was cooled to room temperature and water (10 mL) was added and the resulting mixture was stirred for 30 min. The precipitated product was filtered, washed with water and acetone then dried under vacuum. In most cases no further purification was necessary.

2.3. General procedure for the synthesis of tetrahydropyrazolopyridine under ultrasound irradiation

A 50 mL conical flask was charged with a mixture of hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2.0 mmol) in H_2O (15 mL). The mixture was irradiated for 10 min at room temperature followed by addition of aldehyde (1.0 mmol) and ammonium acetate (4.0 mmol). The reaction mixture was irradiated under sonication at 50°C for appropriate time as shown in Table 2. To maintain the ultrasonic bath temperature, cold/hot water was either added or removed manually. After the starting material was completely consumed, the reaction mixture was cooled to room temperature and water (10 mL) was added and the resulting mixture was

irradiated for 15 min. The precipitated product was filtered, washed with water and acetone then dried under vacuum. In most cases no further purification was necessary.

3,5-Dimethyl-4-phenyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5a)

Off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.07 (6H, s), 4.80 (1H, s), 7.08-7.21 (5, m), 11.19 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.8, 33.5, 104.7, 125.8, 127.9, 128.1, 140.5, 143.9, 161.5; IR (KBr, cm^{-1}): 3274 (NH); HRMS of [$C_{15}H_{15}N_5$ + Na] (m/z): 288.0845 (100%); Calc. Mass: 288.0822.

4-(4-Methoxy-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5b)

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.03 (6H, s), 3.82 (3H, s), 4.53 (1H, s), 7.03 (2H, d, *J* = 8.7 Hz), 7.79 (2H, d, *J* = 8.6 Hz), 8.99 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.3, 31.9, 54.9, 104.4, 113.0, 128.3, 135.1, 139.6, 157.1, 161.0; IR (KBr, cm^{-1}): 3266 (NH); HRMS of [$C_{16}H_{17}N_5O$ + 1] (m/z): 296.1975 (100%); Calc. Mass: 296.1909.

4-(4-Bromo-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5c)

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.07 (6H, s), 4.78 (1H, s), 7.04 (2H, d, *J* = 8.3 Hz), 7.37 (2H, d, *J* = 8.4 Hz), 11.32 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.2, 32.2, 104.4, 118.4, 129.7, 130.4, 131.9, 142.7, 157.5; IR (KBr, cm^{-1}): 3225 (NH); HRMS of [$C_{15}H_{14}BrN_5$ + 1] (m/z): 344.0255 (100%); Calc. Mass: 344.0260.

[4-(3,5-Dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridin-4-yl)-phenyl]-dimethyl-amine (5d)

Off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.05 (6H, s), 2.8 (6H, s), 4.69 (1H, s), 6.56 (2H, d, *J* = 8.8 Hz), 6.92 (2H, d, *J* = 8.5 Hz), 10.91 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.3, 31.7, 40.4, 104.7, 112.2, 127.8, 131.1, 148.5, 159.7, 161.0; IR (KBr, cm^{-1}): 3170 (NH); MS (ESI), *m/z* = 309 (M+1, 100%); Anal. Calcd ($C_{17}H_{20}N_6$): C 66.21, H 6.54, N 27.25%. Found: C 66.19, H 6.51, N 27.20%.

4-(3,5-Dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridin-4-yl)-phenol (5e)

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.06 (6H, s), 4.71 (1H, s), 6.59 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.4 Hz), 9.28 (1H, br, s), 11.04 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.3, 31.8, 104.6, 114.4, 128.2, 133.3, 139.7, 155.0, 161.0; IR (KBr, cm^{-1}): 3267 (NH); HRMS of [$C_{15}H_{14}BrN_5$ + Na] (m/z): 304.1229 (100%); Calc. Mass: 304.1239.

4-(2-Bromo-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5f)

Off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.92 (6H, s), 5.04 (1H, s), 7.05-7.53 (4H, m), 10.79 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.5, 30.6, 102.3, 126.8, 127.7, 128.2, 130.8, 132.3, 138.4, 142.3, 160.6; IR (KBr, cm^{-1}): 3174 (NH); MS (ESI), *m/z* = 366 (M+Na, 100%); Anal. Calcd ($C_{15}H_{14}BrN_5$): C 52.34, H 4.10, N 20.35%. Found: C 52.26, H 4.03, N 20.28%.

4-(2-Methoxy-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5g)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.04 (6H, s), 3.72 (3H, s), 5.05 (1H, s), 6.77-7.52 (4H, m), 10.75 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.3, 30.6, 55.3, 103.8, 110.3, 119.6, 126.6, 128.9, 131.8, 138.3, 155.8, 160.3; IR (KBr, cm^{-1}): 3077 (NH); HRMS of [$C_{16}H_{17}N_5O$ + 1] (m/z): 296.1996 (100%); Calc. Mass: 296.1909.

4-(2-Chloro-phenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5h)

Pale yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.94 (6H, s), 5.08 (1H, s), 7.13-7.55 (4H, m), 10.85 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.3, 30.6, 102.3, 126.3, 127.4, 128.9, 130.5, 132.2, 138.7, 140.6, 160.6; IR (KBr, cm^{-1}): 3199 (NH); HRMS of [$C_{15}H_{14}ClN_5$ + Na] (m/z): 322.1119 (100%); Calc. Mass: 322.1110.

3,5-Dimethyl-4-(2-nitro-phenyl)-1,4,7,8-tetrahydro-dipyrazolo[3,4-b;4',3'-e]pyridine (5i)

Off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.92 (6H, s), 5.44 (1H, s), 7.37-7.68 (4H, m), 10.98 (3H, br, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.0, 28.9, 101.9, 123.8, 127.1, 130.2, 131.6, 136.2, 138.6, 149.5, 160.5; IR (KBr, cm^{-1}): 3381 (NH); HRMS of [$C_{15}H_{14}N_6O_2$ + 1] (m/z): 311.1052 (100%); Calc. Mass: 311.1062.

2.4. General procedure for the synthesis pyrazoles under silent conditions

To a solution of arylaldehyde (2.0 mmol), malanonitrile (2.0 mmol), hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2 mmol) in water (15 mL). The reaction mixture was stirred at 70^{o}C for the period of time as indicated in Table 2. After the completion of the reaction (The reaction was monitored by TLC), the reaction mixture cooled to room temperature, the residue was filtered and was washed with ethanol to produce the desired solid.

2.5. General procedure for the synthesis of pyrazoles under ultrasound irradiation

A 50 mL conical flask was charged with freshly distilled benzaldehyde (2.0 mmol), malanonitrile (2.0 mmol), hydrazine hydrate (2.0 mmol) and ethyl acetoacetate (2 mmol) in water (15 mL). The reaction mixture was irradiated at 50^{o}C for the period of time (The reaction was monitored by TLC) as indicated in Table 2. After the completion of the reaction, the reaction mixture cooled to room temperature, the residue was filtered and was washed with ethanol to produce the desired solid.

6-Amino-3-methyl-4-phenyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7a)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.77 (3H, s), 4.58 (1H, s), 6.85 (2H, s, -NH_2), 7.15-7.32 (5H, m), 12.09 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.6, 36.1, 57.1, 97.6, 120.7, 126.7, 127.4, 128.4, 135.6, 144.3, 154.7, 160.8; IR (KBr, cm^{-1}): 2191 (CN), 3369 (NH_2); HRMS of [$C_{14}H_{12}N_4O$ - 1] (m/z): 251.0929 (100%); Calc. Mass: 251.0933.

6-Amino-4-(4-methoxy-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7b)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.77 (3H, s), 3.71 (3H, s), 4.53 (1H, s), 6.85 (2H, s, -NH_2), 6.85 (2H, d, *J* = 8.6 Hz), 7.06 (2H, d, *J* = 8.6 Hz), 12.07 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.6, 35.3, 54.9, 57.6, 97.8, 113.7, 120.8, 128.4, 135.5, 136.4, 157.9, 160.6; IR (KBr, cm^{-1}): 2191 (CN), 3256 (NH_2); HRMS of [$C_{15}H_{14}N_4O_2$ - 1] (m/z): 281.1039 (100%); Calc. Mass: 281.1039.

6-Amino-4-(4-bromo-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7c)

White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.78 (3H, s), 4.61 (1H, s), 6.91(2H, s, -NH_2), 7.12 (2H, d, *J* = 8.4 Hz), 7.48 (2H, d, *J* = 8.3 Hz), 12.14 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.6, 35.6, 56.7, 97.0, 119.7, 120.6, 129.6, 131.3, 135.7, 143.8, 154.6, 160.8; IR (KBr, cm^{-1}): 2189 (CN), 3395 (NH_2); HRMS of [$C_{14}H_{11}BrN_4O$ - 1] (m/z): 329.0049 (100%); Calc. Mass: 329.0038.

6-Amino-4-(4-dimethylamino-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7d)

Off-white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.78 (3H, s), 2.84 (6H, s), 4.44 (1H, s), 6.63 (2H, d, *J* = 8.6 Hz), 6.73 (2H, s, -NH_2), 6.94 (2H, d, *J* = 8.6 Hz), 12.03 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.7, 35.3, 40.1, 57.9, 98.1, 112.2, 120.9, 127.9, 131.9, 135.4, 149.1,

154.7, 160.5; IR (KBr, cm^{-1}): 2187 (CN), 3344 (NH_2); HRMS of [$C_{16}H_{17}N_5O$ - 1] (m/z): 294.1366 (100%); Calc. Mass: 294.1355.

6-Amino-4-(4-hydroxy-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7e)

White solid; ^1H NMR (400 MHz, DMSO-d_6) δ = 1.77 (3H, s), 4.46 (1H, s), 6.67 (2H, d, *J* = 8.4 Hz), 6.76 (2H, s, -NH_2), 6.93 (2H, d, *J* = 8.4 Hz), 9.29 (1H, s, -OH), 12.04 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.6, 35.4, 57.7, 98.0, 115.0, 120.8, 128.3, 134.7, 135.5, 154.7, 155.9, 160.5; IR (KBr, cm^{-1}): 2174 (CN), 3371 (NH_2); HRMS of [$C_{14}H_{12}N_4O_2$ - 1] (m/z): 267.0878 (100%); Calc. Mass: 267.0882.

6-Amino-4-(2-methoxy-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7f)

White solid; ^1H NMR (400 MHz, DMSO-d_6) δ = 1.78 (3H, s), 3.77 (3H, s), 4.97 (1H, s), 6.78 (2H, s, -NH_2), 6.87-7.20 (4H, m), 12.01 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.4, 29.1, 55.5, 56.3, 97.7, 111.2, 120.7, 120.8, 127.8, 128.5, 132.0, 135.0, 155.0, 156.3, 161.4; IR (KBr, cm^{-1}): 2194 (CN), 3374 (NH_2); HRMS of [$C_{15}H_{14}N_4O_2$ - 1] (m/z): 281.1028 (100%); Calc. Mass: 281.1039.

6-Amino-4-(2-bromo-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7g)

White solid; ^1H NMR (400 MHz, DMSO-d_6) δ = 1.75 (3H, s), 5.06 (1H, s), 6.94 (2H, s, -NH_2), 7.13-7.58 (4H, m), 12.14 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.6, 35.8, 55.9, 97.0, 120.2, 122.3, 128.3, 128.8, 130.9, 132.6, 135.4, 142.5, 154.8, 161.1; IR (KBr, cm^{-1}): 2189 (CN), 3389 (NH_2); HRMS of [$C_{14}H_{11}BrN_4O$ - 1] (m/z): 329.0033 (100%); Calc. Mass: 329.0038.

6-Amino-4-(2-chloro-phenyl)-3-methyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (7h)

White solid; ^1H NMR (400 MHz, DMSO-d_6) δ = 1.75 (3H, s), 5.06 (1H, s), 6.93 (2H, s, -NH_2), 7.16-7.41 (4H, m), 12.13 (1H, s, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.4, 33.4, 55.7, 96.8, 120.3, 127.7, 128.5, 129.4, 130.6, 131.9, 135.3, 140.8, 154.9, 161.2; IR (KBr, cm^{-1}): 2189 (CN), 3389 (NH_2); HRMS of [$C_{14}H_{11}ClN_4O$ - 1] (m/z): 285.0539 (100%); Calc. Mass: 285.0543.

3. Results and discussion

Recently, we have reported some multicomponent reactions that provide easy access to develop eco-sustainable and clean synthetic routes for the synthesis of various heterocyclic derivatives [18] and an ultrasonic-assisted method for synthesis of polysubstituted pyridines [2a].

With sustained interest in development of useful multicomponent reactions, in this communication we report an expedient approach to prepare pyrazole derivatives under ultrasound irradiation for the first time and using water as a solvent.

Literature survey shows that there are no reports either on the synthesis of tetrahydropyrazolopyridines under ultrasound irradiation, with or without catalyst, under solvent-free conditions or by using water as a solvent. Our intention was to develop an eco-friendly, methodology for the synthesis of heterocyclics of biological significance under sonochemical conditions. In that pursuit, we report our success in the one-pot synthesis of tetrahydropyrazolopyridine derivatives (**5a-i**) and pyranopyrazoles (**7a-h**) via four-component coupling reaction under ultrasound irradiation at 50^{o}C in water media (Scheme 1&2).

Preliminary studies were carried out using hydrazine hydrate (2.0 mmol), ethyl acetoacetate (2.0 mmol) and benzaldehyde 4a (1.0 mmol) under silent and ultrasound irradiation at room temperature (rt) separately, with using EtOH and water as a solvent. We did not observe any trace of the desired product under the silent conditions (Table 1, entries 1-3). The reaction was also carried out under silent conditions at increased temperatures above 50^{o}C, reaction occurred, but with low yields. Preliminary experiments with appropriate reagents were conducted using water under ultrasound irradiation at 25 (rt), 40 and 50^{o}C and with conventional heating at 70^{o}C. The increase in the reaction temperature under ultrasonification improved the yields and reduced the reaction times. Impressively, at 50^{o}C, the ultrasonic method gave the preferred product (5a) selectively with 95% yield, which could be possibly due the phenomenon of cavitations produced by ultrasound. Cavitation induces very high local temperatures and pressure inside the bubbles, leading to a turbulent flow in the liquid and enhanced mass transfer in the area. Based on the results, taking 50^{o}C as optimum condition, all the reactions were conducted at that temperature, and obtained results are summarized in Table 1. This study validates that sonochemical approach with water as media is ideal for one-pot, four-component reactions to achieve excellent yields.

The versatility of the protocol is further demonstrated by repeating the procedure for synthesizing an array of tetrahydropyrazolopyridine (**5a-i**) and pyranopyrazoles (**7a-h**) derivatives (Table 2). In this protocol, in addition to aromatic aldehydes, spatially-hindered

aldehydes such as 2-methoxy, 2-bromo and 2-chloro were also found acceptable giving good yields.

All the synthesized compounds could be purified without applying any chromatographic method. Thus escaping the need of volatile organic solvents generally required for work-up and purification in many existing procedures. To our belief, this new technique is an excellent method for the synthesis of tetrahydropyrazolopyridine derivatives and pyranopyrazoles. Moreover, it is worth noting that new C-C and C-heteroatom bonds were formed with concomitant creation of a pyrazoles involving four-component in one-pot process. All the reaction products were totally characterized by various spectroscopic technics including, FTIR, ^{1}H NMR, ^{13}C NMR and MS (Supplementary data).

The results of Table 2 confirm the advantage of ultrasound method over conventional thermal method, in terms of (i) time required for the formation of new C-C and C-heteroatom bonds under ultrasonic irradiation is shorter, (ii) cyclization takes place at low temperature compare to conventional heating, (iii) the isolated products are higher yields, and additionally (iv) the reaction and work-up is simple to execute.

4. Conclusions

In summary, we report a remarkable, eco-friendly and expedient one-pot technique for rapid synthesis of pyrazole derivatives from easily accessible starting materials, within 0.5 - 2.5 h. Ultrasound has accelerated the multicomponent reaction in good to excellent chemical yields are achieved. Furthermore, sterically hindered substrates were also well accepted resulting in good yields. This method will be of choice for the preparation of a variety of pyrazole derivatives some of which are difficult to make *via* silent approaches.

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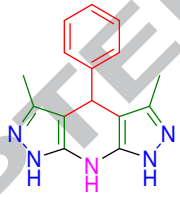
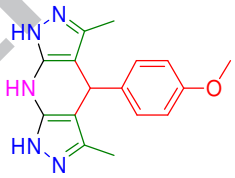
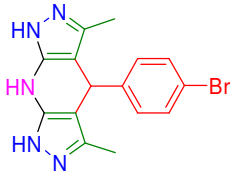
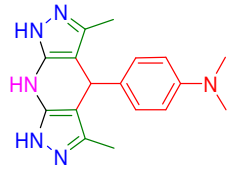
Tables and Schemes Captions

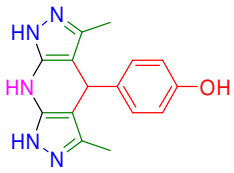
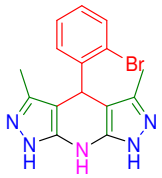
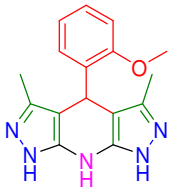
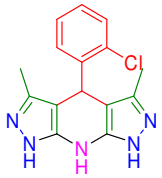
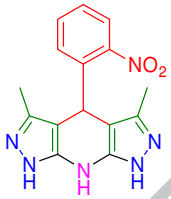
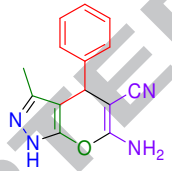
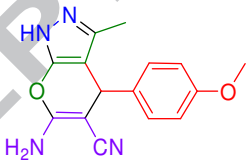
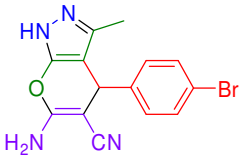
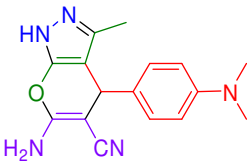
Table 1. Optimization of reaction conditions of the four-component reactions

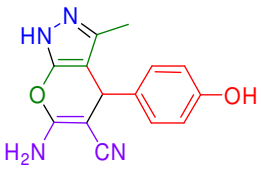
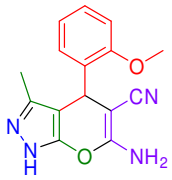
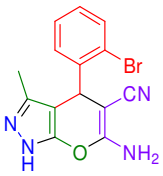
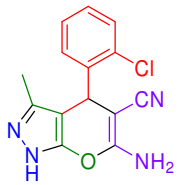
Entry	Product No.	Temperature (°C)	Solvent	Conventional		Sonication	
				Time (h)	Yield [a](%)	Time (h)	Yield [a](%)
1	**5a**	25	EtOH	7.0	b	4.0	b
2	**5a**	25	H_2O/EtOH	8.0	b	4.0	b
3	**5a**	25	H_2O	8.0	b	4.0	38
4	**5a**	70	H_2O	7.0	64	c	c
5	**5a**	50	H_2O	8.0	52	2.0	95
7	**7a**	70	EtOH	6.0	62	c	c
8	**7a**	50	EtOH	8.0	50	1.5	85
9	**7a**	50	H_2O	8.0	59	1.0	92

[a] Isolated yields, [b] Products were not found, [c] Reaction was not performed.

Table 2. Four-component reaction for the synthesis of tetrahydropyrazolopyridine (5**a-i**) and pyranopyrazoles (**7a-h**) under both ultrasonic irradiation and silent condition

Entry	Product No.	Product	Conventional		Sonication		MP/(°C)	
			Time (h)	Yield [a](%)	Time (h)	Yield [a](%)	Found	Reported
1	**5a**		7.0	64.0	2.0	95.0	239-240	240-241 [17]
2	**5b**		6.0	60.0	2.5	96.0	183-184	185-187 [17]
3	**5c**		6.0	58.0	2.0	94.0	165-166	-
4	**5d**		6.5	61.0	2.5	92.0	235-236	-

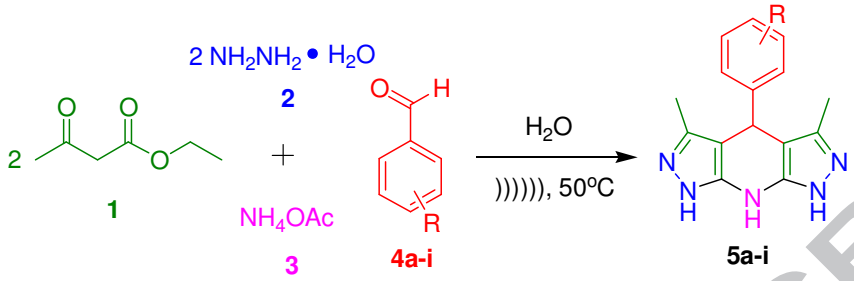
5	**5e**		6.0	63.0	2.5	90.0	267-268	268-270 [17]
6	**5f**		6.0	55.0	2.0	92.0	160-161	-
7	**5g**		5.5	60.0	1.5	91.0	171-172	-
8	**5h**		6.0	64.0	2.0	94.0	164-165	-
9	**5i**		6.5	60.0	2.5	92.0	187-188	-
10	**7a**		3.5	70.0	1.0	92.0	204-205	205-207 [4f]
11	**7b**		2.0	69.0	1.0	94.0	210-211	-
12	**7c**		3.0	80.0	0.5	97.0	214-215	213-215 [4f]
13	**7d**		3.5	64.0	1.0	96.0	217-218	-

14	**7e**		3.5	73.0	1.5	90.0	217-218	219-221 [4f]
15	**7f**		3.0	67.0	1.0	91.0	249-250	-
16	**7g**		3.0	72.0	1.0	94.0	201-202	-
17	**7h**		2.5	78.0	1.0	96.0	220-221	224-226 [4f]

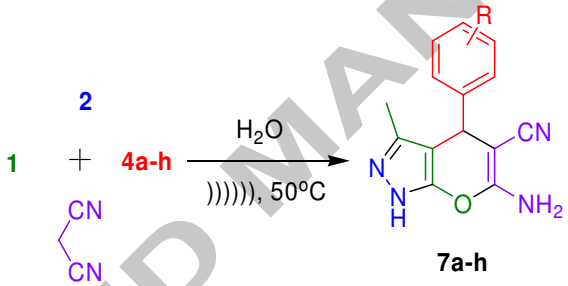
[a] Isolated yields.

Schemes

Scheme 1. multicomponent synthesis of tetrahydropyrazolopyridine **5a-i**



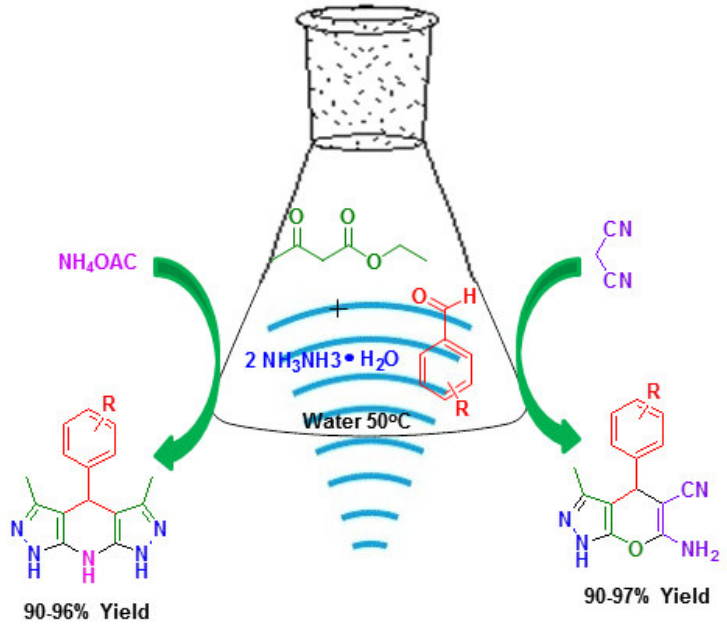
Scheme 2. multicomponent synthesis of pyrazoles derivatives **7a-h**



Catalyst-free sonochemical rapid protocol for the benign methodology and improved synthesis of pyrazoles

Ramakanth Pagadala, Nhlanhla Shabalala, Sreekantha B. Jonnalagadda*

Graphical abstract



Catalyst-free sonochemical rapid protocol for the benign methodology and improved synthesis of pyrazoles

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Highlights

- One-pot multicomponent synthesis with excellent yields and water as solvent.
- Simple, eco-friendly and cost-effective protocol for pyrazole derivatives.
- An efficient method using ultrasound irradiation
- Short reaction times at moderate conditions.