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Ultrasound-promoted an efficient method for one-pot synthesis of 2-amino-4,6-diphenylnicotinonitriles in water: A rapid procedure without catalyst

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ABSTRACT

A green and convenient approach to the synthesis of 2-amino-4,6-diphenylnicotinonitriles via four-component reaction of malononitrile, aromatic aldehydes, acetophenone derivatives and ammonium acetate in water under ultrasound irradiation is described. The combinatorial synthesis was achieved for this methodology with applying ultrasound irradiation while making use of water as green solvent. In comparison to conventional methods, experimental simplicity, good functional group tolerance, excellent yields, short routine, and selectivity without the need for a transition metal or base catalyst are prominent features of this sonocatalyzed procedure.

1. Introduction

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

Multicomponent reactions (MCRs) have received substantial consideration from the organic community for their innumerable advantages over conventional multistep synthesis [4–9]. These reactions provide instantaneous access to large compound libraries with diverse functionality. Moreover, MCRs are both atom and step economic as they avoid time consuming costly purification processes in addition to the protection and deprotection steps [10].

Ultrasonic-assisted organic synthesis (UAOS) as a green synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions [11–15]. UAOS can be extremely efficient and it is applicable to a broad range of practical syntheses. The notable features of the ultrasound approach are enhanced reaction rates, formation of purer products in high yields, easier manipulation and considered a processing aid in terms of energy conservation and waste minimization which compared with traditional methods, this technique is more convenient taking green chemistry concepts into account [16,17]. However, the use of ultrasound in heterocyclic system is not fully explored [18,19].

The pyridine ring system is an important motif in naturally occurring products as well as in many synthetic compounds of pharmaceutical interest. Among them, 2-amino-3-cyanopyridine derivatives have raised considerable attentions [20–22] since this class of compounds allowed an access to many demonstrated bio-active agents [23–25]. For example, recently 2-aminopyridine derivatives (Fig. 1) have been identified as novel IKK-β inhibitors [26], A_{2A}adenosine receptors antagonist [27], and potent inhibitor of HIV-1 integrase [28].

Despite the existence of extensive literature for the synthesis of 2-amino-3-cyanopyridines have been reported, most common procedures need multiple steps [29], using earth Lewis acid catalyst with long reaction time [30], toxic benzene as solvent [31], high temperature and microwave assistance [32,33], resulting in unsatisfactorily low yields. However, a strain forward and efficient one-pot reaction in mild and green conditions is still limited. In this context, clean and rapid multicomponent reactions (MCRs) have played an important role in this process. According to the principle of safe chemistry, synthetic methods should be designed to use substances that exhibit little or no toxicity to human health and environment. Thus, the possibility of performing multicomponent reactions in aqueous conditions under ultrasonic irradiation could enhance their efficiency from an economic as well as a green point of view.

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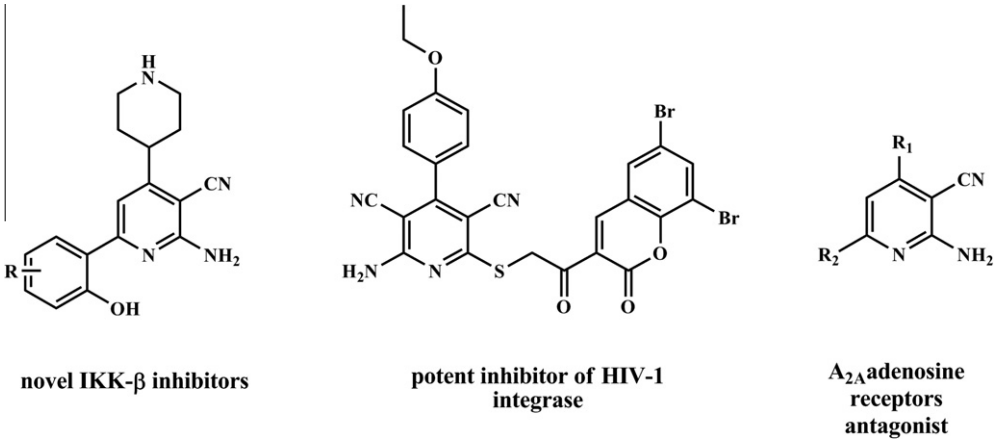


Fig. 1. Examples of biologically active pyridines.

Due to the fact that, there is need for developing multicomponent reactions in water with a suitable conditions and without the use of any harmful catalysts, also as part of our studies on the development of efficient and straightforward methods for the preparation of organic compounds from readily available building blocks [34], in this paper, we have developed a convenient, practical and efficient reaction for the synthesis of 2-amino-4,6-diphenylnicotinonitriles via four-component reaction of malononitrile, aromatic aldehydes, acetophenone derivatives and ammonium acetate under ultrasonic irradiation in water as shown in Scheme 1.

2. Experimental

All reagents were purchased from Merck (Germany) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer FT-IR 550 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in DMSO-d_6 solutions and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used; singlet (s), doublet (d), triplet (t) and multiplate (m). The element analyses for C, H, and N were performed using a Carlo ERBA Model EA 1108 analyzer carried out on Perkin-Elmer 240c analyzer, Sonication was performed in Shanghai Branson-BUG40–06 ultrasonic cleaner (with a frequency of 40 kHz and a nominal power 250 W).

2.1. Typical procedure for the synthesis of 2-amino-4,6-diphenylnicotinonitrile (4a) in water

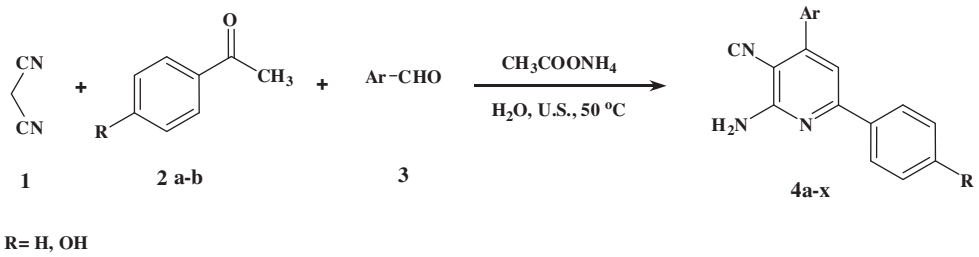
A 50 mL flask was charged with malononitrile (66 mg, 1 mmol), benzaldehyde (1 mmol), acetophenone (1 mmol), and ammonium acetate (1 mmol) in water (5 mL). The mixture was stirred at 50 °C. After the completion of the reaction (monitored by TLC), the reaction was allowed to cool. The residue was filtered and was recrystallized from ethanol to produce the desired product **4a** as white solid in 80% yield.

2.2. Ultrasound-promoted typical procedure for synthesis of 2-amino-4,6-diphenylnicotinonitrile 4a

A 25 mL Erlenmeyer flask was charged with malononitrile (66 mg, 1 mmol), benzaldehyde (1 mmol), acetophenone (1 mmol), ammonium acetate (1 mmol) and water (5 mL). The reaction flask was located in the ultrasonic bath, where the surface of reactants is slightly lower than the level of the water, and irradiated under 30, 40, and 50 kHz at 50 °C (bath temperature, the temperature inside the reactor was also 50 °C) for the period of time (The reaction was monitored by TLC) separately as indicated in Table 3. The reaction temperature was controlled by addition or removal of water from ultrasonic bath. After completion of the reaction, the mixture was diluted with water (10 mL), the solid was filtered, washed with water and dried to give crude product, which was further purified by recrystallization from ethanol to offer pure product **4a** in 91% yield.

2.2.1. Spectral data for new derivatives of 2-amino-4,6-diphenylnicotinonitrile 4h-x

2.2.1.1. 2-Amino-4-(4-methoxyphenyl)-6-phenylnicotinonitrile (4h). Colorless crystals; m.p = 192–195 °C; IR (KBr): 3353 and 3361 (NH_2), 3340 (OH), 2218 (CN) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.89 (s, 3 H, OCH_3), 7.06 (d, J = 8.8 Hz, 2 H, 2 × CH), 7.10 (br s, 2 H, NH_2), 7.20 (s, 1 H, CH), 7.4–7.6 (m, 3 H, 3 × CH), 7.63 (d, J = 8.8 Hz, 2 H, 2 × CH), 7.99 (d, J = 8.2 Hz, 2 H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 55.7 (CH_3), 86.9 (CN), 109.5(CH), 114.6 (2 × CH), 117.8 (C), 127.7 (2 × CH), 129.1



Scheme 1. Synthesis of 2-amino-4,6-diphenylnicotinonitriles under ultrasonic irradiation.

(2 × CH), 129.5 (C), 130.3 (CH), 130.5 (2 × CH), 138.1, 154.9, 158.9, 160.8 and 161.4 (5 × C).

2.2.1.2. 2-Amino-4-(4-bromophenyl)-6-phenylnicotinonitrile (4i). Colorless crystals; m.p = 225–228 °C; IR (KBr): 3351 and 3359 (NH_2), 3340 (OH), 2227 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.98 (s, 2 H, NH_2), 7.81 (s, 1 H, CH), 7.40–7.50 (m, 3 H, 3 × CH), 7.60 (d, J = 8.4 Hz, 2 H, 2 × CH), 7.69 (d, J = 8.4 Hz, 2 H, 2 × CH), 8.10 (d, J = 8.1 Hz, 2 H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 87.9 (CN), 110.9 (CH), 116.9 (2 × CH), 124.4 (C), 127.3 (2 × CH), 128.8 (2 × CH), 129.7 (C), 130.4 (2 × CH), 132.2 (CH), 135.7, 137.7, 153.8, 160.1 and 160.3 (5 × C).

2.2.1.3. 2-Amino-6-phenyl-4,4'-bipyridine-3-carbonitrile (4j). Colorless crystals; m.p = 215–218 °C; IR (KBr): 3356 and 3367 (NH_2), 3344 (OH), 2221 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.11 (s, 2 H, NH_2), 7.15 (s, 1 H, CH), 7.3–7.6 (m, 5 H, 5 × CH), 7.63 (d, J = 5.6 Hz, 2 H, 2 × CH), 7.70 (d, J = 5.6 Hz, 2 H, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 86.1(CN), 110.1 (CH), 113.6 (C), 123.3(2 × CH), 126.2 (C), 127.6 (2 × CH), 129.9 (2 × CH), 139.9 (2 × CH), 144.6 (CH), 149.8, 151.9, 156.4 and 162.6 (4 × C).

2.2.1.4. 2-Amino-6-(4-hydroxyphenyl)-4-(2-methoxyphenyl)nicotinonitrile (4k). Colorless crystals; m.p = 188–191 °C; IR (KBr): 3353 and 3360 (NH_2), 3345 (OH), 2221 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 3.77 (s, 3 H, OCH_3), 6.78 (d, J = 8.3 Hz, 2 H, 2 × CH), 6.99 (s, 2 H, NH_2), 7.12 (s, 1 H,CH), 7.20–7.40 (m, 4 H, 4 × CH), 7.95 (d, J = 8.3 Hz, 2 H, 2 × CH), 9.90 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 54.3 (OCH_3), 84.9 (CN), 108.2 (CH), 114.4 (CH), 115.5 (C), 115.3 (CH), 116.2 (C), 117.5 (CH), 118.8 (CH), 124.8 (CH), 127.4 (CH), 129.1 (C), 135.9 (CH), 137.9 (C), 153.1 (CH), 157.2, 160.8, 161.6 and 162.7 (4 × C).

2.2.1.5. 2-Amino-4-(2-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4l). Colorless crystals; m.p = 181–184 °C; IR (KBr): 3352 and 3359 (NH_2), 3341 (OH), 2221 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.78 (d, J = 7.9 Hz, 2 H, 2 × CH), 7.07 (s, 2 H, NH_2), 7.28 (s, 1 H, CH), 7.30–750 (m, 4 H, 4 × CH), 7.63 (d, J = 7.9 Hz, 2 H, 2 × CH), 9.84 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 87.5 (CN), 111.2 (CH), 116.3 (CH), 124.8 (d, C-F, $^3J_{FC}$ = 8.0 Hz, CH), 126.5 (CH), 129.2 (C), 129.7 (CH),131.1 (C), 131.9 (d, C-F, $^2J_{FC}$ = 22.0 Hz, CH), 132.5 (d, C-F, $^3J_{FC}$ = 7.9 Hz, C), 136.1 (d, C-F, $^2J_{FC}$ = 23.0 Hz, CH), 137.8 (CH), 154.4 (d, C-F, $^1J_{FC}$ = 244.0 Hz, C), 160.7 and 161.4 (2 × CH).

*2.2.1.6. **2**-Amino-4-(2-chlorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4m)*. Colorless crystals; m.p = 194–196 °C; IR (KBr): 3354 and 3361 (NH_2), 3344 (OH), 2220 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.81 (d, J = 8.2 Hz, 2 H, 2 × CH), 6.97 (s, 2 H, NH_2), 7.07 (s, 1 H, CH), 7.40–7.80 (m, 4 H, 4 × CH), 7.92 (d, J = 8.2 Hz, 2 H, 2 × CH), 10.05 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 85.4 (CN), 108.4 (CH), 115.8 (CH), 117.6 (CH), 123.5 (C), 128.7 (C), 129.4 (C), 130.9 (CH), 132.1 (CH), 136.8 (CH), 153.7, 159.2, 160.1 and 161.2 (4 × C).

2.2.1.7. 2-Amino-4-(3-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4n). Colorless crystals; m.p = 231–234 °C; IR (KBr): 3353 and 3360 (NH_2), 3339 (OH), 2228 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.81 (d, J = 9.2 Hz, 2 H, 2 × CH), 6.81 (s, 2 H, NH_2), 7.20 (s, 1 H, CH), 7.36 (t, J = 8.4 Hz, 1 H, CH), 7.40–7.60 (m, 3 H, 3 × CH), 8.0 (d, J = 9.2 Hz, 2 H, 2 × CH), 9.94 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 85.6 (CN), 108.7 (CH), 115.7 (CH), 115.9 (CH), 116.7 (d, $^2J_{FC}$ = 21 Hz, C-F, CH), 116.8 (C), 117.6 (CH), 125.0 (C), 128.7 (CH), 129.5 (C), 131.1 (d, $^3J_{FC}$ = 8.0 Hz, C-F, C), 139.8 (d, $^3J_{FC}$ = 8.0 Hz, C-F, CH), 153.4 (CH), 159.3, 160.1 and (3 × C), 161.2 (CH), 162.5 (d, $^1J_{FC}$ = 240 Hz, C-F, CH).

2.2.1.8. 2-Amino-6-(4-hydroxyphenyl)-4-(3-methoxyphenyl)nicotinonitrile (4o). Colorless crystals; m.p = 215–218 °C; IR (KBr): 3352 and 3363 (NH_2), 3335 (OH), 2225 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 3.82 (s, 3 H, OCH_3), 6.83 (d, J = 8.4 Hz, 2 H, 2 × CH), 6.90 (s, 2 H, NH_2), 7.16 (s, 1 H, CH), 7.20 (d, J = 7.2 Hz, 2 H, 2 × CH), 7.44 (dd, J = 8.0 Hz, J = 7.2 Hz, 1 H, CH), 7.70 (d, J = 8.0 Hz, 1 H, CH), 8.0 (d, J = 8.4 Hz, 2 H, 2 × CH), 9.93 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 55.4 (OCH_3), 85.3 (CN), 109.5 and 114.6 (2 × CH), 115.9 (C) and 116.3 (2 × C), 117.8 (CH), 119.4 (C), 125.4 (CH), 127.5 and 128.9 (2 × C), 132.2 and 139.3 (2 × CH), 153.4 (CH), 158.2, 160.8, 161.7, 163.5 (4 × C).

2.2.1.9. 2-Amino-4-(3-bromophenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4p). Colorless crystals; m.p = 226–229 °C; IR (KBr): 3354 and 3364 (NH_2), 3342 (OH), 2220 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.83 (d, J = 8.0 Hz, 2 H, 2 × CH), 6.95 (s, 2 H, NH_2), 7.20 (s, 1 H, CH), 7.50 (d, J = 7.2 Hz, 1 H, CH), 7.61 (dd, J = 7.2 Hz, J = 6.8 Hz, 1 H, CH), 7.64 (d, J = 6.8 Hz, 1 H, CH), 7.84 (s, 1 H, CH), 8.02 (d, J = 8.0 Hz, 2 H, 2 × CH), 9.94 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 87.5 (CN), 107.8, 114.6, 115.5 and 115.9 (4 × CH), 116.5 (C), 118.2 (CH), 126.5 (2 × CH), 127.8 (C), 128.9, 132.8 and 135.8 (3 × CH), 154.3, 158.5, 160.8, 161.9 and 162.9 (5 × C).

2.2.1.10. 2-Amino-4-(3-chlorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4q). Colorless crystals; m.p = 196–198 °C; IR (KBr): 3354 and 3361 (NH_2), 3344 (OH), 2220 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.83 (d, J = 8.1 Hz, 2 H, 2 × CH), 6.96 (s, 2 H, NH_2), 7.19 (s, 1 H, CH), 7.50–760 (m, 3 H, 3 × CH), 7.72 (s, 1 H, CH), 8.02 (d, J = 8.0 Hz, 2 H, 2 × CH), 9.95 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 87.3 (CN), 110.3, 114.2, 115.3 and 116.9 (4 × CH), 117.5 (C), 119.3 (CH), 123.7 and 127.3 (2 × CH), 128.9, 130.7 and 137.4 (3 × C), 154.4 (CH), 158.2, 160.8, 161.9 and 164.9 (4 × C).

2.2.1.11. 2-Amino-4-(3-hydroxyphenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4r). Colorless crystals; m.p = 185–189 °C; IR (KBr): 3353 and 3358 (NH_2), 3341 (OH), 2229 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.84 (d, J = 8.8 Hz, 2 H, 2 × CH), 6.87 (s, 2 H, NH_2), 6.89 (d, J = 8.0 Hz, 1 H, CH), 6.99 (s, 1 H, CH), 7.02 (d, J = 7.6 Hz, 1 H, CH), 7.11 (s, 1 H, CH), 7.32 (dd, J = 8.0, J = 7.6 Hz, 1 H, CH), 7.97 (d, J = 8.8 Hz, 2 H, 2 × CH), 9.76 (s, 1 H, OH), 9.93 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 84.9 (CN), 111.2, 113.8 and 114.6 (3 × CH), 115.9 (C), 116.4, 118.9 and 126.8 (2 × CH), 127.2 (C), 128.3, 132.8, 140.8 and 156.9 (4 × CH), 158.6, 163.7, 164.8 and 165.5 (4 × C).

2.2.1.12. 2-Amino-4-(4-bromophenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4s). Colorless crystals; m.p = 234–237 °C; IR (KBr): 3352 and 3356 (NH_2), 3348 (OH), 2231 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.83 (d, J = 8.1 Hz, 2 H, 2 × CH), 6.93 (s, 2 H, NH_2), 7.14 (s, 1 H, CH), 7.59 (d, J = 7.9 Hz, 2 H, 2 × CH), 7.65 (d, J = 7.9 Hz, 2 H, 2 × CH), 8.0 (d, J = 8.1 Hz, 2 H, 2 × CH), 9.93 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 87.9 (CN), 110.9, 116.9 and 124.4 (3 × CH), 127.3 (C), 128.8 (CH), 129.7 and 130.4 (2 × C), 132.2 (C), 135.7 (CH), 137.7, 153.8, 160.1 and 160.3 (4 × C).

2.2.1.13. 2-Amino-6-(4-hydroxyphenyl)-4-(4-nitrophenyl)nicotinonitrile (4t). Colorless crystals; m.p = 205–208 °C; IR (KBr): 3355 and 3366 (NH_2), 3342 (OH), 1350 (N-O), 1510 (N = O), 2219 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.94 (d, J = 8.1 Hz, 2 H, 2 × CH), 6.99 (s, 2 H, NH_2), 7.22 (s, 1 H, CH), 7.27 (d, J = 7.8 Hz, 2 H, 2 × CH), 7.39 (d, J = 7.8 Hz, 2 H, 2 × CH), 7.75 (d, J = 8.1 Hz, 2 H, 2 × CH), 9.94 (1 H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 86.8 (CN), 112.2, 115.5 and 116.4 (3 × CH), 122.4 (CH), 128.8

and 132.7(C), 144.6 (CH), 148.8, 152.1, 156.6, 156.9, 159.2 and 163.2 (6 × C).

2.2.1.14. 2-Amino-6-(4-hydroxyphenyl)-4,4'-bipyridine-3-carbonitrile (4u). Colorless crystals; m.p = 237–239 °C; IR (KBr): 3354 and 3363 (NH_2), 3346 (OH), 2228 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.90 (d, J = 8.2 Hz, 2 H, 2 × CH), 6.97 (s, 2 H, NH_2), 7.18 (s, 1 H, CH), 7.21 (d, J = 5.8 Hz, 2 H, 2 × CH), 7.34 (d, J = 5.8 Hz, 2 H, 2 × CH), 7.81 (d, J = 8.2 Hz, 2 H, 2 × CH), 9.91 (1 H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 87.1 (CN), 111.5 and 115.9 (2 × CH), 116.7 (C), 123.8 and 129.3 (2 × CH), 131.9, 144.4 and 149.8 (3 × C), 151.6 (CH), 156.3, 157.9 and 162.5 (3 × C).

2.2.1.15. 2-Amino-4-(4-fluorophenyl)-6-(4-hydroxyphenyl)nicotinonitrile (4v). Colorless crystals; m.p = 201–203 °C; IR (KBr): 3357 and 3364 (NH_2), 3348 (OH), 2222 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.84 (d, J = 8.4 Hz, 2 H, 2 × CH), 6.92 (s, 2 H, NH_2), 7.15 (s, 1 H, CH), 7.40 (t, J = 6.8 Hz, 2 H, 2 × CH), 7.71 (t, J = 6.8 Hz, 2 H, 2 × CH), 7.99 (d, J = 8.4 Hz, 2 H, 2 × CH), 9.94 (1 H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 88.2 (CN), 112.4 (CH), 114.6 (C), 116.3 (d, $^3J_{FC}$ = 8.0 Hz, C-F, CH), 123.7 and 128.2 (2 × C), 131.3 (d, $^2J_{FC}$ = 22.0 Hz, C-F, CH), 146.5, 149.3 and 152.5 (C), 155.9 (CH), 157.4 (C), 163.3 (d, $^1J_{FC}$ = 242.0 Hz, C-F, C).

2.2.1.16. 2-Amino-4-(furan-2-yl)-6-(4-hydroxyphenyl)nicotinonitrile (4w). Colorless crystals; m.p = 200–203 °C; IR (KBr): 3351 and 3359 (NH_2), 3342 (OH), 2219 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.76 (d, J = 5.1 Hz, 1 H, CH), 6.84 (d, J = 8.1, 2 H, 2 × CH), 6.88 (s, 2 H, NH_2), 7.41 (s, 1 H, CH), 7.46 (d, J = 4.0 Hz, 1 H, CH), 7.96 (dd, J = 5.1 Hz, J = 4.0 Hz, 1 H, CH), 8.11 (d, J = 8.1 Hz, 2 H, 2 × CH), 9.96 (1 H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_c = 80.6 (CN), 103.7 and 113.1 (2 × CH), 113.2 (C), 115.9 and 118.1 (2 × CH), 128.7 (C), 129.2 (CH), 141.4 (C), 145.7 (CH), 149.3, 159.3, 160.1, and 161.5 (4 × C).

2.2.1.17. 2-Amino-6-(4-hydroxyphenyl)-4-(thiophen-2-yl)nicotinonitrile (4x). Colorless crystals; m.p = 220–223 °C; IR (KBr): 3354 and 3359 (NH_2), 3343 (OH), 2215 (CN) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 6.83 (d, J = 8.0 Hz, 2 H, 2 × CH), 6.93 (s, 2 H, NH_2), 7.22 (s, 1 H, CH), 7.25 (d, J = 4.2 Hz, 1 H, CH), 7.82 (d, J = 5.2 Hz, 1 H, CH), 7.86 (dd, J = 5.2 Hz, J = 4,2 Hz, 1 H, CH), 7.97 (d, J = 8.0 Hz, 2 H, 2 × CH), 9.67 (s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 81.2 (CN), 103.5 and 113.6 (2 × CH), 114.5 (C), 116.5 and 118.9 (2 × CH), 129.2 (C), 129.9 (CH), 142.6 (C), 146.3 (CH), 149.6, 159.1, 160.5 and 161.9 (4 × C).

3. Results and discussion

To find out the suitable conditions for the reaction, a series of experiments were performed with the standard reaction of malononitrile **1**, acetophenone **2a**, benzaldehyde **3a**, and ammonium acetate as a model reaction (Scheme 2).(see Scheme 3).

3.1. Effects of the solvents under ultrasound irradiation

At the onset study, we try to optimize the model process mentioned above by detecting the efficiency of several classic solvents chosen as the medium for comparison. In each case, the substrates were mixed together with 5 ml solvent under ultrasonic irradiation (40 kHz) and high speed stirring conditions. Among the tested solvents such as methanol, ethanol, acetonitrile, THF, dichloromethane, water and solvent-free conditions, the formation of product **4a** was more facile and proceeded to give not only in high yield but also with high reaction rate in water (83 yield in 45 min) (Table 1**, entry 7**). Polar protic solvents such as ethanol and methanol afforded moderate yields of desired products but took comparatively longer reaction time (Table 1**, entries 1 and 2**). When the reaction was performed in acetonitrile, THF and dichloromethane (DCM), unfortunately, the desired product was only obtained in 35%, 40% and 30% yield respectively (Table 1**, entries 3, 4, 5**). In solvent-free conditions the desert products **4a** was obtained in low yield 60% (Table 1**, entry 6**). In order to verify the effect of ultrasound irradiation, the reaction was also performed in mentioned solvents by high stirring alone under silent condition (Table 1). As shown in Table 1, in all cases, the experimental results show that the yields of the products are lower than sonication within same reaction times. Based on the results of this study, it's clear that the ultrasound improves the yields of products. In our opinion, production of ammonia from ammonium acetate in water is well and is stable by forming hydrogen bond with water in 50 °C. But this phenomenon in other solvents such as ethanol or methanol occurs less frequently. Therefore water was chosen as solvent of reaction.

3.2. Effects of reaction temperature under ultrasonic irradiation

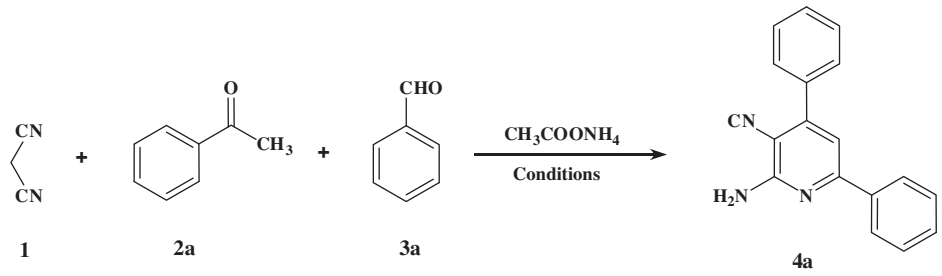
In order to further improve the yield of the reaction, we tried to perform three experiments in 30, 50, and 60 °C under ultrasonic irradiation (40 kHz) (Table 1**, entries 7, 8, and 9**). It was observed that a lower reaction temperature led to a lower yield. As shown in Table 1, entry 8, we found that high temperature could improve the reaction yield and shorten the reaction time. As shown in Table 1-entry 9, the model reaction preceded in a considerably lower yield under 60 °C due to remove of ammonia from reaction vessel in high temperature. With having these results in hand, we selected the water as solvent under ultrasound irradiation conditions for the one-pot reaction of malononitrile, acetophenone derivatives, aldehyde and ammonium acetate to give corresponding 2-amino-4,6-diphenylnicotinonitrile derivatives at 50 °C. These results were indicated that there was remarkable ultrasonic temperature effect on this reaction.

3.3. Comparison of ultrasonic irradiation and conventional method

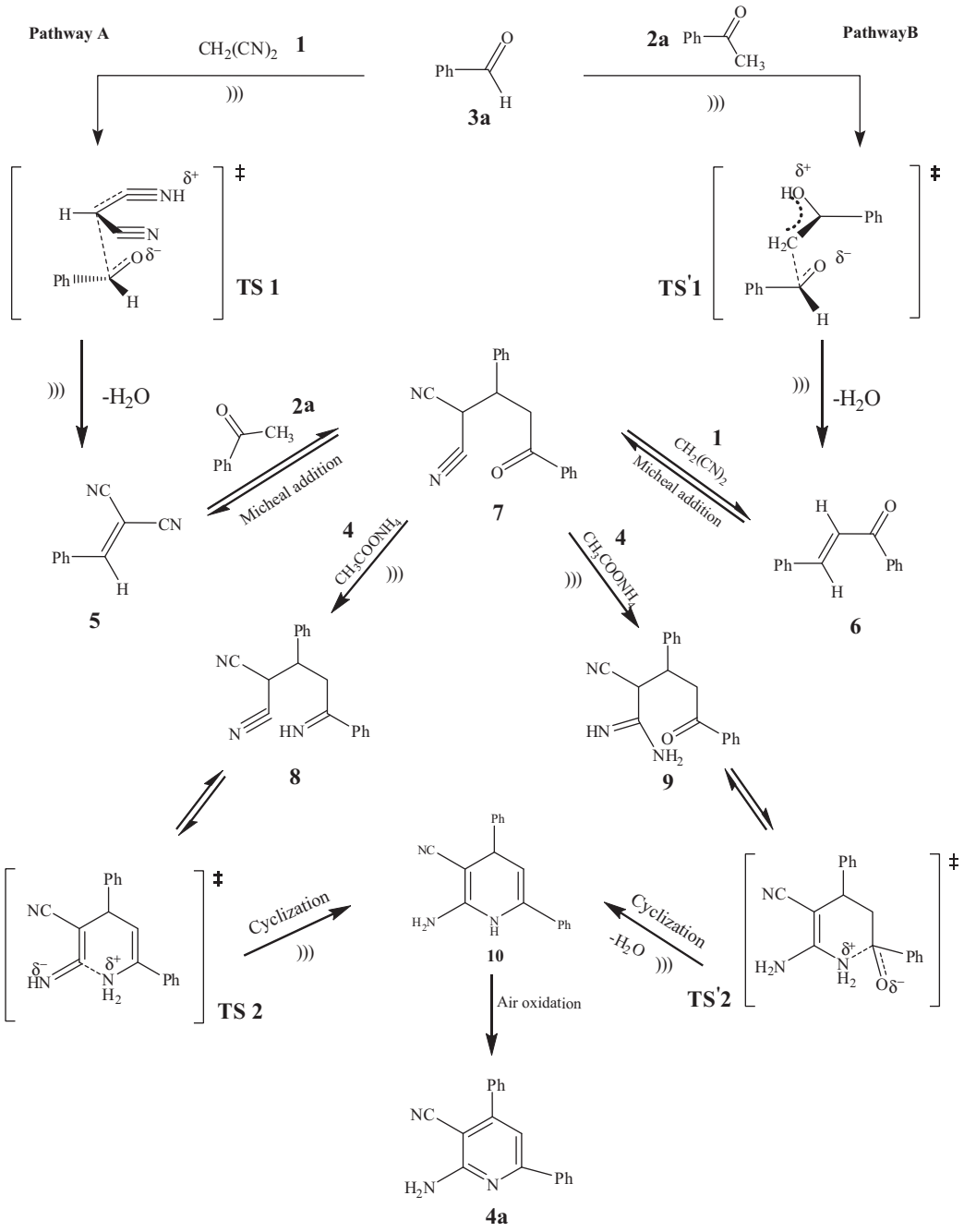
In order to verify the effect of irradiation frequency, the reaction was also performed in 30, 40, and 50 kHz. When the frequency was 40 kHz, the yield of **4a** (91%) (Table 2, entry 2) was better than that with 30 kHz irradiation within 25 min (78%, Table 2, entry 1). With increase of irradiation frequency from 40 to 50 kHz (Table 2**, entries 2, 3**), the reaction yield did not change a considerable amount (91% in the similar time). The results are shown that there is an optimum frequency for effective synthesis of **4a** in the frequency of 40 kHz in 50 °C.

3.4. High efficiency and generality of synthesis by ultrasound irradiation

After detecting more efficient solvent (water), temperature (50 °C), and frequently (40 kHz) to delineate the role of ultrasound, this methodology was examined by the reaction of several substituted aryl or heteroaryl aldehydes, malononitrile, acetophenones and ammonium acetate with and without ultrasonic irradiation at the same temperature (50 °C) in water (Table 3). When the reaction was carried out under conventional method it gave comparatively low yields of products and took longer reaction time, while the same reaction carried in the influence of ultrasonic irradiation gave excellent yields of product in short reaction time (Table 3). Thus, ultrasonic irradiation was found to have beneficial effect on the synthesis of 2-amino-4,6-diphenylnicotinonitrile derivatives



Scheme 2. Standard model reaction.



Scheme 3. Possible mechanism for the formation of product **4a**.

which was superior to the traditional method with respect to yield, reaction time.

From the results shown in Table 3, it is evident that both electron-deficient and electronrich aromatic aldehydes afford fairly

Table 1
The effect of reaction condition on the synthesis of **4a** under various conditions.

Entry	Solvent	Temperature (°C)	With sonication[a]		Without sonication[b]	
			Time (min)	Yield[c] (%)	Time (min)	Yield[c] (%)
1	Ethanol	30	75	70	75	57
2	Methanol	30	70	65	70	55
3	Acetonitrile	30	150	35	150	Trace
4	THF	30	120	40	120	25
5	DCM	30	160	30	160	Trace
6	Solvent-free	30	110	60	110	35
7	Water	30	45	83	45	60
8	Water	50	25	91	25	83
9	Water	60	25	87	25	77

[a] *Reaction conditions*: Malononitrile (1 mmol), acetophenone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (1 mmol) and solvent (5 mL) at ultrasonic frequencies of 40 kHz, the ultrasonic power was kept at 250 W.
[b] *Reaction condition*: Malononitrile (1 mmol), acetophenone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (1 mmol) and solvent (5 mL) under high stirring condition.
[c] Isolated yields.

Table 2
The synthesis of **4a** under ultrasound irradiation in various frequency.[a].

Entry	Frequency (kHz)	Temperature (°C)	Time (min)	Yield[b] (%)
1	30	50	21	78
2	40	50	21	91
3	50	50	21	91

[a] *Reaction conditions*: Malononitrile (1 mmol), acetophenone (1 mmol), benzaldehyde (1 mmol), ammonium acetate (1 mmol) and water (5 mL) at various ultrasonic frequencies, the ultrasonic power was kept at 250 W.
[b] Isolated yields.

high yields of the desired cyclocondansation in reaction with malononitrile, benzaldehyde derivatives, acetophenones, and ammonium acetate under ultrasonic irradiation in water at 50 °C.

Literature survey shows that a number of 2-amino-4,6-diphenylnicotinopyridines have been synthesized using various aldehydes [29–33]. But not a single reference has been found where spatially-hindered aldehyde such as 2-methoxy, 2-fluoro, and 2-chloro are used under ultrasonic in water. One of the advantages of this methodology is that spatially-hindered aldehydes such as 2-methoxy, 2-fluoro, and 2-chloro also give the desired products (Table 3, entries 11–13) which were not possible by using the methodology of Wang et al. [30]. Compared with the recent reported method [29–33], the dramatic improvement observed is with regard to reaction time and yield. Performance of reaction under ultrasonic irradiation in water at 50 °C permitted that these aldehydes function smoothly in this reaction. The results in Table 3 highlight a variety of structures accepted by the method to give fairly excellent yields of the desired products, the scope of the method is expected to be even wider due to its mild conditions with applying ultrasonic energy without any base, or acid catalysts.

Table 3
Synthesis of 2-amino-3-cyanopyridine derivatives under sonication and conventional conditions.

Entry	Product	R	Ar	With sonication[a]		Without sonication[b]	
				Time (min)	Yield[c] (%)	Time (h)	Yield[c] (%)
1	**4a**	H	C_6H_5	25	91	1.5	80
2	**4b**	H	4-MeC_6H_4	20	89	2.5	76
3	**4c**	OH	C_6H_5	25	93	1.5	74
4	**4d**	OH	4-$MeOC_6H_4$	23	85	2.5	68
5	**4e**	OH	4-ClC_6H_4	18	93	1.2	76
6	**4f**	OH	3-$NO_2C_6H_4$	30	95	1.2	77
7	**4g**	H	4-ClC_6H_4	20	95	1.0	85
8	**4h**	H	4-$MeOC_6H_4$	20	87	3.0	70
9	**4i**	H	4-BrC_6H_4	22	98	1.5	85
10	**4j**	H	4-pyridyl	15	95	1.2	75
11	**4k**	OH	2-$MeOC_6H_4$	30	75	3.0	–[d]
12	**4l**	OH	2-FC_6H_4	35	80	3.0	–[d]
13	**4m**	OH	2-ClC_6H_4	35	78	3.0	–[d]
14	**4n**	OH	3-FC_6H_4	15	96	1.5	82
15	**4o**	OH	3-$MeOC_6H_4$	17	90	2.0	80
16	**4p**	OH	3-BrC_6H_4	15	90	1.5	76
17	**4q**	OH	3-ClC_6H_4	15	95	1.5	82
18	**4r**	OH	3-OHC_6H_4	20	97	2.0	82
19	**4s**	OH	4-BrC_6H_4	18	97	1.5	84
20	**4t**	OH	4-$NO_2C_6H_4$	10	99	1.5	85
21	**4u**	OH	4-Pyridyl	15	98	2.2	77
22	**4v**	OH	4-FC_6H_4	15	97	1.3	82
23	**4w**	OH	2-Furyl	18	90	2.5	73
24	**4x**	OH	2-Thienyl	15	93	2.3	76

[a] *Reaction condition*: Reaction of aryl or heteroaryl aldehydes, malononitrile, acetophenones and ammonium acetate in water at 50 °C under ultrasound irradiation.
[b] *Reaction condition*: Reaction of aryl or heteroaryl aldehydes, malononitrile, acetophenones and ammonium acetate in water at 50 °C under high stirring condition.
[c] Yields of isolated products.
[d] Only obtained the intermediate benzylidenemalononitrile.

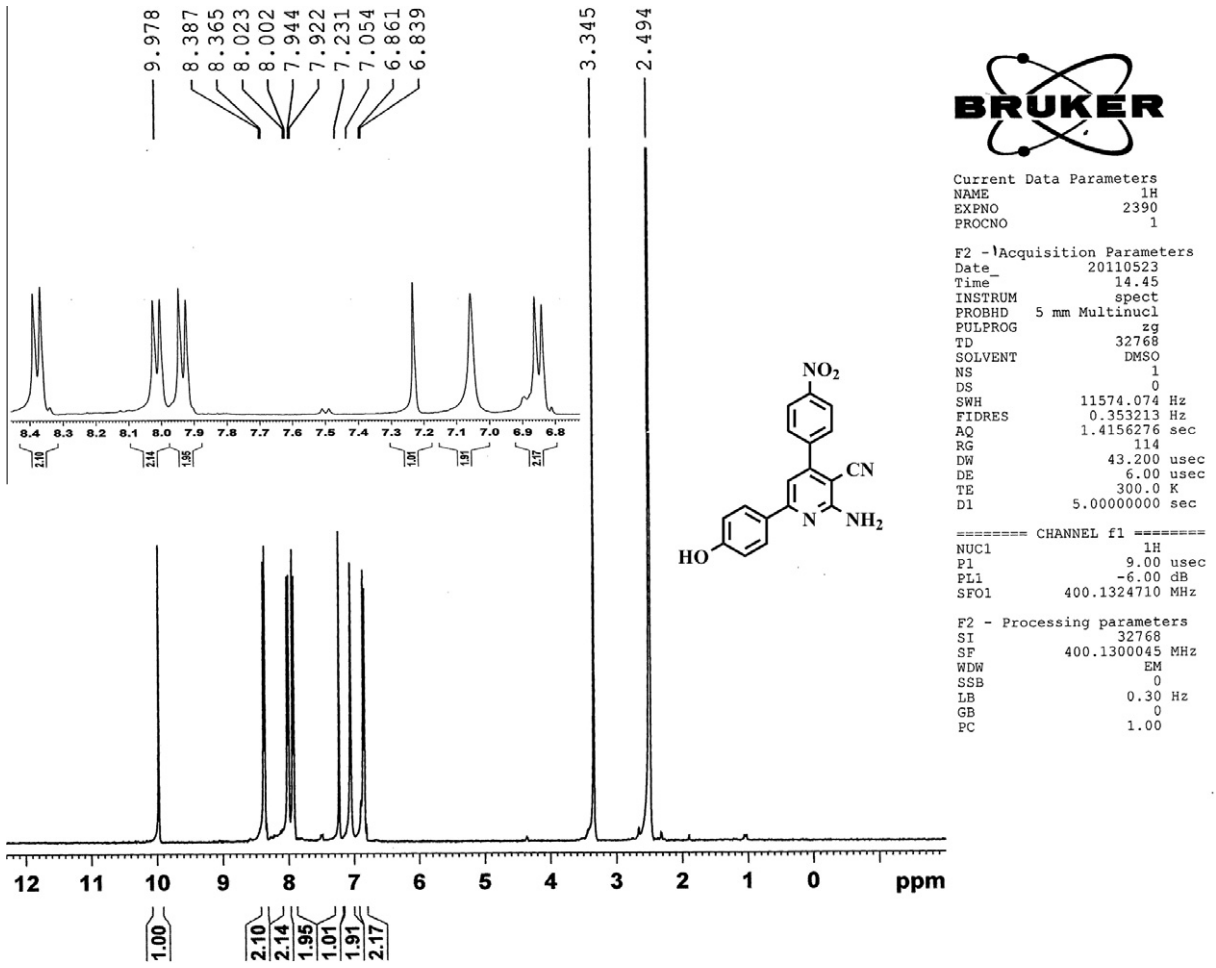


Fig. 2. ^{1}H NMR spectra of compound **4t**.

Through the experiments mentioned above, it was observed that there was a great amount of liquid in this system originally because of the bad solubility of acetophenoe and benzaldehyde in water at 50 °C. As the reaction went on under sonication, the reactants were gradually dispersed in the reaction solvent and then disappeared after about 5 min, while the classical condition needs 1.5 h. When the reaction was over (monitored by TLC), more and more solids had appeared which TLC spot (RF) was different with that of acetophenone and benzaldehyde. After separation and analysis such as ^{1}H NMR, it was surprising to find that the product is the desired one. Then, we put two experiments to further study the acceleration mechanism under sonication. After dissolution of insoluble substrates which were irradiated under sonication, we carry out the comparison between with and without ultrasound. We found that the reaction without sonication for follow-up process took a long time and the yields were relatively low. Therefore, in the present system, ultrasound was found to have beneficial effect on solubility behavior and the synthesis of **4a**.

In the heterogeneous reactions involving immiscible liquid, the reaction between these species can only occur in the interfacial region between the liquids. Sonication can be used to produce very fine emulsions from immiscible liquids. This is possible because cavitational collapse at or near the interface disrupts it and imples jets of one liquid into the other to form the emulsion [11]. These can cause the reaction to take place rapidly. The structures of isolated new products **4h-x** were deducted by physical and spectroscopic data such as: IR, ^{1}H NMR and ^{13}C NMR spectroscopy, and elemental analysis. In IR spectra, symmetrical and unsymmetrical stretching frequency of NH_2 is formed in region between ν = 3340–3360 Cm^{-1}. The stretching vibration of C≡N in nitrile group was appeared in the region between ν = 2200–2210 Cm^{-1}. In the ^{1}H NMR spectra in DMSO-d_6 was shown the two singlet signals around δ = 7.0–7.20 and δ = 7.20–7.30 ppm corresponding to NH_2 group and =C–H pyridine ring in 2-amino-4,6-diphenylnicotinopyridines was confirmed the formation of desired products in reaction (Fig. 2).

In the ^{13}C NMR spectra, one carbon link to C–C≡N has chemical shift in δ = 85.0–86.0 ppm because of anisotropic effect of triple bond of nitrile group and the signal around δ = 117.0–117.5 is assigned by one carbon of C≡N of nitrile group (Fig. 3).

3.5. The study of acceleration mechanism under irradiation of ultrasound

We have not established an exact mechanism for the formation of 2-amino-4,6-diphenylnicotinopyridines, however, a plausible mechanism explaining the aforementioned results and the selectivity is depicted in Scheme 2. The process represents a typical cascade of Knoevenagel condensation, Michael addition, and a cyclocondensation, which might initiate via two pathways, namely A and B (Scheme 2). Once the four components are mixed, benzaldehyde **3a** undergoes Knoevenagel condensation with malononitrile **1** under ultrasonic irradiation to afford benzilidene malononitrile **5**, which is subsequently attacked by **2a** to furnish the central intermediate **7** (path A). Alternatively, intermediate **7** is likely formed from initial condensation of **3a** with **2a** to afford

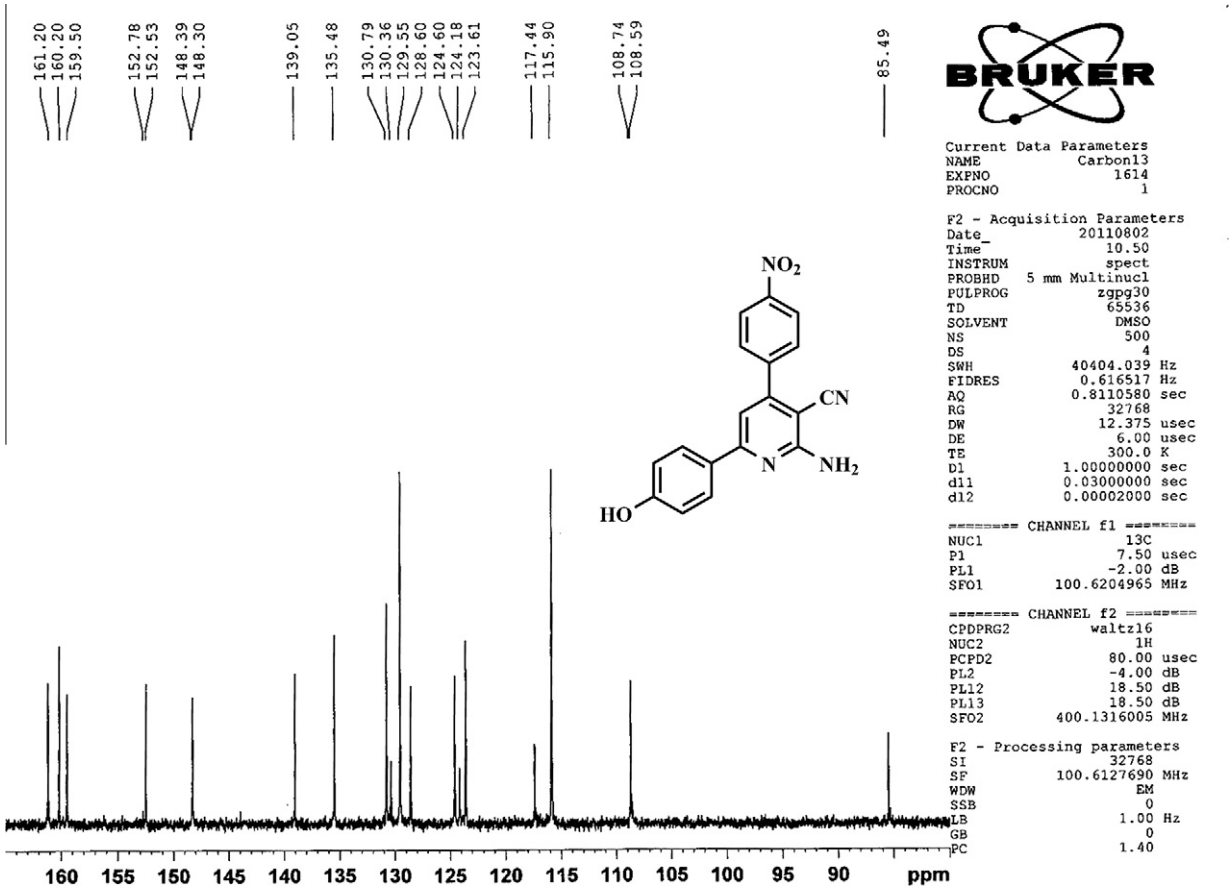


Fig. 3. ^{13}C NMR spectra of compound **4t**.

6, followed by nucleophilic addition of malononitrile **1** (path B). The two pathways go through transition states **TS1** and **TS′1** wherefrom as a consequent vibration interactions with the ultrasonic irradiation in cavities require less activation energy to give **5** or **6**. Catalysis effect of ultrasonic irradiation can also be foreseen when considering the following step where the cyclization of **8** or **9** occur also via a dipolar transition states **TS2** and **TS′2** amenable to establish favored interaction with the ultrasound in cavities. The intermediate **7** along with the two other conceivable 1,1-disubstituted methyl benzenes, i.e., those derive from addition of **1** onto **5** and addition of **2a** onto **6**, apparently exist in a complex equilibrium, which reasonably is inclined toward substitution of the weaker carbon-acid, i.e., malononitrile. Presumably, among the 1,1-disubstituted methyl benzenes involved in the equilibrium only the mixed substituted compound **7** could undergo cyclization via intermediates **8** or **9** to **10** and subsequently oxidized to the more stable aromatic compound **4a**. Thus, ultrasound irradiation activates the reaction mixture by inducing high local temperatures and pressure generated inside the cavitation bubble and its interfaces when it collapses and accelerates the reaction rate and shortens the reaction time. Also this phenomena, cavitation, cause to remove water in condensation and cyclization steps and accelerate produce of ammonia from ammonium acetate in water efficiently. Cavitation is the origin of sonochemistry, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer and allowing chemical reactions to occur. The creation of the so-called hot spots in the reaction mixture produces intense local temperatures and high pressures generated inside the cavitation bubble and its interfaces when it collapses. Under these conditions, very reactive chemical species are produced, with a very short lifetime, giving rise to the nicotinonitriles (**4a–x**) in shorter times, thus facilitating the produce of ammonia from ammonium acetate, cyclization, and dehydration step that is critical in this type of multi-component reactions. Furthermore, compared with traditional methods, this technique is more efficient and environmental-friendly, particularly when considering the basic green chemistry concepts. It is noteworthy to mention that, the effect of the nature of the substituent on the aromatic aldehydes ring showed obvious effect on this conversion. The electron-withdrawing groups not only obvious effect on the yield of this conversion but also effect on the reaction time (Table 2**, entries 20, 22**). The electron-withdrawing groups on aromatic aldehydes ring facile nucleophilic addition of acetophenone to arylidinemalononitrile **5** in pathway A or malononitrile to **6** in pathway B. The nature of the substituent on the aromatic acetophenones ring showed no obvious effect on yield and time of conversion, because they were obtained in high yields in relatively short reaction times (Table 3**. entries 1, 4**). These results stimulated us to use heteroaromatic aldehydes to show validity of this methodology. In this step, we selected 2-thiophen, 2-furan, and 4-pyridine carbaldehydes and these were employed instead of benzaldehyde derivatives to react with *p*-hydroxy acetophenone **2b**, malononitrile **1**, and ammonium acetate under ultrasonic irradiation at 50 °C in water. Surprisingly, we could get the expected 2-amino-4,6-diphenylnicotinonitrile skeletons in good yields in any cases without isolation any intermediate (Table 3**, entries 23, 24**).

4. Conclusion

In summary, an efficient method for the synthesis of the 2-amino-4,6-diphenylnicotinonitrile ring system by using simple and

readily available starting materials under ultrasonic irradiation in water was developed here. In this sonocatalyzed methodology, enabled spatially-hindered aldehydes such as 2-methoxy, 2-fluoro and 2-chloro function smoothly in this reaction. Good functional group tolerance, broad scope of usable substrates, excellent yields and short routine are prominent of the present sonocatalyzed methodology. This method provides several advantages such as environmental friendliness, shorter reaction time, excellent yields, no requirement base, earth metal Lewis acid, and simple workup procedure. We expect this method will find extensive applications in the field of combinatorial chemistry, diversity-oriented synthesis, sonochemistry, and drug discovery.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ultsonch.2012.01.005.

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