

Article

Ultrasound-Promoted One-Pot, Four-Component Synthesis of Pyridin-2(1H)-One Derivatives

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Abstract: An efficient one-pot synthesis of 1,6-diamino-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile derivatives by four-component piperidine-catalyzed reactions of a ketone, malononitrile, ethyl cyanoacetate and hydrazine hydrate under ultrasound irradiation is described. This method provides several advantages such as shorter reaction times, excellent yields, and a simple workup procedure.

Keywords: pyridin-2(1H)-one; ultrasound irradiation; multicomponent reaction

1. Introduction

Multi-component reactions (MCRs) have been designed to produce elaborate biologically active compounds and have become an important area of research in organic, combinatorial, and medicinal chemistry [1–4]. MCRs offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedure, thus avoiding the complicated purification operations and

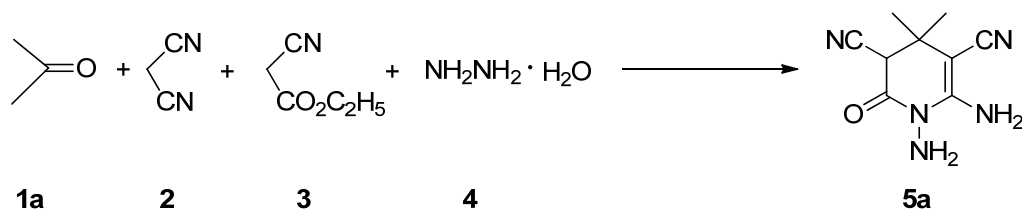
allowing savings of both solvents and reagents, making them perfectly amenable to automation for combinatorial synthesis. In the past decade there have been tremendous developments in MCRs and great efforts continue to be made to develop new MCRs [5–9].

Nitrogen-containing heterocyclic compounds are widespread in natural products and medicinal agents [10], and their applications in biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [11,12]. Among them, pyridinone derivatives have been received considerable attention as a result of their biological activities and as an interesting template for medicinal chemistry [13–16]. The conventional method for the synthesis of pyridinones is ammonization of pyranone at a high temperature or in a sealed tube [17,18]. Recently, a number of improved methods have been reported in the literatures for the synthesis of this heterocyclic system [19–21]. However, most of these methodologies suffer from disadvantages such as multi-step procedures, long reaction times, unsatisfactory yields, and the use of organic solvents or toxic reagents. These facts prompted us towards further investigation in search for a more efficient methods for the preparation of this kind of compounds.

Ultrasound irradiation has been increasingly used in organic synthesis in recent years. A large number of organic reactions can be carried out in a higher yield, shorter reaction time and under milder reaction conditions under ultrasonication. Compared with traditional methods, this method is more convenient and can be easily controlled [22]. Nevertheless, the use of ultrasound in heterocyclic systems has not been fully explored [23,24]. As a consequence of our interest in the synthesis of heterocyclic compounds under ultrasound irradiation [25–30], we report herein for the first time a facile one-pot synthesis of pyridin-2(*1H*)-one derivatives via four-component reactions of a ketone, malononitrile, ethyl cyanoacetate and hydrazine catalyzed by piperidine under ultrasound irradiation.

2. Results and Discussion

Initially, the four-component reaction of acetone (**1a**), malononitrile (**2**), ethyl cyanoacetate (**3**) and hydrazine hydrate (**4**) as a simple model was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Scheme 1). The effects of solvents and catalysts were evaluated for this model reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out without any catalysts only traces of product were detected, even after 10 h under ultrasound irradiation (Table 1, entry 1). To improve the yields, we examined this reaction using different bases (Table 1, entries 2–6). Based on the reaction times and the yields, piperidine was identified as the optimal catalyst with **5a** being isolated in 93% yield (Table 1, entry 2). In order to further improve the product yields, we tried to perform the reaction in higher temperatures under ultrasound irradiation, but the yield did not increase (Table 1, entries 7–8). Subsequently, we turned to testing the effect of solvents. MeOH, CH₃CN, THF, and water showed no superiority to EtOH (Table 1, entries 9–12). Therefore, EtOH is the solvent of choice for this reaction. To optimize the catalyst loading, 5, 10, 15, 20 and 25 mol% of piperidine was tested, respectively (Table 1, entries 13, 2, 14–16). A 10 mol% loading of piperidine was sufficient to push the reaction forward and 5 mol% of piperidine was not enough. Higher amounts of piperidine did not lead to a significant changes in the reaction yields.

Scheme 1. The model reaction.**Table 1.** Optimization of reaction conditions ^a.

Entry	Solvent	Temperature (°C)	Catalyst	Time (min)	Isolated Yield (%)
1	EtOH	rt	No catalyst	600	trace
2	EtOH	rt	Piperidine (10%)	30	93
3	EtOH	rt	NaOH (10%)	240	80
4	EtOH	rt	KOH (10%)	180	78
5	EtOH	rt	Na ₂ CO ₃ (10%)	360	62
6	EtOH	rt	EtONa (10%)	240	83
7	EtOH	40	Piperidine (10%)	30	89
8	EtOH	50	Piperidine (10%)	30	85
9	MeOH	rt	Piperidine (10%)	40	85
10	CH ₃ CN	rt	Piperidine (10%)	120	65
11	THF	rt	Piperidine (10%)	90	79
12	Water	rt	Piperidine (10%)	120	trace
13	EtOH	rt	Piperidine (5%)	60	86
14	EtOH	rt	Piperidine (15%)	60	90
15	EtOH	rt	Piperidine (20%)	30	91
16	EtOH	rt	Piperidine (25%)	30	89

^a Reaction conditions: acetone (1 nmol), malononitrile (1 nmol), ethyl cyanoacetate (1 nmol), hydrazine hydrate (1 nmol) and piperidine (0.1 nmol) in solvent (10 mL) under ultrasonic waves and the ultrasonic power 250 W, irradiation frequency 40 kHz.

Using the optimal conditions, we investigated the substrate scope of the transformation (Scheme 2). The results are summarized in Table 2. As shown in Table 2, aliphatic chain ketones and cyclic ketones were well tolerated under the reaction conditions, leading to the final products in satisfactory yields. However, when the aromatic ketones (such as acetophenone, 4-bromoacetophenone, and 4-methylacetophenone) and aromatic aldehyde (such as benzaldehyde) were used, only traces of products were detected.

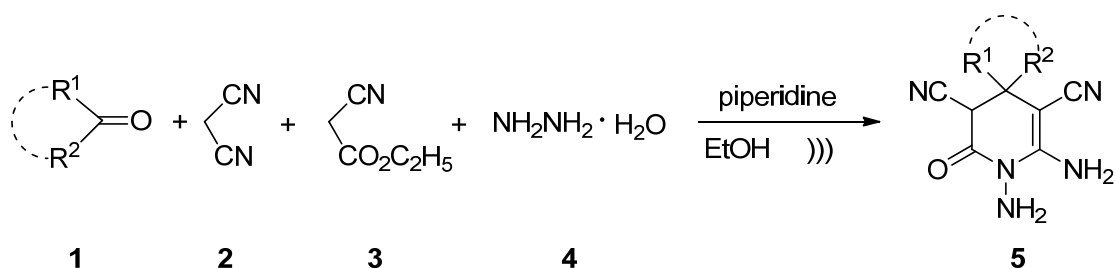
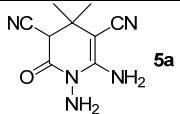
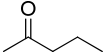
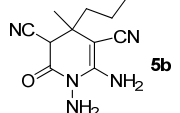
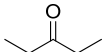
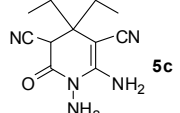
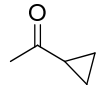
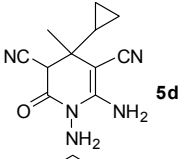
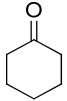
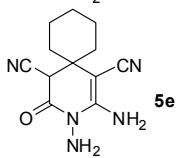
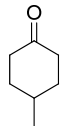
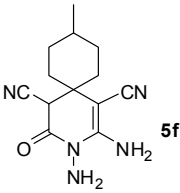
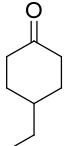
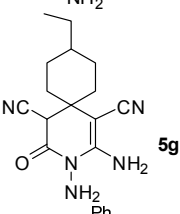
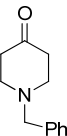
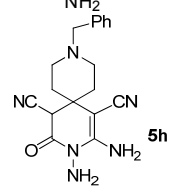
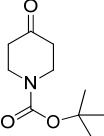
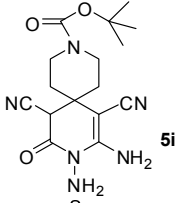
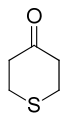
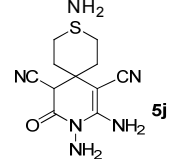
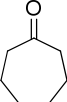
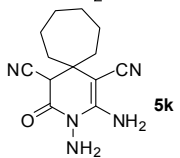
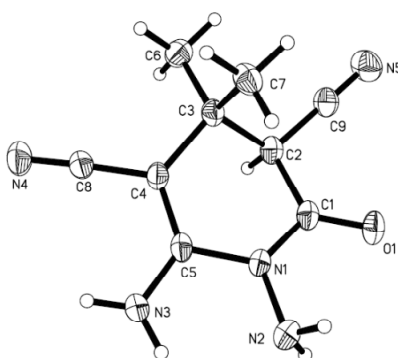
Scheme 2. The synthesis of pyridin-2(*1H*)-one derivatives **5**.

Table 2. Synthesis of pyridin-2(*1H*)-one derivatives **5**.

Entry	Ketone	Product	With US		Without US	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1		 5a	30	94	120	72
2		 5b	30	92	120	69
3		 5c	30	93	180	70
4		 5d	30	92	180	60
5		 5e	35	92	180	65
6		 5f	40	91	180	67
7		 5g	40	90	180	62
8		 5h	40	91	240	59
9		 5i	40	89	300	60
10		 5j	35	88	300	60
11		 5k	35	89	180	64

The structures of **5** were characterized using IR, ^1H -NMR, and ^{13}C -NMR spectroscopies, and HRMS analysis. Compound **5a** exhibited characteristic IR stretching frequencies in the 3415, 3346, 3305, 2175, 1702, and 1632 cm^{-1} regions for NH_2 , CN, $\text{C}=\text{O}$, and $\text{C}=\text{C}$, respectively. In the ^1H -NMR spectrum of compound **5a** the amino group protons show two singlets at δ 6.61 and 5.15. The methyl group protons show two singlets at δ 1.20 and 1.04 due to the two methyl groups. A singlet appearing at δ 4.50 was assigned to the C-3 proton of the pyridine ring. In addition, HRMS analyses were consistent with the structures. The structure of **5a** was further confirmed by X-ray diffraction. The molecular structure of **5a** is shown in Figure 1.

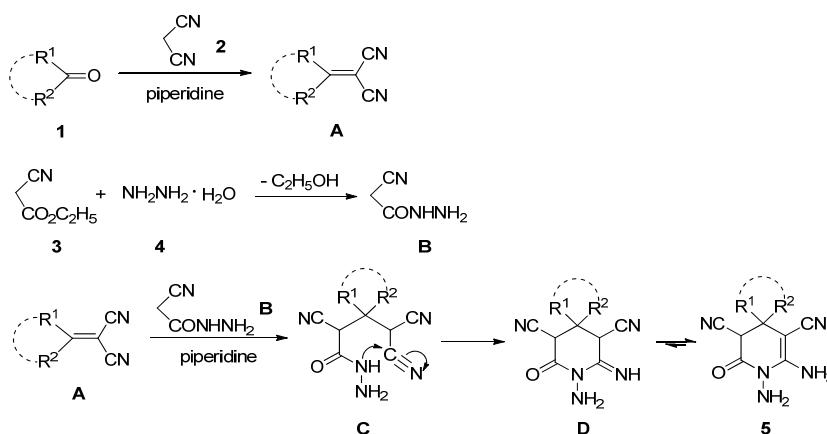
Figure 1. The crystal structure of compound **5a**.



In this tetrahydropyridine ring, because of the existence of conjugation, the distance C4–N4 [1.338(3) Å] is significantly shorter than the typical $\text{Csp}^2\text{--N}$ bond distance (1.426 Å) [31]. The tetrahydropyridine ring adopts a distorted boat conformation, atoms C3, N1, C4 and C5 are coplanar, while C1 and C2 deviate from the plane by 0.4358(39) and $-0.3639(38)$ Å, respectively.

Although the detailed mechanism of this reaction has not yet been clarified, the formation of compounds **5** can be explained by the possible mechanism presented in Scheme 3. First, a Knoevenagel condensation of ketone **1** with malononitrile **2** is proposed to give the intermediate **A**. A condensation of ethyl cyanoacetate **3** with hydrazine hydrate **4** is also proposed to give the intermediate **B**. Michael addition of intermediate **B** to **A** catalyzed by piperidine should then occur to provide intermediate **C**, which undergoes intramolecular cyclization to give intermediate **D**. In the last step, the intermediate **D** is tautomerized to afford the product **5**.

Scheme 3. The proposed mechanism for the synthesis of compound **5**.



3. Experimental

3.1. General Information

Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1} . All ^1H -NMR data were determined on a Varian Inova-400 MHz but the ^{13}C -NMR spectra had been run on the Varian Inova-300 MHz instrument, J values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS analyses were carried out using a Bruker microTOF-Q instrument. X-ray diffraction was recorded on a Smart-1000 CCD diffractometer. Ultrasonication was performed in a KQ-250E medical ultrasound cleaner with a frequency of 40 kHz and an output power of 250 W. The reaction flask was located at the maximum energy area in the cleaner, and the surface of the reactions was placed slightly lower than the level of the water. Observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs. The reaction temperature was controlled by addition or removal of water from the ultrasonic bath.

3.2. General Procedure for the Synthesis of 1,6-Diamino-2-oxo-1,2,3,4-Tetrahydro-Pyridine-3,5-Dicarbonitrile Derivatives **5**

A 100 mL flask was charged with ketone **1** (1 mmol), malononitrile **2** (1 mmol), ethyl cyanoacetate **3** (1 mmol), hydrazine hydrate **4** (1 mmol) and piperidine (10 mol%, 0.1 mmol) in ethanol (10 mL). The mixture was sonicated in the water bath of an ultrasonic cleaner at 25–30 °C. After the completion of the reaction (monitored by TLC), the reaction mixture was concentrated in *vacuo* to remove the solvent. The residue was quenched with water and then filtered. The crude products were purified by recrystallization from ethanol to afford the pure products **5**.

1,6-Diamino-4,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile (5a). White solid, 147.7 mg, 72% yield; m.p.: 198–200 °C. IR (KBr, cm^{-1}): 3415, 3346, 3305, 2175, 1702, 1632, 1569, 1428, 1340, 1218, 917, 858; ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ (ppm) 1.04 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 4.50 (s, 1H, CH), 5.15 (s, 2H, NH_2), 6.61 (s, 2H, NH_2). ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6$): δ (ppm) 24.6, 27.0, 33.0, 47.9, 62.4, 115.8, 119.8, 153.8, 162.8; HRMS: calculated for $\text{C}_9\text{H}_{10}\text{N}_5\text{O}$ $[\text{M}-\text{H}]^+$: 204.0885, found 204.0867.

1,6-Diamino-4-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile (5b). Black solid, 160.9 mg, 69% yield; m.p.: 136–138 °C. IR (KBr, cm^{-1}): 3426, 3318, 2999, 2187, 1709, 1641, 1582, 1418, 1326, 1200, 942, 878, 785; ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ (ppm) 0.85–0.86 (m, 3H, CH_3), 1.10–1.27 (m, 7H, $2 \times \text{CH}_2\text{CH}_3$), 4.65 (s, 1H, CH), 5.21 (s, 2H, NH_2), 6.66 (s, 2H, NH_2); ^{13}C -NMR (75 MHz, $\text{DMSO}-d_6$): δ (ppm) 13.7, 16.4, 23.9, 34.7, 43.9, 47.0, 59.1, 114.7, 119.5, 152.9, 162.0; HRMS: calculated for $\text{C}_{11}\text{H}_{14}\text{N}_5\text{O}$ $[\text{M}-\text{H}]^+$: 232.1198, found 232.1186.

1,6-Diamino-4,4-diethyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile (5c). White solid, 163.3 mg, 70% yield; m.p.: 170–172 °C. IR (KBr, cm^{-1}): 3445, 3317, 2988, 2195, 1707, 1645, 1576, 1418, 1369, 1206, 989, 886, 736; ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ (ppm) 0.83 (t, $J = 7.2$ Hz, 3H, CH_3), 0.91 (t, $J = 7.2$ Hz, 3H, CH_3), 1.33–1.39 (m, 2H, CH_2), 1.48–1.55 (m, 1H, CH), 1.78–1.82 (m, 1H, CH), 4.19

(s, 1H, CH), 5.20 (s, 2H, NH₂), 6.72 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 8.4, 8.9, 28.6, 30.8, 40.0, 43.7, 57.4, 115.4, 120.5, 155.0, 163.3; HRMS: calculated for C₁₁H₁₄N₅O [M-H]⁺: 232.1198, found 232.1186.

1,6-Diamino-4-cyclopropyl-4-methyl-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile (5d). Gray solid, 138.6 mg, 60% yield; m.p.: 181–182 °C. IR (KBr, cm^{−1}): 3624, 3446, 2880, 2189, 1713, 1637, 1565, 1431, 1284, 1224, 1166, 940, 839, 691; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) −0.04–0.02 (m, 1H, CH), 0.10–0.16 (m, 1H, CH), 0.31–0.40 (m, 2H, CH₂), 0.84–0.91 (m, 1H, CH), 1.32 (s, 3H, CH₃), 4.72 (s, 1H, CH), 5.23 (s, 2H, NH₂), 6.72 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) −0.7, 0.6, 16.1, 24.8, 34.8, 47.2, 54.9, 114.8, 119.6, 153.9, 161.9; HRMS: calculated for C₁₁H₁₂N₅O [M-H]⁺: 230.1042, found 230.1039.

2,3-Diamino-4-oxo-3-azaspiro[5.5]undec-1-ene-1,5-dicarbonitrile (5e). White solid, 159.4 mg, 65% yield; m.p.: 156–158 °C. IR (KBr, cm^{−1}): 3499, 3296, 2899, 2169, 1699, 1632, 1561, 1400, 1376, 1258, 914, 864, 681; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 1.04–1.07 (m, 1H, CH), 1.20–1.36 (m, 1H, CH), 1.45–1.70 (m, 8H, 4 × CH₂), 4.52 (s, 1H, CH), 5.26 (s, 2H, NH₂), 6.71 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 21.4, 21.6, 25.3, 33.4, 34.2, 35.4, 45.8, 60.8, 115.9, 121.0, 154.8, 162.4; HRMS: calculated for C₁₂H₁₄N₅O [M-H]⁺: 244.1198, found 244.1172.

2,3-Diamino-9-methyl-4-oxo-3-azaspiro[5.5]undec-1-ene-1,5-dicarbonitrile (5f). White solid, 173.6 mg, 67% yield; m.p.: 175–176 °C. IR (KBr, cm^{−1}): 3426, 3318, 2164, 1709, 1626, 1538, 1410, 1299, 1148, 902, 836, 687; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 0.89 (d, *J* = 6.4 Hz, 3H, CH₃), 1.14–1.22 (m, 1H, CH), 1.26–1.41 (m, 2H, CH₂), 1.45–1.61 (m, 4H, 2 × CH₂), 1.64–1.77 (m, 2H, CH₂), 4.49 (s, 1H, CH), 5.23 (s, 2H, NH₂), 6.68 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 22.5, 30.4, 30.5, 31.6, 32.8, 34.1, 34.9, 48.8, 59.4, 115.8, 121.7, 155.2, 163.0; HRMS: calculated for C₁₃H₁₆N₅O [M-H]⁺: 258.1335, found 258.1336.

2,3-Diamino-9-ethyl-4-oxo-3-azaspiro[5.5]undec-1-ene-1,5-dicarbonitrile (5g). White solid, 169.5 mg, 62% yield; m.p.: 184–186 °C. IR (KBr, cm^{−1}): 3418, 3216, 2186, 1712, 1656, 1566, 1432, 1240, 1121, 956, 812, 662; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 0.86 (t, *J* = 6.4 Hz, 3H, CH₃), 1.10–1.25 (m, 4H, 2 × CH₂), 1.37 (t, *J* = 8.0 Hz, 1H, CH), 1.50–1.70 (m, 5H, 2 × CH₂, CH), 1.77 (d, *J* = 9.6 Hz, 1H, CH), 4.50 (s, 1H, CH), 5.24 (s, 2H, NH₂), 6.68 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 11.7, 28.1, 29.4, 32.8, 34.1, 35.3, 38.2, 48.8, 59.4, 107.9, 115.8, 121.7, 155.2, 163.0; HRMS: calculated for C₁₄H₁₈N₅O [M-H]⁺: 272.1511, found 272.1484.

2,3-Diamino-9-benzyl-4-oxo-3,9-diazaspiro[5.5]undec-1-ene-1,5-dicarbonitrile (5h). Yellow solid, 198.5 mg, 59% yield; m.p.: 114–116 °C. IR (KBr, cm^{−1}): 3602, 3425, 3330, 2932, 2174, 1715, 1625, 1561, 1427, 1345, 1229, 1078, 985, 795, 740; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 1.68 (s, 4H, 2 × CH₂), 2.28–2.60 (m, 4H, 2 × CH₂), 3.48 (s, 2H, NCH₂), 4.57 (s, 1H, CH), 5.25 (s, 2H, NH₂), 6.78 (s, 2H, NH₂), 7.25–7.35 (m, 5H, ArH); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 33.1, 33.7, 33.8, 46.3, 48.9, 49.2, 59.6, 62.5, 115.7, 121.2, 127.4, 128.6, 129.2, 138.8, 155.2, 162.5; HRMS: calculated for C₁₈H₁₉N₆O [M-H]⁺: 335.1620, found 335.1619.

tert-Butyl-8,9-diamino-7,11-dicyano-10-oxo-3,9-diazaspiro[5.5]undec-7-ene-3-carboxylate (**5i**). White solid, 207.8 mg, 60% yield; m.p.: 222–224 °C. IR (KBr, cm^{−1}): 3422, 3315, 3216, 2971, 2189, 1703, 1672, 1635, 1571, 1479, 1170, 897, 858, 769, 665; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 1.36–1.42 (m, 9H, C(CH₃)₃), 1.43–1.44 (m, 2H, CH₂), 1.55–1.68 (m, 6H, 3 × CH₂), 4.65 (s, 1H, CH), 5.24 (s, 2H, NH₂), 6.86 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 28.4, 32.7, 33.3, 33.9, 45.9, 58.6, 79.5, 115.5, 121.0, 154.3, 162.2; HRMS: calculated for C₁₆H₂₁N₆O₃ [M-H]⁺: 345.1675, found 345.1683.

8,9-Diamino-10-oxo-3-thia-9-azaspiro[5.5]undec-7-ene-7,11-dicarbonitrile (**5j**). Yellow solid, 158.0 mg, 60% yield; m.p.: 165–167 °C. IR (KBr, cm^{−1}): 3427, 3340, 3041, 2926, 2179, 1725, 1633, 1552, 1430, 1349, 1064, 945, 829, 795; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 1.75–1.91 (m, 5H, 2 × CH₂ and CH), 2.58–2.66 (m, 3H, CH₂ and CH), 4.64 (s, 1H, CH), 5.20 (s, 2H, NH₂), 6.18 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 22.2, 22.3, 33.6, 33.7, 34.1, 44.6, 58.6, 114.6, 120.1, 154.1, 161.1; HRMS: calculated for C₁₁H₁₂N₅OS [M-H]⁺: 262.0763, found 262.0741.

2,3-Diamino-4-oxo-3-azaspiro[5.6]dodec-1-ene-1,5-dicarbonitrile (**5k**). Gray solid, 165.9 mg, 64% yield; m.p.: 179–181 °C. IR (KBr, cm^{−1}): 3356, 3189, 2198, 1703, 1686, 1589, 1453, 1256, 1141, 988, 852, 701; ¹H-NMR (400 MHz, DMSO-*d*₆): δ (ppm) 1.10 (s, 1H, CH), 1.26 (s, 1H, CH), 1.34–1.90 (m, 10H, 5 × CH₂), 4.46 (s, 1H, CH), 5.24 (s, 2H, NH₂), 6.67 (s, 2H, NH₂); ¹³C-NMR (75 MHz, DMSO-*d*₆): δ (ppm) 22.5, 23.0, 27.0, 30.3, 33.0, 35.8, 38.5, 47.8, 63.0, 116.3, 121.1, 154.2, 162.7; HRMS: calculated for C₁₃H₁₆N₅O [M-H]⁺: 258.1355, found 258.1328.

4. Conclusions

In conclusion, we have described a novel approach to exploit the use of ultrasound irradiation for the synthesis of pyridin-2(*1H*)-one derivatives in ethanol solution at room temperature within 30–40 min. Compared with traditional methods, the procedure offers several advantages, including excellent yields, shorter reaction times, and a simple workup procedure.

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Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **5a–k** are available from the authors.