Asian Journal of Chemistry; Vol. 35, No. 12 (2023), 3118-3126

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.30778

Ultrasonic Assisted Three Component Synthesis of 3-Cyano-pyridine-2(1*H*)-ones

NEELAM YADAV[1,*], RAVI KUMAR[1,2,3,*], SARITA SANGWAN[1], SONU CHAUHAN[1], VIDHI DHANDA[1], REENA RANI[1], SHEETU DEVI[1] and ANIL DUHAN[1]

[1]Department of Chemistry, Chaudhary Charan Singh Haryana Agricultural University, Hisar-125004, India
[2]MAP Section, Department of Genetics and Plant Breeding, Charan Singh Haryana Agricultural University, Hisar-125004, India
[3]Center for Bio-Nanotechnology, Charan Singh Haryana Agricultural University, Hisar-125004, India

*Corresponding authors: E-mail: raon5577@gmail.com; ravibeniwal@hau.ac.in

Received: 28 October 2023; *Accepted*: 28 November 2023; *Published online*: 2 December 2023; AJC-21477

The requirements of sustainability and the green chemistry principles have prompted organic chemistry researchers to come up with novel methods for the synthesis of organic compounds that require minimum energy consumption and pose lesser environment harm. Ultrasonication of reaction mixtures is one such methodology. High frequency sound waves are known to emit energy that is utilized in product generation. Attempts were made to synthesize 2-pyridone derivatives using ultrasonication assisted method of synthesizing 3-cyano-pyridine-2(1*H*)-one starting from a three component one pot reaction. The reaction between cyanoacetamide, aromatic ketones and substituted aromatic aldehydes in the presence of NaOH as base yielded 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives as a result of one-pot multicomponent reaction. The synthesized 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives were characterized by ^{1}H NMR, ^{13}C NMR, HRMS and FTIR spectra. Ultrasonication has been found to significantly reduce reaction time, enhance reaction rate and yield compared to conventional heating methods.

Keywords: Ultrasonication, Heterocycles, 3-Cyano-pyridine-2(1*H*)-ones, Multicomponent reaction.

INTRODUCTION

Over the past decade, significant efforts have been made to modify chemical processes to promote sustainability and environmental improvement. In recent years, numerous approaches, including microwave [1,2], ionic liquids [3], electrosynthesis [4-6], mechanochemical [7] and others [8], have been developed for the organic syntheses. Among them, ultrasonication in chemical reactions is also considered as one of the greatest achievements in this scenario [9,10]. This method offers greater convenience, control and suitability for the synthesis of heterocyclic compounds compared to the conventional method as drawbacks like long reaction times, high temperatures, low yields and use of toxic reagent, *etc.* [11].

Nitrogen containing heterocycle, especially 2-pyridone core's versatility and utility are evident in its frequent presence in bioactive natural products and pharmaceuticals [12]. 2-Pyridones are the privileged structural core in naturally occurring compounds with numerous biological activities, such as antitumor [13], anti-inflammatory [14], anti-HIV [15], antimalarial [16], antifungal [17], SARS-CoV-2 main protease inhibitor [18], antibacterial [19], antioxidant [20], anti-Hepatitis B [21], cardiotonic [22], antifibrosis [23] and anti-neurodegenerative [24] disorders.

Ultrasonic irradiation is one of the highly efficient techniques utilized in various industries such as chemical synthesis [25], pharmaceuticals [26], microbiology, food and material science [27]. Moreover, ultrasonication is a significant, cost-effective and eco-friendly method for various types of organic reactions, offering a straightforward, sustainable and convenient approach to synthesize biologically significant molecules [28]. Chemical reactions typically occur under ultrasonic conditions, specifically high-frequency sound waves ranging from 20-100 KHz in the sonic spectrum [29,30]. According to the literature, ultrasonic irradiation can speed up the synthesis of heterocyclic compounds [10]. Modern organic chemists are currently focusing on utilizing one-pot multi-component methods and ultrasonic application to synthesize biologically important heterocycles. Therefore, a ultrasonic-assisted synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives was

accomplished as a one-pot multicomponent reaction between cyanoacetamide, aromatic ketones and substituted aromatic aldehydes in the presence of NaOH as base at 70 ºC. It has been observed that several strategies have been established for the synthesis of substituted 3-cyano-2-pyridones. Hernendez *et al.* [22] synthesized 3-cyano-2-pyridone derivatives using a four component reaction between aromatic aldehyde, malononitrile, ethylacetoacetate and ammonium hydroxide. Sunil *et al.* [31] reported a cascade reaction between acrylamide and ketones for the synthesis of 4,6-disubstituted 3-cyano-2-pyridone. Thereafter, imidazole substituted 3-cyano-2-oxopyridine derivatives were synthesized by Abbas *et al*. [32] using four component reaction between aromatic aldehydes, malononitrile, ketones and ammonium hydroxide. A one pot three component reaction for the synthesis of substituted 3-cyano-pyridine-2(1*H)*-one is first time developed using ultrasonication. Ultrasonication in organic synthesis aligns with green and sustainable chemistry goals due to its advantages over traditional thermal methods in reaction rates, yields, product purity and selectivity.

EXPERIMENTAL

Progress of reaction was monitored by thin layer chromatography (TLC) on Merck silica gel GF_{254} plates using methanol in chloroform and visualizing in UV light and iodine vapours. Melting points were measured in unsealed capillaries in an electrically heated melting point apparatus. IR spectra were recorded on a Thermo-Fisher Nicolet iS50 Fourier transform infrared (FTIR) spectrophotometer in the range of 4000-400 cm^{-1} using ATR. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400-MHz and 100-MHz nuclear magnetic resonance spectrometer in DMSO-d_6 as solvent using TMS as internal standard. The HRMS (ESI) spectra were recorded with Bruker Daltonics APEXII instrument (Bruker Corp.).

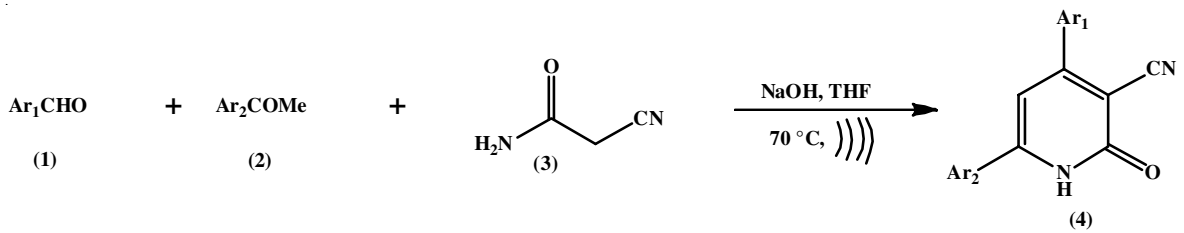
General procedure for the synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile: In a pear shaped flask, cyanoacatamide (1 mmol), appropriate aromatic aldehydes (1 mmol) and aromatic ketones (1 mmol) were mixed in THF (5 mL) and NaOH (2 mmol) as base was used to catalyze the reaction. Then the reaction mixture was placed in ultrasonic bath (40 kHz) for 2-3 min at 60 ºC. Progress of reaction was observed through TLC using UV lamp and iodine vapour. Distilled water was added in the reaction mixture after the completion of reaction. The reaction mixture was cooled at 0-5 ºC for precipitation. Solid product was formed in the reaction mixture was filtered followed by washing with water 2-3 times, dried in air and recrystallized using absolute alcohol (**Scheme-I**). The desired product (4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile) was obtained with excellent yield and same pattern was followed for the synthesis of 37 new 3-cyano-2-pyridone derivatives.

4-(4-Chlorophenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4a): Yield: 92%; white solid; m.p.: > 300 ºC; ^1H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, *J* = 8 Hz, 2H, ArH), 7.61 (d, *J* = 8 Hz, 2H, ArH), 7.55 (d, *J* = 8 Hz, 2H, ArH), 7.45 (d, *J* = 8 Hz, 2H, ArH), 6.60 (s, 1H, C5–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.48, 158.12, 154.08, 139.16, 138.17, 133.90, 133.73, 130.38, 129.16, 128.87, 128.63, 121.36, 102.45, 91.93; IR (ATR, ν_{max}, cm^{-1}): 3169, 2201, 1645, 1593, 1538, 1486, 1356, 1215, 1092, 1012, 960, 803; HRMS *m/z* (ESI) calcd. for $C_{18}H_{11}Cl_2N_2O^+$ (M+H$^+$) 341.0248, found 341.0224.

4-(2,4,5-Trimethoxyphenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4b): Yield: 88%; white solid; m.p.: 270-271 ºC; ^1H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 8 Hz, 2H, ArH), 7.44 (d, *J* = 8 Hz, 2H, ArH), 6.85 (s, 1H, ArH), 6.79 (s, 1H, ArH), 6.52 (s, 1H, C5 –H), 3.86 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.73 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.90, 156.93, 153.35, 151.02, 150.22, 142.84, 139.10, 133.73, 129.12, 128.60, 121.13, 119.50, 114.67, 104.39, 98.98, 95.35, 56.73, 56.62, 56.29; IR (ATR, ν_{max}, cm^{-1}): 2981, 2198, 1652, 1487, 1349, 1218, 1091, 815, 781; HRMS *m/z* (ESI) calcd. for $C_{21}H_{18}ClN_2O_4^+$ (M+H$^+$) 397.0955, found 397.0945.

4-(4-Fluorophenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4c): Yield: 85%; cream solid; m.p.: > 300 ºC; ^1H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, *J* = 8 Hz, 2H, ArH), 7.64 (d, *J* = 8 Hz, 1H, ArH), 7.59 (d, *J* = 8 Hz, 1H, ArH), 7.33 (d, *J* = 8 Hz, 2H, ArH), 6.60 (s, 1H, C5–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.56, 163.93, 161.49, 158.01, 154.31, 139.22, 135.77, 133.86, 130.71, 130.62 (*J* = 36 Hz), 129.16, 128.61, 121.43, 11 5.81, 115.60, 102.66, 92.14; IR (ATR, ν_{max}, cm^{-1}): 3067, 2200, 1638, 1576, 1511, 1476, 1360, 1214, 1073, 1008, 959, 802.

4-(3-Bromophenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4d): Yield: 87%; white solid; m.p.: > 300 ºC; ^1H NMR (400 MHz, DMSO-d_6): δ 8.07 (d, *J* = 8 Hz, 2H, ArH), 7.75 (s, *J* = 8 Hz, 1H, ArH), 7.64 (d, *J* = 8 Hz, 1H, ArH), 7.59 (d, *J* = 8 Hz, 1H, ArH), 7.43-7.47 (m, 3H, ArH), 6.63 (s, 1H, C5–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.46, 158.19, 153.69, 141.66, 139.10, 133.95, 131.75, 131.00, 129.23, 128.60, 127.71, 122.08, 121.18, 102.58, 91.90; IR (ATR, ν_{max}, cm^{-1}): 3103, 2204, 1601, 1567, 1535, 1474, 1360, 1216, 1093, 1012, 815, 732; HRMS *m/z* (ESI) calcd. for $C_{18}H_{10}BrClN_2O^+$ (M+H$^+$) 383.9665, found 341.9640.



Scheme-I: Ultrasonicated synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles

4-(4-Methylphenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4e): Yield: 88%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, *J* = 8 Hz, 2H, ArH), 7.49 (d, *J* = 8 Hz, 2H, ArH), 7.45 (d, *J* = 8 Hz, 2H, ArH), 7.29 (d, *J* = 8 Hz, 2H, ArH), 6.58 (s, 1H, C5–H), 2.37 (s, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.74, 157.85, 155.38, 139.29, 138.42, 136,48, 133.79, 129.37, 129.13, 128.58, 128.36, 121.51, 102.67, 92.17, 21.29; IR (ATR, ν_{max}, cm^{-1}): 3194, 2208, 1654, 1594, 1538, 1489, 1362, 1213, 1090, 1010, 961, 803; HRMS *m/z* (ESI) calcd. for $C_{19}H_{14}ClN_2O^+$ (M+H$^+$) 321.0795, found 321.0758.

4-(4-Ethoxyphenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4f): Yield: 80%; cream solid; m.p.: 270-271 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, *J* = 8 Hz, 2H, ArH), 7.68 (d, *J* = 8 Hz, 2H, ArH), 7.56 (d, *J* = 8 Hz, 2H, ArH), 7.08 (d, *J* = 8 Hz, 2H, ArH), 6.79 (s, 1H, C5–H), 4.12 (q, *J* = 8 Hz, 2H, CH_2), 1.37 (t, *J* = 8 Hz, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.26, 160.49, 158.36, 152.35, 135.69, 133.83, 130.35, 129.82, 129.14, 129.06, 118.38, 114.97, 105.83, 96.47, 63.82, 15.05; IR (ATR, ν_{max}, cm^{-1}): 2981, 2210, 1638, 1592, 1535, 1486, 1352, 1217, 1177, 1093, 1009, 961, 804; HRMS *m/z* (ESI) calcd. for $C_{20}H_{16}ClN_2O_2^+$ (M+H$^+$) 351.0900, found 351.0898.

4-(3-Methylphenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4g): Yield: 75%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, *J* = 8 Hz, 2H, ArH), 7.44 (d, *J* = 8 Hz, 2H, ArH), 7.40-7.36 (m, 3H, ArH), 7.26 (d, *J* = 8 Hz, 1H, ArH), 6.63 (s, 1H, C5–H), 2.38 (s, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.86, 157.87, 155.66, 139.25, 139.10, 138.04, 133.90, 129.62, 129.23, 129.02, 128.71, 128.60, 125.63, 121.28, 103.07, 92.28, 21.50; IR (ATR, ν_{max}, cm^{-1}): 3149, 2200, 1623, 1577, 1538, 1484, 1348, 1220, 1091, 1011, 813, 782; HRMS *m/z* (ESI) calcd. for $C_{19}H_{14}ClN_2O^+$ (M+H$^+$) 321.0795, found 321.0782.

4-(4-Methoxyphenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4h): Yield: 89%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, *J* = 8 Hz, 2H, ArH), 7.57 (d, *J* = 8 Hz, 2H, ArH), 7.45 (d, *J* = 8 Hz, 2H, ArH), 7.04 (d, *J* = 8 Hz, 2H, ArH), 6.61 (s, 1H, C5 – H), 3.82 (s, 3H, OMe): ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.85, 160.08, 157.75, 155.11, 139.20, 133.84, 131.48, 129.83, 129.19, 128.59, 121.57, 114.25, 102.87, 92.11, 55.70; IR (ATR, ν_{max}, cm^{-1}): 3067, 2200, 1638, 1591, 1533, 1510, 1424, 1361, 1241, 1092, 1008, 959, 795; HRMS *m/z* (ESI) calcd. for $C_{19}H_{14}ClN_2O_2^+$ (M+H$^+$) 337.0744, found 337.0735.

4-(Phenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4i): Yield: 90%; cream solid; m.p.: > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, *J* = 8 Hz, 2H, ArH), 7.58 (d, *J* = 8 Hz, 2H, ArH), 7.49-7.44 (m, 5H, ArH), 6.63 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.79, 157.96, 155.52, 139.30, 139.13, 133.90, 129.21, 129.01, 128.85, 128.62, 128.49, 121.34, 103.00, 92.24; IR (ATR, ν_{max}, cm^{-1}): 2991, 2210, 1699, 1582, 1496, 1399, 1230, 1151, 1094, 1001, 824, 760; HRMS *m/z* (ESI) calcd. for $C_{18}H_{12}ClN_2O^+$ (M+H$^+$) 307.0638, found 307.0636.

4-(3-Methoxyphenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4j): Yield: 82%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (d, *J* = 8 Hz, 2H, ArH), 7.45 (d, *J* = 8 Hz, 2H, ArH), 7.40 (t, *J* = 8 Hz, 1H, ArH), 7.15 (d, *J* = 8 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 7.01 (d, *J* = 8 Hz, 1H, ArH), 6.66 (s, 1H, C5 –H), 3.82 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.79, 159.55, 157. 95, 155.32, 140.65, 139.14, 133.90, 129.95, 129.24, 128. 60, 121.31, 120.79, 114.63, 113.99, 102.92, 92.19, 55.62; IR (ATR, ν_{max}, cm^{-1}): 2981, 2204, 1641, 1592, 1538, 1483, 1360, 1215, 1093, 1010, 961, 806; HRMS *m/z* (ESI) calcd. for $C_{19}H_{14}ClN_2O_2^+$ (M+H$^+$) 337.0744, found 337.0714.

4-(Furfuryl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (4k): Yield: 85%; Yellow solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 8 Hz, 2H, ArH), 7.95 (d, *J* = 4 Hz, 1H, ArH), 7.51 (d, *J* = 8 Hz, 2H, ArH), 7.46 (d, *J* = 4 Hz, 1H, ArH), 7.00 (s, 1H, C5 –H), 6.75 (dd, *J* = 4 Hz, *J*' = 2 Hz 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.27, 155.70, 149.85, 145.45, 143.31, 136.61, 134.78, 129.34, 128.90, 120.08, 113.15, 113.03, 99.41, 89.30; IR (ATR, ν_{max}, cm^{-1}): 2981, 2203, 1700, 1639, 1592, 1557, 1483, 1425, 1216, 1093, 1010, 962, 806; HRMS *m/z* (ESI) calcd. for $C_{16}H_{10}ClN_2O_2^+$ (M+H$^+$) 297.0431, found 297.0411.

4-(4-Chlorophenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4l): Yield: 92%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 8 Hz, 2H, ArH), 7.62 (d, *J* = 8 Hz, 2H, ArH), 7.58 (d, *J* = 8 Hz, 2H, ArH), 7.55 (d, *J* = 8 Hz, 2H, ArH), 6.62 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.60, 158.20, 154.16 139.43, 138.09, 133.79, 131.56, 130.38, 129.52, 128.88, 122.75, 121.22, 102.67, 92.05; IR (ATR, ν_{max}, cm^{-1}): 3192, 2210, 1638, 1557, 1538, 1485, 1364, 1216, 1094, 1009, 961, 806; HRMS *m/z* (ESI) calcd. for $C_{18}H_{11}BrClN_2O^+$ (M+H$^+$) 384.9743, found 384.9709.

4-(4-Bromophenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4m): Yield: 93%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (d, *J* = 8 Hz, 2H, ArH), 7.68 (d, *J* = 8 Hz, 2H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.55 (d, *J* = 8 Hz, 2H, ArH), 6.62 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.59, 158.22, 154.19, 139.45, 138.48, 131.81, 131.55, 130.66, 129.51, 122.75, 122.42, 121.22, 102.55, 91.97; IR (ATR, ν_{max}, cm^{-1}): 2981, 2199, 1638, 1579, 1513, 1435, 1361, 1174, 1090, 1026, 959, 867; HRMS *m/z* (ESI) calcd. for $C_{18}H_{11}Br_2N_2O^+$ (M+H$^+$) 428.9238, found 428.9231.

4-(4-Fluorophenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4n): Yield: 88%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (d, *J* = 8 Hz, 2H, ArH), 7.69 (d, *J* = 8 Hz, 2H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.55 (d, *J* = 8 Hz, 2H, ArH), 6.63 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.09, 157.90, 154.40, 139.11, 138.35, 131.83, 131.59, 130.67, 129.54, 122.87, 122.52, 121.01, 102.77, 92.30; IR (ATR, ν_{max}, cm^{-1}): 3084, 2199, 1645, 1538, 1511, 1479, 1349, 1216, 1073, 1008, 961, 804; HRMS *m/z* (ESI) calcd. for $C_{18}H_{11}BrFN_2O^+$ (M+H$^+$) 369.0039, found 369.0031.

4-(4-Methylphenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4o): Yield: 87%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98

(d, *J* = 8 Hz, 2H, ArH), 7.58 (d, *J* = 8 Hz, 2H, ArH), 7.49 (d, *J* = 8 Hz, 2H, ArH), 7.29 (d, *J* = 8 Hz, 2H, ArH), 6.60 (s, 1H, C5 –H), 2.37 (s, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.84, 157.94, 155.47, 139.57, 138.51, 136.39, 131.54, 129.50, 129.41, 128.38, 122.63, 121.43, 102.85, 92.26, 21.30; IR (ATR, ν_{max}, cm^{-1}): 3204, 2209, 1652, 1591, 1560, 1493, 1364, 1213, 1073, 1006, 961, 803; HRMS *m/z* (ESI) calcd. for $C_{19}H_{14}BrN_2O^+$ (M+H$^+$) 365.0290, found 365.0288.

4-(4-Methoxyphenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4p): Yield: 89%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (d, *J* = 8 Hz, 2H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.57 (d, *J* = 8 Hz, 2H, ArH), 7.05 (d, *J* = 8 Hz, 2H, ArH), 6.63 (s, 1H, C5 –H), 3.82 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.32, 160.18, 157.42, 155.39, 139.13, 131.57, 131.27, 129.88, 129.56, 122.78, 121.28, 114.29, 103.17, 92.51, 55.71; IR (ATR, ν_{max}, cm^{-1}): 2981, 2198, 1645, 1592, 1556, 1477, 1362, 1215, 1091, 1009, 961, 803; HRMS *m/z* (ESI) calcd. for $C_{19}H_{14}BrN_2O_2^+$ (M+H$^+$) 381.0239, found 381.0230.

4-(4-Ethoxyphenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4q): Yield: 84%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, *J* = 8 Hz, 2H, ArH), 7.59 (d, *J* = 8 Hz, 4H, ArH), 7.04 (d, *J* = 8 Hz, 2H, ArH), 6.66 (s, 1H, C5 –H), 4.09 (q, *J* = 8 Hz, 2H, CH_2), 1.36 (t, *J* = 8 Hz, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.03, 159.66, 156.50, 155.93, 138.25, 131.65, 130.75, 129.96, 129.65, 123.09, 120.75, 114.76, 103.65, 93.23, 63.68, 15.11; IR (ATR, ν_{max}, cm^{-1}): 2981, 2204, 1652, 1525, 1464, 1347, 1214, 1026, 1009, 968, 812; HRMS *m/z* (ESI) calcd. for $C_{20}H_{16}BrN_2O_2^+$ (M+H$^+$) 395.0395, found 395.0381.

4-(Furfuryl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4r): Yield: 85%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, *J* = 4 Hz, 1H, ArH), 7.87 (d, *J* = 8 Hz, 2H, ArH), 7.70 (d, *J* = 8 Hz, 2H, ArH), 7.57 (d, *J* = 4 Hz, 1H, ArH), 7.04 (s, 1H, C5 –H), 6.79 (dd, *J* = 4 Hz, *J*' = 2 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.40, 153.63, 149.19, 146.39, 144.20, 134.95, 132.05, 129.83, 124.30, 118.88, 114.71, 113.40, 100.33, 90.87; IR (ATR, ν_{max}, cm^{-1}): 3065, 2200, 1638, 1591, 1576, 1423, 1360, 1214, 1092, 1072, 1007, 959, 802; HRMS *m/z* (ESI) calcd. for $C_{16}H_{10}BrN_2O_2^+$ (M+H$^+$) 340.9926, found 340.9895.

4-(3,4-Dimethoxyphenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4s): Yield: 78%; white solid; m.p.: 289-290 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, *J* = 8 Hz, 2H, ArH), 7.62 (d, *J* = 8 Hz, 2H, ArH), 7.22 (s, 1H, ArH), 7.19 (d, *J* = 8 Hz, 1H, ArH), 7.07 (d, *J* = 8 Hz, 1H, ArH), 6.68 (s, 1H, C5 –H), 3.83 (s, 3H, OMe), 3.82 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.59, 156.27, 156.15, 149.95, 148.86, 138.20, 131.66, 131.06, 129.65, 123.09, 121.21, 120.85, 112.37, 112.02, 103.50, 93.42, 56.08, 56.05; IR (ATR, ν_{max}, cm^{-1}): 3138, 2200, 1656, 1538, 1485, 1348, 1277, 1219, 1091, 1011, 812, 798; HRMS *m/z* (ESI) calcd. for $C_{20}H_{16}BrN_2O_3^+$ (M+H$^+$) 411.0344, found 411.0342.

4-(3-Bromophenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4t): Yield: 88%; white solid; m.p.: 295-296 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, *J* = 8 Hz, 2H, ArH), 7.75 (s, 1H, ArH), 7.65 (d, *J* = 8 Hz, 1H, ArH), 7.58 (d, *J* = 8 Hz, 3H, ArH), 7.45 (t, *J* = 12 Hz, 1H, ArH), 6.62 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.41, 158.25, 153.69, 141.66, 139.49, 131.74, 131.53, 131.00, 129.53, 127.71, 122.72, 122.08, 121.21, 102.47, 91.95; IR (ATR, ν_{max}, cm^{-1}): 3271, 2213, 1634, 1556, 1539, 1473, 1363, 1218, 1073, 1009, 813, 783; HRMS *m/z* (ESI) calcd. for $C_{18}H_{11}Br_2N_2O^+$ (M+H$^+$) 428.9238, found 428.9237.

4-(2,4,5-Trimethoxyphenyl)-2-oxo-6-(4-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4u): Yield: 89%; cream solid; m.p.: 300-301 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, *J* = 8 Hz, 2H, ArH), 7.60 (d, *J* = 8 Hz, 2H, ArH), 6.89 (s, 1H, ArH), 6.80 (s, 1H, ArH), 6.58 (s, 1H, C5 –H), 3.86 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.74 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.94, 155.64, 154.26, 151.07, 150.56, 142.89, 138.06, 131.69, 129.58, 123.03, 120.27, 118.79, 114.58, 105.25, 98.90, 96.55, 56.75, 56.62, 56.31; IR (ATR, ν_{max}, cm^{-1}): 3145, 2200, 1700, 1652, 1560, 1479, 1346, 1208, 1028, 1008, 808, 779; HRMS *m/z* (ESI) calcd. for $C_{21}H_{18}BrN_2O_4^+$ (M+H$^+$) 441.0450, found 441.0447.

4-(4-Bromophenyl)-2-oxo-6-(2,4-dimethoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4v): Yield: 75%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, *J* = 8 Hz, 2H, ArH), 7.62 (s, 1H, ArH), 7.56 (d, *J* = 8 Hz, 1H, ArH), 7.53 (d, *J* = 8 Hz, 2H, ArH), 7.97 (d, *J* = 8 Hz, 1H, ArH), 6.56 (s, 1H, C5 –H), 3.83 (s, 3H, OMe), 3.79 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.49, 159.14, 153.89, 150.10, 148.95, 138.84, 133.02, 131.75, 130.65, 122.21, 121.58, 120.03, 111.71, 110.94, 102.09, 90.72, 55.99; IR (ATR, ν_{max}, cm^{-1}): 3150, 2200, 1647, 1602, 1514, 1447, 1423, 1367, 1171, 1068, 1009, 992, 885, 807; HRMS *m/z* (ESI) calcd. for $C_{20}H_{16}BrN_2O_3^+$ (M+H$^+$) 411.0344, found 411.0306.

4-(4-Bromophenyl)-2-oxo-6-(3-bromophenyl)-1,2-dihydropyridine-3-carbonitrile (4w): Yield: 86%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (s, 1H, ArH), 8.00 (d, *J* = 8 Hz, 1H, ArH), 7.68 (d, *J* = 8 Hz, 2H, ArH), 7.56 (d, *J* = 8 Hz, 3H, ArH), 7.37 (t, *J* = 8 Hz, 1H, ArH), 6.63 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.42, 157.71, 154.21, 142.72, 138.45, 131.82, 131.78, 130.81, 130.70, 130.01, 126.27, 122.40, 121.19, 102.68, 92.31; IR (ATR, ν_{max}, cm^{-1}): 3235, 2206, 1685, 1592, 1538, 1492, 1431, 1364, 1217, 1076, 1010, 885, 817; HRMS *m/z* (ESI) calcd. for $C_{18}H_{11}Br_2N_2O^+$ (M+H$^+$) 428.9238, found 428.9235.

4-(4-Bromophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (4x): Yield: 80%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, *J* = 8 Hz, 2H, ArH), 7.70 (d, *J* = 8 Hz, 2H, ArH), 7.57 (d, *J* = 8 Hz, 2H, ArH), 7.43-7.40 (m, 3H, ArH), 6.64 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.97, 158.96, 154.48, 139.61, 138.34, 131.86, 130.67, 129.46, 128.72, 127.51, 122.57, 120.91, 103.21, 92.08; IR (ATR, ν_{max}, cm^{-1}): 3150, 2195, 1538, 1482, 1470, 1431, 1277, 1109, 1075, 1010, 808, 782; HRMS *m/z* (ESI) calcd. for $C_{18}H_{12}BrN_2O^+$ (M+H$^+$) 351.0133, found 351.0129.

4-(4-Fluorophenyl)-2-oxo-6-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4y): Yield: 75%; cream solid; m.p.: 282-283 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, *J* = 8 Hz, 2H, ArH), 7.79 (d, *J* = 8 Hz, 2H, ArH), 7.41 (t, *J* = 8 Hz, 2H, ArH), 7.06 (d, *J* = 8 Hz, 2H, ArH), 6.76 (s, 1H, C5

–H), 3.84 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.79, 163.95, 162.33, 161.97, 158.36, 133.55, 131.21, 131.13 (*J* = 36 Hz), 129.79, 117.83, 116.28, 116.06, 114.73, 105.10, 55.95; IR (ATR, ν_{max}, cm^{-1}): 2981, 2200, 1645, 1594, 1534, 1493, 1360, 1218, 1093, 1013, 960, 806; HRMS *m/z* (ESI) calcd. for $C_{19}H_{14}FN_2O_2^+$ (M+H$^+$) 321.1039, found 321.1034.

4-(4-Methylphenyl)-2-oxo-6-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4z): Yield: 78%; white solid; m.p.: 272-273 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, *J* = 8 Hz, 2H, ArH), 7.50 (d, *J* = 8 Hz, 2H, ArH), 7.29 (d, *J* = 8 Hz, 2H, ArH), 6.97 (d, *J* = 8 Hz, 2H, ArH), 6.54 (s, 1H, C5 –H), 3.80 (s, 3H, OMe), 2.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.38, 160.59, 157.80, 155.80, 138.61, 136.37, 129.41, 128.89, 128.39, 121.24, 114.32, 114.08, 102.55, 55.65, 21.31; IR (ATR, ν_{max}, cm^{-1}): 3310, 2204, 1606, 1557, 1508, 1427, 1352, 1213, 1025, 1011, 959, 795; HRMS *m/z* (ESI) calcd. for $C_{20}H_{17}N_2O_2^+$ (M+H$^+$) 317.1290, found 317.1284.

4-(4-Methoxyphenyl)-2-oxo-6-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4aa): Yield: 80%; cream solid; m.p.: 290-291 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, *J* = 8 Hz, 2H, ArH), 7.69 (d, *J* = 8 Hz, 2H, ArH), 7.10 (d, *J* = 8 Hz, 2H, ArH), 7.05 (d, *J* = 8 Hz, 2H, ArH), 6.70 (s, 1H, C5 –H), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.74, 161.16, 158.58, 130.31, 129.62, 126.64, 118.55, 114.64, 114.55, 104.62, 55.86; IR (ATR, ν_{max}, cm^{-1}): 2933, 2204, 1645, 1596, 1537, 1473, 1350, 1247, 1073, 1012, 964, 840.

4-(4-Bromophenyl)-2-oxo-6-(3,4-dimethoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4ab): Yield: 77%; yellow solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, *J* = 8 Hz, 2H, ArH), 7.62 (d, *J* = 8 Hz, 1H, ArH), 7.55 (d, *J* = 8 Hz, 2H, ArH), 7.52 (s, 1H, ArH), 6.97 (d, *J* = 8 Hz, 1H, ArH), 6.56 (s, 1H, C5 –H), 3.83 (s, 3H, CH_3), 3.79 (s, 3H, CH_3) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.44, 159.11, 153.89, 150.08, 148.93, 138.84, 132.99, 131.76, 130.66, 122.21, 121.61, 120.01, 111.68, 110.88, 102.05, 90.72, 55.97; IR (ATR, ν_{max}, cm^{-1}): 3205, 2209, 1685, 1591, 1557, 1485, 1362, 1214, 1093, 1009, 961, 806.

4-(4-Fluorophenyl)-2-oxo-6-(3,4-dimethoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4ac): Yield: 72%; yellow solid; m.p.: 301-302 ºC; ^{1}H NMR (400 MHz, DMSO-d_6); δ 7.65 (d, *J* = 8 Hz, 2H, ArH), 7.62 (s, 1H, ArH), 7.56 (d, *J* = 8 Hz, 1H, ArH), 7.32 (t, *J* = 8 Hz, 2H, ArH), 6.96 (d, *J* = 8 Hz, 1H, ArH), 6.57 (s, 1H, C5 –H), 3.84 (s, 3H, CH_3), 3.79 (s, 3H, CH_3) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.49, 163.89, 161.45, 158.93, 154.16, 150.09, 148.94, 135.97, 135.94, 132.91, 130.69, 130.61 (*J* = 36 Hz), 121.0, 120.05, 115.78, 115.57, 111.68, 110.95, 102.48, 91.08, 55.99; IR (ATR, ν_{max}, cm^{-1}): 3065, 2204, 1695, 1588, 1575, 1491, 1359, 1214, 1072, 1007, 960, 823; HRMS *m/z* (ESI) calcd. for $C_{20}H_{16}FN_2O_3$ (M+H$^+$) 351.1145, found 351.1143.

4-(4-Chlorophenyl)-2-oxo-6-(3,4-dimethoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4ad): Yield: 76%; yellow solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85 (d, *J* = 8 Hz, 1H, ArH), 7.73 (d, *J* = 8 Hz, 2H, ArH), 7.63 (d, *J* = 8 Hz, 2H, ArH), 7.56 (d, *J* = 8 Hz, 1H, ArH), 7.52 (s, 1H, ArH), 6.56 (s, 1H, C5 –H), 3.88 (s, 3H, CH_3), 3.76 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.08, 151.66, 150.65, 149.19, 136.88, 136.03, 135.30, 134.65, 130.61, 129.28, 129.20, 121.35, 120.27, 112.12, 112.06, 111.16, 110.88, 56.15; IR (ATR, ν_{max}, cm^{-1}): 3193, 2209, 1645, 1557, 1483, 1362, 1216, 1093, 1009, 961, 806; HRMS *m/z* (ESI) calcd. for $C_{20}H_{16}ClN_2O_3^+$ (M+H$^+$) 367.0849, found 367.0829.

4-(4-Methoxyphenyl)-2-oxo-6-(3,4-dimethoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4ae): Yield: 75%; yellow solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71 (d, *J* = 8 Hz, 2H, ArH), 7.53 (d, *J* = 8 Hz, 1H, ArH), 7.49 (s, 1H, ArH), 7.12 (d, *J* = 8 Hz, 2H, ArH), 7.07 (d, *J* = 8 Hz, 1H, ArH), 6.78 (s, 1H, C5 –H), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.50, 161.37, 159.34, 151.80, 151.68, 149.19, 130.41, 128.99, 128.75, 125.43, 121.35, 117.92, 114.61, 112.09, 111.18, 105.11, 96.58, 56.16, 55.89; IR (ATR, ν_{max}, cm^{-1}): 3211, 2209, 1653, 1557, 1485, 1362, 1214, 1093, 1009, 961, 806; HRMS *m/z* (ESI) calcd. for $C_{21}H_{19}N_2O_4^+$ (M+H$^+$) 363.1345, found 363.1331.

4-(4-Methylphenyl)-2-oxo-6-(3,4-dimethoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4af): Yield: 73%; yellow solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 (d, *J* = 8 Hz, 2H, ArH), 7.53 (d, *J* = 8 Hz, 1H, ArH), 7.50 (s, 1H, ArH), 7.37 (d, *J* = 8 Hz, 2H, ArH), 7.07 (d, *J* = 8 Hz, 1H, ArH), 6.79 (s, 1H, C5 –H), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.80, 159.60, 152.33, 151.66, 149.19, 140.47, 134.18, 129.72, 128.62, 125.69, 121.33, 117.82, 112.08, 111.17, 105.23, 96.71, 56.15, 21.38; IR (ATR, ν_{max}, cm^{-1}): 3215, 2207, 1628, 1592, 1538, 1429, 1344, 1214, 1077, 1010, 848, 805; HRMS *m/z* (ESI) calcd. for $C_{21}H_{19}N_2O_3^+$ (M+H$^+$) 347.1396, found 347.1395.

4-(3,4-Dimethoxyphenyl)-2-oxo-6-(3,4-dimethoxyphenyl)-1,2-dihydropyridine-3-carbonitrile (4ag): Yield: 74%; yellow solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60 (s, 1H, ArH), 7.56 (d, *J* = 8 Hz, 1H, ArH), 7.22 (s, 1H, ArH), 7.19 (d, *J* = 8 Hz, 1H, ArH), 7.07 (d, *J* = 8 Hz, 1H, ArH), 6.99 (d, *J* = 8 Hz, 1H, ArH), 6.67 (s, 1H, C5 –H), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.82, 166.95, 157.24, 156.04, 150.39, 149.90, 148.99, 148.83, 131.40, 131.27, 121.17, 121.01, 120.35, 112.38, 112.05, 111.09, 103.30, 92.24, 56.08, 56.03; IR (ATR, ν_{max}, cm^{-1}): 3119, 2158, 1675, 1557, 1504, 1489, 1344, 1255, 1079, 1020, 781, 713.

4-(4-Methoxyphenyl)-2-oxo-6-(4-methylphenyl)-1,2-dihydropyridine-3-carbonitrile (4ah): Yield: 74%; white solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (d, *J* = 8 Hz, 2H, ArH), 7.59 (d, *J* = 8 Hz, 2H, ArH), 7.23 (d, *J* = 8 Hz, 2H, ArH), 7.05 (d, *J* = 8 Hz, 2H, ArH), 6.61 (s, 1H, C5 –H), 3.82 (s, 3H, OMe), 2.34 (s, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.82, 160.35, 157.47, 155.93, 139.24, 135.95, 131.02, 129.94, 129.40, 127.50, 120.81, 114.34, 103.49, 92.70, 55.73, 21.32; IR (ATR, ν_{max}, cm^{-1}): 2933, 2204, 1645, 1595, 1539, 1473, 1350, 1296, 1073, 1011, 961, 839; HRMS *m/z* (ESI) calcd. for $C_{20}H_{17}N_2O_2^+$ (M+H$^+$) 317.1290, found 317.1257.

4-(2-Nitrophenyl)-2-oxo-6-(3-pyridyl)-1,2-dihydropyridine-3-carbonitrile (4ai): Yield: 70%; white solid; m.p.:

> 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H, ArH), 8.58 (d, *J* = 4 Hz, 1H, ArH), 8.35 (d, *J* = 8 Hz, 1H, ArH), 7.83 (d, *J* = 8 Hz, 1H, ArH), 7.63 (d, *J* = 8 Hz, 1H, ArH), 7.54 (t, *J* = 8 Hz, 2H, ArH), 7.46 (d *J* = 8 Hz, 1H, ArH), 6.67 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.22, 154.22, 149.96, 148.71, 148.49, 138.05, 135.55, 134.68, 130.41, 129.33, 129.13, 128.88, 123.92, 123.79, 111.63, 102.77, 92.42; IR (ATR, ν_{max}, cm^{-1}): 3161, 2205, 1700, 1652, 1589, 1532, 1483, 1421, 1360, 1216, 1073, 1007, 960, 709.

4-(4-Chlorophenyl)-2-oxo-6-(3-pyridyl)-1,2-dihydropyridine-3-carbonitrile (4aj): Yield: 74%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 9.20 (s, 1H, ArH), 8.56 (d, *J* = 4 Hz, 1H, ArH), 8.37 (d, *J* = 8 Hz, 1H, ArH), 7.64 (d, *J* = 8 Hz, 2H, ArH), 7.56 (d, *J* = 8 Hz, 2H, ArH), 7.43 (d, *J* = 8 Hz, 1H, ArH), 6.70 (s, 1H, C5 –H): ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.63, 157.22, 154.30, 150.01, 148.76, 137.94, 135.41, 134.74, 133.88, 130.42, 128.90, 123.80, 121.06, 103.02, 92.42; IR (ATR, ν_{max}, cm^{-1}): 3188, 2209, 1639, 1591, 1557, 1485, 1362, 1216, 1093, 1009, 961, 806; HRMS *m/z* (ESI) calcd. for $C_{17}H_{11}ClN_3O^+$ (M+H$^+$) 308.0591, found 308.0587.

4-(4-Fluorophenyl)-2-oxo-6-(3-pyridyl)-1,2-dihydropyridine-3-carbonitrile (4ak): Yield: 72%; cream solid; m.p.: > 300 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 1H, ArH), 8.57 (d, *J* = 4 Hz, 1H, ArH), 8.38 (d, *J* = 8 Hz, 1H, ArH), 7.70 (d, *J* = 8 Hz, 2H, ArH), 7.57 (d, *J* = 12 Hz, 2H, ArH), 7.43 (dd, *J* = 8 Hz, *J* = 4 Hz, 1H, ArH), 6.72 (s, 1H, C5 –H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.74, 157.24, 154.40, 150.06, 148.79, 138.25, 135.31, 134.78, 131.85, 130.71, 123.80, 122.57, 120.96, 103.15, 92.38; IR (ATR, ν_{max}, cm^{-1}): 3067, 2210, 1685, 1572, 1538, 1476, 1319, 1214, 1072, 1010, 965, 867; HRMS *m/z* (ESI) calcd. for $C_{17}H_{11}FN_3O^+$ (M+H$^+$) 292.0886, found 292.0881.

RESULTS AND DISCUSSION

A simple and efficient method for the synthesis of new 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitriles has been developed. A reaction between substituted aromatic aldehydes (**1**), aromatic ketones (**2**) and cyanoacetamide (**3**) in the presence of NaOH as base using ultrasonic bath was carried out for synthesis of substituted 3-cyano-pyridine-2(1*H*)-one (**4**) with good yield.

For optimization, 4-chlorobenzaldehyde, cyanoacetamide and 4-chloroacetophenone were selected as substrates in the model reaction. To identify the ideal reaction condition, first of all, conventional heating method was used to study the effect of base/catalyst, solvents and temperature. The reaction was performed with various bases (NEt_3, piperidine, DBU, KOH and NaOH) or catalyst (*p*-TSA and *L*-proline) as no reaction occurred in the absence of a catalyst/base (Table-1). Organic bases such as NEt_3, DBU and catalysts like *p*-TSA, *L*-proline only promotes Knoevenagel condensation reaction between aromatic aldehyde and cyanoacetamide affording intermediate arylidene of cyanoacetamide and no further reaction ensured with the third substrate. The Michael addition process and intramolecular cyclization, which yield the target molecule (product), are catalyzed by piperidine and KOH with a very low yield 40% and 30%, respectively. Targeted compound with a very low yield can be produced by the DBU-promoted reaction. The reaction was also tried with DBU in EtOH, however, with a very low yield (< 4%). The results indicates that the reaction proceed smoothly with high yield (65%) in the presence of NaOH base. Readily accessible solvents including EtOH, MeOH, THF, DMF, CH_3CN, IPA and water were also evaluated in this process, THF was the best solvent as it afforded desired product in excellent yield. It was observed that the reaction time increases and yield decreases as the temperature of the reaction decreases upto room temperature (Table-1).

TABLE-1
OPTIMIZATION PARAMETERS (SOLVENTS AND BASE) FOR THE SYNTHESIS OF 4,6-DIARYL-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILES

Entry	Catalyst/base	Solvent	Time (h)	Yield (%)
1	NEt_3	EtOH	4	–
2	NEt_3	THF	4	–
3	Piperidene	EtOH	3	40
4	Piperidene	DMF	3	30
5	Piperidene	THF	3	15
6	Piperidene	IPA	3	–
7	DBU	EtOH	3	Traces
8	DBU	CH_3CN	3	–
9	DBU	DMF	4	–
10	DBU	THF	4	Traces
11	*p*-TSA	H_2O	4	–
12	*L*-Proline	EtOH	4	–
13	*L*-Proline	DMF	5	–
14	–	EtOH	3	–
15	–	THF	5	–
16	KOH	EtOH/H_2O	4	30
17	KOH	DMF	4	20
18	KOH	CH_3CN	4	–
19	NaOH	H_2O	3	–
20	NaOH	EtOH	3	45
21	NaOH	–	5	Traces
22	NaOH	DMF	1	50
23	NaOH	THF	1	65

Finally, the synthesis of 3-cyano-pyridine-2(1*H*)-one were accelerated by ultrasonication, which promote the chemical reaction. Both the conventional heating method and ultrasonic-bath were tried for the synthesis of heterocyclic 3-cyano-pyridine-2(1*H*)-one, however ultrasonication was more suitable and convenient. In ultrasonication method, the desired product 3-cyano-pyridine-2(1*H*)-one was obtained in the presence of promoter NaOH at 70 ºC with excellent yield 92% (Table-2). The results revealed that any change in the temperature from 70 °C, leads to decrease in yield of the product, time of reaction

TABLE-2
OPTIMIZATION WITH HEATING/ULTRASONICATION METHOD FOR SYNTHESIS OF 3-CYANO-PYRIDINE-2(1*H*)-ONE

Entry	Base/solvent THF	Condition	Temp. (°C)	Time (min)	Yield (%)
1	NaOH	Heating	50	120	45
2	NaOH	Heating	80	60	65
3	NaOH	Heating	rt	300	30
4	NaOH	Ultrasonic bath	rt	9	55
5	NaOH	Ultrasonic bath	100	5	40
6	NaOH	Ultrasonic bath	50	10	78
7	NaOH	Ultrasonic bath	70	3	92

increases (Table-2). The advantages of ultrasonication over conventional heating included a shorter reaction time and a higher reaction yield.

The substrates scope of the reaction was also examined at the prescribed reaction conditions as summarized in Table-3. Various substituted aromatic aldehydes such as (NO_2, Cl, Br, F, H, Me, OMe, CN, *etc*.) could be used to obtain the corresponding *C*-4 substituted phenyl derivatives on 2-pyridones. Aromatic ketones were also varied from 4-chloroacetophenone, 4-bromoacetophenone, 4-methylacetophenone, 2,4-dimethoxyacetophenone, 3,4-dimethoxyacetophenone to 3-pyridylmethyl ketone. The reaction occurred readily with substituted aromatic aldehydes as well as aromatic ketones which reacted with cyanoacetamide furnishing corresponding 3-cyano-pyridine-2(1*H*)-one in excellent yield. Electron donating groups such as –Me, –OMe and –OEt at the aromatic aldehydes and ketones decrease the rate of reaction. Meanwhile, the electron withdrawing substitutents including Cl, Br, F, CN, NO_2, *etc*. increased the yield (92%) and reduced the time of completion of reaction. Substituents at the *para*-postion of aromatic aldehyde and ketones did not adversely affect the yield of the reaction while, substituents at *meta*– and *ortho*–position significantly decreased the yield of the product probably due to the steric hindrance.

TABLE-3
PHYSICAL DATA FOR SYNTHESIS OF SUBSTITUTED OF 4,6-DIARYL-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILES

Compd.	Ar_1	Ar_2	Time (min)	Yield (%)
4a	4-Cl-C_6H_4	4-Cl-C_6H_4	3	93
4b	2,4,5-$(OMe)_3$-C_6H_2	4-Cl-C_6H_4	25	88
4c	4-F-C_6H_4	4-Cl-C_6H_4	5	85
4d	3-Br-C_6H_4	4-Cl-C_6H_4	12	87
4e	4-Me-C_6H_4	4-Cl-C_6H_4	7	88
4f	4-EtO-C_6H_4	4-Cl-C_6H_4	10	80
4g	3-Me-C_6H_4	4-Cl-C_6H_4	20	75
4h	4-MeO-C_6H_4	4-Cl-C_6H_4	13	89
4i	C_6H_5	4-Cl-C_6H_4	6	90
4j	3-MeO-C_6H_4	4-Cl-C_6H_4	12	82
4k	OC_4H_3	4-Cl-C_6H_4	9	85
4l	4-Cl-C_6H_4	4-Br-C_6H_4	3	93
4m	4-Br-C_6H_4	4-Br-C_6H_4	2	92
4n	4-F-C_6H_4	4-Br-C_6H_4	9	88
4o	4-Me-C_6H_4	4-Br-C_6H_4	15	87
4p	4-MeO-C_6H_4	4-Br-C_6H_4	7	89
4q	4-EtO-C_6H_4	4-Br-C_6H_4	10	84
4r	OC_4H_3	4-Br-C_6H_4	10	85
4s	3,4-$(MeO)_2$-C_6H_3	4-Br-C_6H_4	25	78
4t	3-Br-C_6H_4	4-Br-C_6H_4	20	88
4u	2,4,5-$(MeO)_3$-C_6H_2	4-Br-C_6H_4	15	89
4v	4-Br-C_6H_4	2,4-$(MeO)_2$-C_6H_3	10	75
4w	4-Br-C_6H_4	3-Br-C_6H_4	5	86
4x	4-Br-C_6H_4	C_6H_5	15	80
4y	4-F-C_6H_4	4-MeO-C_6H_4	9	75
4z	4-Me-C_6H_4	4-MeO-C_6H_4	10	78
4aa	4-MeO-C_6H_4	4-MeO-C_6H_4	7	80
4ab	4-Br-C_6H_4	3,4-$(MeO)_2$-C_6H_3	9	77
4ac	4-F-C_6H_4	3,4-$(MeO)_2$-C_6H_3	12	72
4ad	4-Cl-C_6H_4	3,4-$(MeO)_2$-C_6H_3	13	76
4ae	4-MeO-C_6H_4	3,4-$(MeO)_2$-C_6H_3	15	75
4af	4-Me-C_6H_4	3,4-$(MeO)_2$-C_6H_3	13	73
4ag	3,4-$(MeO)_2$-C_6H_3	3,4-$(MeO)_2$-C_6H_3	10	74
4ah	4-MeO-C_6H_4	4-Me-C_6H_4	12	74
4ai	2-NO_2-C_6H_4	C_5H_4N	15	70
4aj	4-Cl-C_6H_4	C_5H_4N	8	74
4ak	4-F-C_6H_4	C_5H_4N	11	73

The structure of all the synthesized compounds were characterized by ^1H, ^{13}C NMR, IR as well as HRMS techniques. From spectral study, it was observed that ^1H NMR spectrum of 4-(4-chlorophenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (**4a**) in DMSO, exhibited a singlet at the chemical shift δ 6.60 ppm integrating for one protons at *C*-5 position of substituted 2-pyridone, four doublets at δ 7.45, 7.55, 7.61 and 8.05 ppm that integrated for two aryl group protons. In HRMS spectral data, molecular mass ($M+H^+$) of 4-(4-chlorophenyl)-2-oxo-6-(4-chlorophenyl)-1,2-dihydropyridine-3-carbonitrile (**4a**) is found to be 341.0224 which is equal to calculated mass 341.0248.

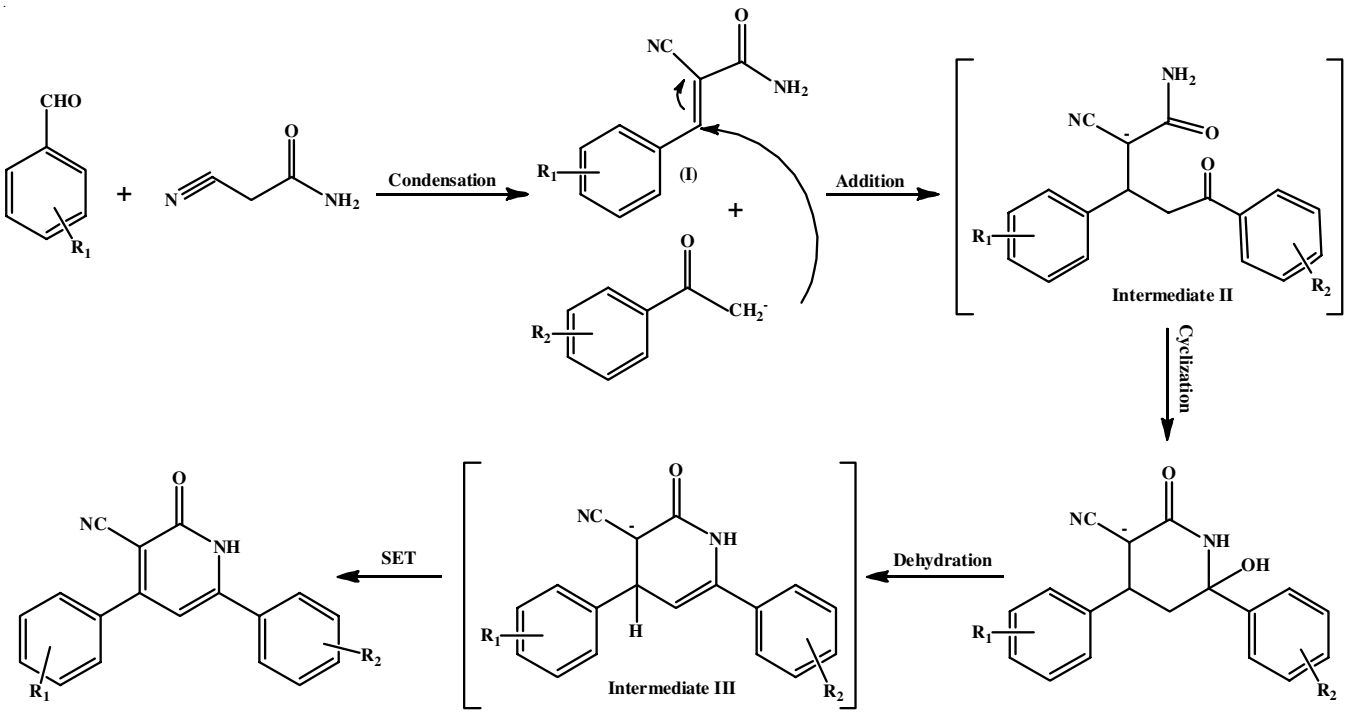
The plausible mechanism for the synthesis of substituted 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives is shown in **Scheme-II**. It is proposed that first step of the reaction involve Knoevenagel condensation reaction between aromatic aldehydes and cyanoacetamide affording intermediate I (acrylamide). In 2nd step, acrylamide intermediate I undergoes nucleophilic addition reaction by the enolates resulting in the formation of intermediate II bearing anion at α-position stabilized by the nitrile group of acrylamide. Intermediate II undergoes cyclization followed by dehydration affords intermediate III and which is subsequently converted to product *via* single electron transfer from the intervening radical.

Conclusion

A protocol for the synthesis of 4,6-diaryl-2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives was developed as one pot three component reaction between cyanoacetamide, aromatic ketones and substituted aromatic aldehydes in the presence of NaOH as base using ultrasound radiations without intermediate separation. This protocol explores the use of ultrasonication as an eco-friendly alternative to conventional heating for synthesis of 3-cyano-pyridine-2(1*H*)-one derivatives. Both electron-rich and electron-deficient aldehydes were well tolerated and gave high yields of products. Sterically hindered aldehydes substituted at *ortho*-position gave relatively lower yields than that of *meta*- and *para*-substituted isomers. Ultrasound irradiation enhances performance in various aspects such as rate of reaction, selectivity of product, increase the yield and purity as compared to conventional heating, eliminating toxic catalysts and solvents and demonstrating its sustainability and user-friendly capabilities in bioactive molecule construction.

ACKNOWLEDGEMENTS

Two of the authors, NY and SS, acknowledge the Junior Research Fellowships from Council of Scientific and Industrial Research, India and University Grants Commission, India, respectively. The authors also acknowledged to Centre for Bionanotechnology for providing research facilities.



Scheme-II: Proposed mechanism for synthesis of substituted 3-cyano-pyridine-2(1*H*)-ones

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. C.O. Kappe, *Angew. Chem. Int. Ed.*, **43**, 6250 (2004); https://doi.org/10.1002/anie.200400655
2. A. De la Hoz, A. Diaz-Ortiz and A. Moreno, *Chem. Soc. Rev.*, **34**, 164 (2005); https://doi.org/10.1039/B411438H
3. M.A. Martins, C.P. Frizzo, D.N. Moreira, N. Zanatta and H.G. Bonacorso, *Chem. Rev.*, **108**, 2015 (2008); https://doi.org/10.1021/cr078399y
4. G.M. Martins, G.C. Zimmer, S.R. Mendes and N. Ahmed, *Green Chem.*, **22**, 4849 (2020); https://doi.org/10.1039/D0GC01324B
5. S. Aslam, N. Sbei, S. Rani, M. Saad, A. Fatima and N. Ahmed, *ACS Omega*, **8**, 6175 (2023); https://doi.org/10.1021/acsomega.2c07378
6. Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, **118**, 4485 (2018); https://doi.org/10.1021/acs.chemrev.7b00271
7. S.L. James, C.J. Adams, C. Bolm, D. Braga, P. Collier, T. Frišèic, F. Grepioni, K.D. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A.G. Orpen, I.P. Parkin, W.C. Shearouse, J.W. Steed and D.C. Waddell, *Chem. Soc. Rev.*, **41**, 413 (2012); https://doi.org/10.1039/C1CS15171A
8. R.N. Baig and R.S. Varma, *Chem. Soc. Rev.*, **41**, 1559 (2012); https://doi.org/10.1039/C1CS15204A
9. B. Banerjee, *Ultrason. Sonochem.*, **35**, 1 (2017); https://doi.org/10.1016/j.ultsonch.2016.09.023
10. G. Mohammadi Ziarani, Z. Kheilkordi and P. Gholamzadeh, *Mol. Divers.*, **24**, 771 (2020); https://doi.org/10.1007/s11030-019-09964-1
11. N.N. Gharat and V.K. Rathod, Ultrasound-Assisted Organic Synthesis, In: Green Sustainable Process for Chemical and Environmental Engineering and Science, Sonochemical Organic Synthesis, Elsevier Chap. 1, pp 1-44 (2020); https://doi.org/10.1016/B978-0-12-819540-6.00001-2
12. S. Sangwan, N. Yadav, R. Kumar, S. Chauhan, V. Dhanda, P. Walia and A. Duhan, *Eur. J. Med. Chem.*, **232**, 114199 (2022); https://doi.org/10.1016/j.ejmech.2022.114199
13. W. Xie, Y. Wu, J. Zhang, Q. Mei, Y. Zhang, N. Zhu, R. Liu and H. Zhang, *Eur. J. Med. Chem.*, **145**, 35 (2018); https://doi.org/10.1016/j.ejmech.2017.12.038
14. A.R. Juvekar, M.N. Gambhire and S.S. Wankhede, *J. Young Pharm.*, **1**, 220 (2009); https://doi.org/10.4103/0975-1483.57068
15. W. Chen, P. Zhan, D. Rai, E. De Clercq, C. Pannecouque, J. Balzarini, Z. Zhou, H. Liu and X. Liu, *Bioorg. Med. Chem.*, **22**, 1863 (2014); https://doi.org/10.1016/j.bmc.2014.01.054
16. S. Zhu, T.H. Hudson, D.E. Kyle and A.J. Lin, *J. Med. Chem.*, **45**, 3491 (2002); https://doi.org/10.1021/jm020104f
17. E.S. Darwish, A.M.A. Fattah, F.A. Attaby and O.N. Al-Shayea, *Int. J. Mol. Sci.*, **15**, 1237 (2014); https://doi.org/10.3390/ijms15011237
18. K.L. Forrestall, D.E. Burley, M.K. Cash, I.R. Pottie and S. Darvesh, *Chem. Biol. Interact.*, **335**, 109348 (2021); https://doi.org/10.1016/j.cbi.2020.109348
19. N.C. Desai, N.R. Shihory, G.M. Kotadiya and P. Desai, *Eur. J. Med. Chem.*, **82**, 480 (2014); https://doi.org/10.1016/j.ejmech.2014.06.004
20. I.V. Kulakov, M.V. Matsukevich, Z.T. Shulgau, S. Sergazy, T.M. Seilkhanov, A. Puzari and A.S. Fisyuk, *Chem. Heterocycl. Compd.*, **51**, 991 (2015); https://doi.org/10.1007/s10593-016-1809-7
21. Z. Lv, C. Sheng, T. Wang, Y. Zhang, J. Liu, J. Feng, H. Sun, H. Zhong, C. Niu and K. Li, *J. Med. Chem.*, **53**, 660 (2010); https://doi.org/10.1021/jm901237x
22. F. Hernández, A. Sánchez, P. Rendón-Vallejo, C. Millán-Pacheco, Y. Alcaraz, F. Delgado, M.A. Vazquez and S. Estrada-Soto, *Eur. J. Med. Chem.*, **70**, 669 (2013); https://doi.org/10.1016/j.ejmech.2013.10.018
23. J. Chen, M.M. Lu, B. Liu, Z. Chen, Q.B. Li, L.J. Tao and G.Y. Hu, *Bioorg. Med. Chem. Lett.*, **22**, 2300 (2012); https://doi.org/10.1016/j.bmcl.2012.01.073.
24. K. Schmidt, U. Riese, Z. Li and M. Hamburger, *J. Nat. Prod.*, **66**, 378 (2003); https://doi.org/10.1021/np020430y

25. N.M. Abd EL-Rahman, T.S. Saleh and M.F. Mady, *Ultrason. Sonochem.*, **16**, 70 (2009); https://doi.org/10.1016/j.ultsonch.2008.05.001
26. V. Kumar, A. Sharma, M. Sharma, U.K. Sharma and A.K. Sinha, *Tetrahedron*, **63**, 9718 (2007); https://doi.org/10.1016/j.tet.2007.07.018
27. K.S. Suslick and G.J. Price, *Annu. Rev. Mater. Sci.*, **29**, 295 (1999); https://doi.org/10.1146/annurev.matsci.29.1.295
28. D.S. Al-Shamary, Z.A. Al-Othman and M.A. Al-Alshaikh, *Asian J. Chem.*, **25**, 6569 (2013); https://doi.org/10.14233/ajchem.2013.14364
29. H. Zang, Q. Su, Y. Mo, B.-W. Cheng and S. Jun, *Ultrason. Sonochem.*, **17**, 749 (2010); https://doi.org/10.1016/j.ultsonch.2010.01.015
30. H. Zang, M. Wang, B.W. Cheng and J. Song, *Ultrason. Sonochem.*, **16**, 301 (2009); https://doi.org/10.1016/j.ultsonch.2008.09.003
31. S. Rai, S. Khanam, R.S. Khanna and A.K. Tewari, *RSC Advances*, **4**, 44141 (2014); https://doi.org/10.1039/C4RA06619G
32. I. Abbas, S. Gomha, M. Elaasser and M. Bauomi, *Turk. J. Chem.*, **39**, 334 (2015); https://doi.org/10.3906/kim-1410-25