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A facile one-pot ultrasound assisted for an efficient synthesis of 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitriles

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ABSTRACT

A convenient one-pot protocol was developed for the synthesis of 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitrile derivatives. This reaction was carried out through a three component condensation reaction of isatins, malononitrile, and anilinolactones in the presence of a catalytic amount of Et_3N as an inexpensive and available basic catalyst in THF under ultrasound irradiation. The products were obtained in high yields and short reaction times. The main advantage of this synthetic method is that the obtained products in ultrasonic irradiations are different from classical heating.

1. Introduction

Multicomponent reactions (MCRs), in which multiple starting materials react together *via* a one-pot procedure to form a final product without isolating the intermediates, are special types of synthetically important organic reactions in combinatorial and medicinal chemistry [1–3]. Such reactions present remarkable advantages for the efficient construction of highly complex molecules in a single procedural step such as; operational simplicity, reduction in reaction steps and the number of workup, reduction in energy consumption, and high degree of atom economy [4,5]. In the past decade there have been tremendous development in three- and four component reactions and great efforts continue to be made to develop new MCRs [6].

Recently, the application of ultrasound as a powerful technique in synthetic organic chemistry became extremely efficient and attractive. The prominent features of the ultrasound approach are enhanced organic reaction rates, formation of purer products in high yields, mild reaction conditions, and considered a processing aid in terms of energy conservation and waste minimization compared with traditional methods [7,8]. Ultrasonic irradiation is widely used today in organic synthesis and has an intense impact on the way chemists approach organic and parallel synthesis, and a large number of organic reactions have been done by using ultrasonic irradiation [9–11].

Isatin (1*H*-indole-2,3-dione) and its derivatives exhibit various biological activities such as anticancer [12], anticonvulsant [13], anti-inflammatory [14], antimicrobial, antiviral [15] and antineoplastic activities [16]. These compounds are versatile building blocks for the synthesis of a large variety of heterocyclic compounds such as indoles, isatoic anhydride, quinolines, spirooxindoles, and etc. Spirooxindoles have a special place in heterocyclic chemistry due to their highly pronounced pharmacological and biological activities [17–21] as well as presence in a number of natural products, such as: *Horsfiline*, *Spirotryprostatin A* and *B*, *Elacomine*, *Pteropodine* (Fig. 1) [22–24]. The unique structural array of these compounds has made them attractive synthetic targets in chemistry [25].

As part of our current studies on the development of new efficient strategies for the preparation of spirooxindoles [26–28], in this research, we report a highly efficient one-pot, three component condensation reaction for the synthesis of 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline 3-carbonitrile derivatives **4** in the presence of catalytic amount of Et_3N as an inexpensive and available catalyst in THF under ultrasound irradiation in high yields.

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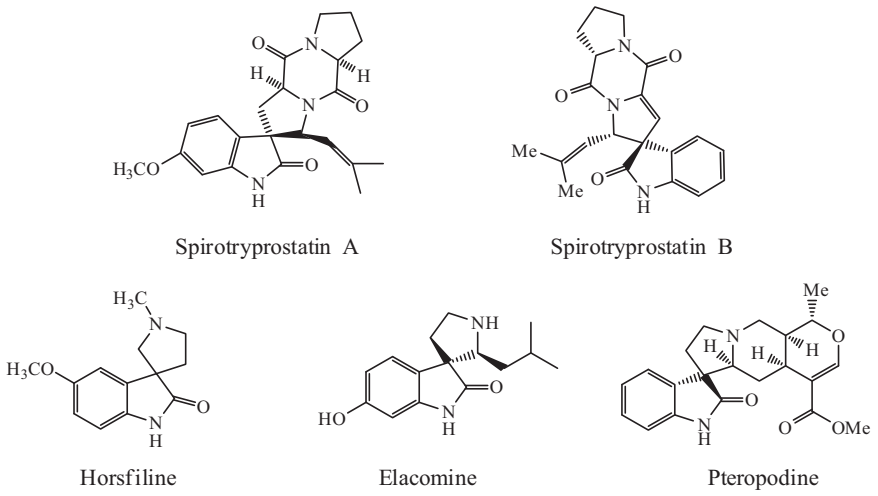


Fig. 1. Selected spirooxindolic natural products.

2. Experimental section

2.1. Materials

The chemicals used in this work were obtained from Fluka and Merck Chemical Company and were used without purification.

2.2. Apparatus

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a shimadzu QP 1100 Ex mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded as KBr pellets on a Perkin-Elmer 781 spectrophotometer and an Impact 400 Nicolet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. Ultrasound assisted reactions were carried out using a EUROSONIC® 4D ultrasound cleaner with a frequency of 50 kHz and a nominal power of 350 W. The reactions were carried out in an open glass tube (diameter: 25 mm; thickness: 1 mm; volume: 20 mL) at 50 °C. The reaction flask was located in the maximum energy area in the cleaner; where the surface of reactants (reaction vessel) is slightly lower than the level of the water. The temperature of the water bath was controlled by the addition or removal of circulated water. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

2.3. Typical procedure for the preparation of 2-amino-2′,5-dioxo-1-p-tolyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4b)

A mixture of isatin **1a** (1 mmol), malononitrile **2** (1 mmol), 4-(4-methylphenylamino) furan-2(3*H*)-one **3b** (1 mmol), and Et_3N (15 mol%) in THF (5 mL) was sonicated at 50 °C. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and the precipitate washed with EtOH (2 × 5 ml) to afford the pure product **4b** as white powder (0.337 g, 88%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3425, 2185, 1721, 1682. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 2.37 (3H, s, CH_3), 4.47–4.64 (2H, m, OCH_2) 5.99 (2H, s, NH_2), 6.82–7.44 (8H, m, ArH), 10.48 (1*H*, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 21.2, 48.2, 60.0, 66.1, 99.0, 109.8, 119.5, 122.5, 125.3, 128.9, 129.3, 131.2, 131.7, 134.3, 140.3, 141.8, 152.8, 159.6, 170.1, 178.0. Anal. Calcd for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58%; Found C, 68.69; H, 4.24; N, 14.53%. MS: *m/z* 384.

2.3.1. 2-Amino-2′,5-dioxo-1-phenyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′ indoline]-3-carbonitrile (4a)

White powder (0.266 g, 72%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3385, 2180, 1750, 1683. ^{1}H NMR (DMSO-d_6, 400 MHz): δppm: 4.34–4.65 (2H, m, OCH_2) 6.03 (2H, s, NH_2), 6.81–7.56 (9H, m, ArH), 10.49 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta_{ppm:}$ 48.2, 60.2, 66.1, 99.2, 109.9, 119.5, 122.5, 125.3, 129.3, 130.7, 134.3, 134.4, 141.8, 152.7, 159.5, 170.0, 178.0. Anal. Calcd for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.81; N, 15.13%; Found C, 68.16; H, 3.87; N, 15.08%; MS: *m/z* 370.

2.3.2. 2-Amino-1-(4-chlorophenyl)-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4c)

Cream powder (0.298 g, 74%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3334, 2185, 1722, 1683. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.52–4.71 (2H, m, OCH_2) 6.21 (2H, s, NH_2), 6.81–7.63 (8H, m, ArH), 10.50 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.2, 60.5, 66.8, 99.3, 109.8, 115.6, 122.5, 125.4, 129.3, 130.7, 131.3, 133.4, 134.3, 135.3, 141.8, 152.7, 159.4, 170.0, 178.0. Anal. Calcd for $C_{21}H_{13}ClN_4O_3$: C, 62.31; H, 3.24; N%, 13.84; Found C, 62.36; H, 3.30; N, 13.79%. MS: *m/z* 406, 404.

2.3.3. 2-Amino-1-(3-chlorophenyl)-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4d)

Gray powder (0.306 g, 76%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3454, 2186, 1720, 1686. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.51–4.73 (2H, m, OCH_2) 6.24 (2H, s, NH_2), 6.81–7.82 (8H, m, ArH), 10.51 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.2, 60.2, 66.1, 99.4, 109.8, 119.4, 122.5, 125.4, 128.2, 129.3, 129.7, 130.8, 132.1, 134.2, 134.6, 135.8, 141.8, 152.6, 159.2, 170.0, 177.9. Anal. Calcd for $C_{21}H_{13}ClN_4O_3$: C, 62.31; H, 3.24; N, 13.84%; Found C, 62.36; H, 3.19; N, 13.78%. MS: *m/z* 406, 404.

2.3.4. 2-Amino-2′,5-dioxo-1-p-tolyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4e)

White powder (0.291 g, 76%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3448, 2187, 1713, 1680. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 2.30 (3H, s, CH_3), 4.33–4.70 (2H, m, CH_2O) 6.06 (2H, s, NH_2), 6.83–7.46 (8H, m, ArH), 10.52 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz):

δ_{ppm}: 17.2, 48.3, 59.7, 66.0, 99.2, 110.0, 119.5, 122.6, 124.8, 128.3, 129.3, 129.8, 131.1, 132.3, 132.9, 134.4, 137.9, 141.7, 152.5, 159.2, 170.0, 177.9. Anal. Calcd for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58%; Found C, 68.69; H, 4.14; N, 14.63%. MS: *m/z* 384.

2.3.5. 2-Amino-1-(2,4-dichlorophenyl)-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4f)

Cream powder (0.315 g, 72%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3453, 2186, 1753, 1687. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.41–4.80 (2H, m, OCH_2) 6.43 (2H, s, NH_2), 6.83–7.98 (7H, m, ArH), 10.56 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.2, 59.7, 66.0, 100.1, 110.0, 119.3, 122.8, 124.9, 129.4, 129.8, 130.6, 131.1, 133.4, 134.2, 135.4, 136.7, 141.7, 152.3, 158.7, 169.8, 177.7. Anal. Calcd for $C_{21}H_{12}Cl_2N_4O_3$: C, 57.42; H, 2.75; N, 12.76%; Found C, 57.48; H, 2.69; N, 12.81%. MS: *m/z* 440, 438.

Due to very low solubility of the products **4g**, we cannot report the ^{13}C NMR data for this product.

2.3.6. 2-Amino-1-(4-bromophenyl)-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4g)

Cream powder (0.336 g, 75%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3448, 2192, 1742, 1694. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.51–4.72 (2H, m, OCH_2) 6.21 (2H, s, NH_2), 6.81–7.78 (7H, m, ArH), 10.47 (1H, s, NH). Anal. Calcd for $C_{21}H_{13}BrN_4O_3$: C, 56.14; H, 2.92; N, 12.47; Found C, 56.19; H, 2.87; N, 12.53. Ms: *m/z* 450, 448.

2.3.7. 2-Amino-5′-bromo-2′,5-dioxo-1-phenyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4h)

White powder (0.344 g, 77%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3340, 2182, 1726, 1675. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.45–4.66 (2H, m, OCH_2) 6.12 (2H, s, NH_2), 6.80–7.65 (8H, m, ArH), 10.64 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.5, 59.4, 66.3, 98.3, 111.9, 114.3, 119.3, 128.2, 129.2, 129.5, 130.7, 132.1, 134.3, 136.5, 141.2, 152.9, 159.9, 170.1, 177.7. Anal. Calcd for $C_{21}H_{13}BrN_4O_3$: C, 56.14; H, 2.92; N, 12. 47%; Found C, 56.20; H, 2.87; N, 12.52%. Ms: *m/z* 450, 448.

2.3.8. 2-Amino-5′-bromo-2′,5-dioxo-1-o-tolyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4i)

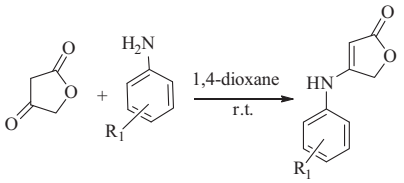
Cream powder (0.341 g, 74%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3348, 2178, 1718, 1680. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 2.36 (3H, s, CH_3), 4.43–4.84 (2H, m, OCH_2) 6.07 (2H, s, NH_2), 6.78–7.54 (7H, m, ArH), 10.70 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 21.3, 48.5, 59.3, 66.2, 98.2, 111.9, 114.3, 119.4, 128.2, 128.9, 129.2, 130.0, 131.2, 131.6, 132.1, 136.6, 140.4, 141.1, 153.0, 160.0, 170.1, 177.6. Anal. Calcd for $C_{22}H_{15}BrN_4O_3$: C, 57.04; H, 3.26; N, 12. 09%; Found C, 57.10; H, 3.32; N, 12.14%. Ms: *m/z* 464, 462.

2.3.9. 2-Amino-5′-nitro-2′,5-dioxo-1-phenyl-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4j)

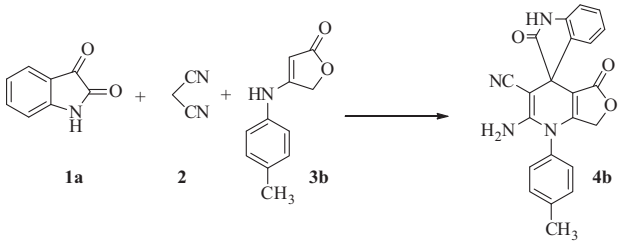
Cream powder (0.351 g, 85%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3352, 2188, 1735, 1674. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.50–4.68 (2H, m, OCH_2) 6.23 (2H, s, NH_2), 7.05–8.31 (8H, m, ArH), 11.25 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.5, 58.6, 66.5, 97.7, 110.2, 119.2, 121.2, 126.8, 129.2, 129.5, 130.7, 134.2, 135.0, 143.3, 148.4, 153.2, 160.4, 170.1, 178.7. Anal. Calcd for $C_{21}H_{13}N_5O_5$: C, 60.72; H, 3.15; N, 16. 86%; Found C,60.68; H, 3.20; N, 16.91%. Ms: *m/z* 415.

2.3.10. 2-Amino-1-(4-bromophenyl)-5′-nitro-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4k)

Cream powder (0.409 g, 83%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3362, 2187, 1735, 1692. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.57–4.69 (2H, m, OCH_2) 6.40 (2H, s, NH_2), 7.07–8.33 (7H, m, ArH), 11.24 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.5, 58.5, 66.5, 97.9, 110.2, 119.1, 121.3, 124.2, 126.8, 131.5, 133.6, 133.7, 135.0, 143.3, 148.4, 153.1, 160.1, 170.0, 196.2. Anal. Calcd for $C_{21}H_{12}BrN_5O_5$: C, 51.03; H, 2.45; N, 14. 17%; Found C, 51.09; H, 2.51; N, 14.12%. Ms: *m/z* 495, 493.



Scheme 1. Synthetic rout of anilinolactones.



Scheme 2. Model reaction for the synthesis of 1*H* spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitriles **4**.

Table 1
Solvent optimization on the model reaction.[a]

Solvent (%)	H_2O	EtOH	MeOH	CH_3CN	THF	CH_2Cl_2	CH_3COOH
Yield[b]	–	–	–	68	88	<30	73

[a] Reaction conditions: isatin **1a** (1 mmol), malononitrile **2** (1 mmol), and 4-(4-methylphenylamino) furan-2(3*H*)-one **3b**; Et_3N (15 mol%); THF (5 ml), at 50 °C, 3 h.
[b] Isolated yields.

Table 2
Temperature effect on the model reaction.[a]

Temperature (°C)	25	40	45	50	55
Yield (%)[b]	44	63	79	88	89

[a] Reaction conditions: isatin **1a** (1 mmol), malononitrile **2** (1 mmol), and 4-(4-methylphenylamino) furan-2(3*H*)-one **3b**; Et_3N (15 mol%); THF (5 ml), 3 h.
[b] Isolated yields.

2.3.11. 2-Amino-1-(3-chlorophenyl)-5′-nitro-2′,5-dioxo-5,7-dihydro-1H-spiro[furo[3,4-b]pyridine-4,3′-indoline]-3-carbonitrile (4l)

Cream powder (0.312 g, 79%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3362, 2180, 1741, 1689. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.56–4.74 (2H, m, OCH_2) 6.42 (2H, s, NH_2), 7.07–8.37 (7H, m, ArH), 11.24 (1H, s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 48.5, 58.5, 66.6, 97.9, 110.3, 119.3, 121.5, 126.9, 128.2, 129.6, 131.0, 132.1, 134.6, 135.0, 135.5, 143.3, 148.4, 153.1, 160.1, 170.1, 195.9. Anal. Calcd for $C_{21}H_{12}ClN_5O_5$: C, 56.07; H, 2.69; N, 15. 57%; Found C, 56.12; H, 2.64; N, 15.61%. Ms: *m/z* 451, 449.

2.3.12. 2-Amino-1-(4-bromophenyl)-1′,3′,5-trioxo-1′,3′,5,7-tetrahydro-1H-spiro[furo[3,4-b]pyridine-4,2′-indene]-3-carbonitrile (10a)

Yellow powder (0.345 g, 75%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3354, 2192, 1728, 1697. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.77 (2H, s, OCH_2), 6.65 (2H, s, NH_2), 7.46–8.11 (8H, m,

Table 3
Synthesis of 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitriles **4**.[a]

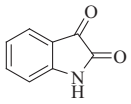
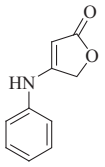
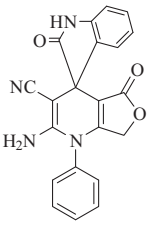
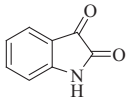
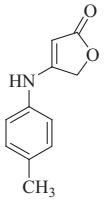
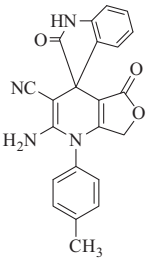
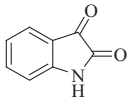
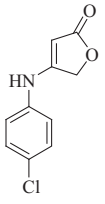
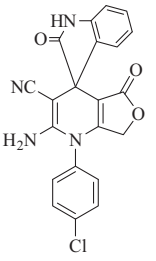
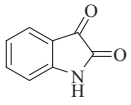
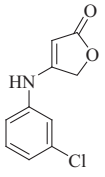
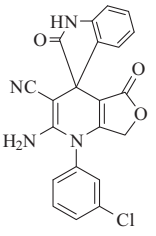
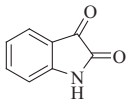
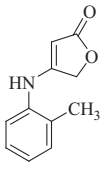
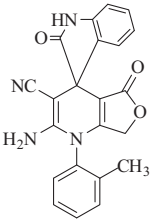
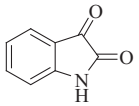
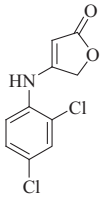
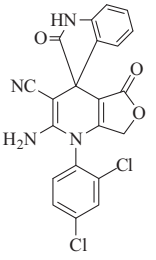
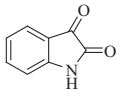
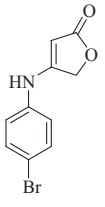
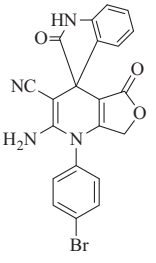
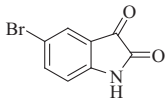
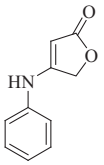
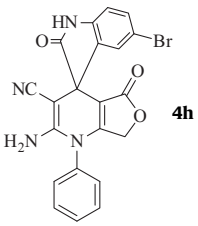
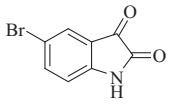
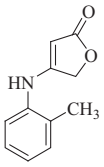
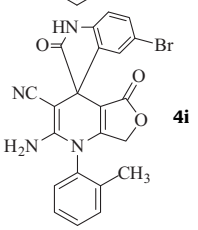
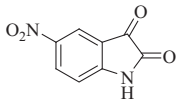
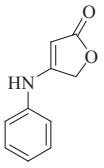
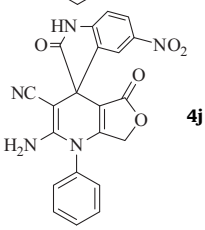
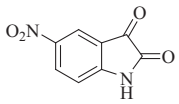
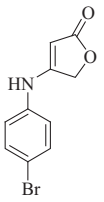
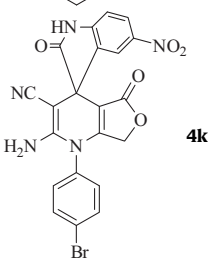
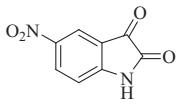
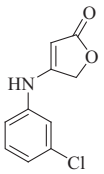
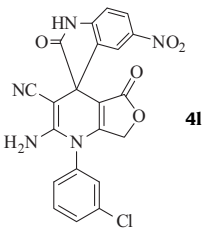
Entry	1	3	Product 4	Time (h)/yield (%)[b]
1			 **4a**	3/72
2			 **4b**	3/88
3			 **4c**	4/74
4			 **4d**	4/76
5			 **4e**	4/76
6			 **4f**	5/72
7			 **4g**	3/75

Table 3 (*continued*)

Entry	1	3	Product 4	Time (h)/yield (%)[b]
8			 **4h**	4/77
9			 **4i**	3/74
10			 **4j**	4/85
11			 **4k**	3/83
12			 **4l**	4/79

[a] Reaction conditions: isatins **1a** (1 mmol), malononitrile **2** (1 mmol), and anilinolactones **3** (1 mmol); Et_3N (15 mol%); THF (5 ml), at 50 °C, under ultrasound conditions.
[b] Isolated yields.

ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 56.7, 59.8, 66.5, 98.3, 111.4, 119.8, 122.0, 126.7, 131.9, 133.7, 135.2, 148.2, 154.0, 160.4, 171.2, 196.5. Anal. Calcd for $C_{22}H_{12}BrN_3O_4$: C, 57.16; H, 2.62; N, 9.09. %; Found C, 57.22; H, 2.66; N, 9.04%. Ms: *m/z* 463, 461.

2.3.13. 2-Amino-1-(3-chlorophenyl)-1′,3′,5-trioxo-1′,3′,5,7-tetrahydro-1H-spiro[furo[3,4-b]pyridine-4,2′-indene]-3-carbonitrile (10b)

(0.300 g, 72%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3359, 2189, 1730, 1683. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 4.78 (2H, m, OCH_2) 6.66 (2H, s, NH_2), 7.47–8.14 (8H, m, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 58.2, 62.0, 66.7, 99.8, 110.3, 119.8, 122.8, 125.9, 130.4, 131.5, 132.5, 134.7, 136.4, 142.3, 153.4, 160.3, 172.3, 179.2. Anal. Calcd for $C_{22}H_{12}ClN_3O_4$: C, 63.24; H, 2.89; N, 10. 06%; Found C,63.29; H, 2.93; N, 10.10%. Ms: *m/z* 419, 417.

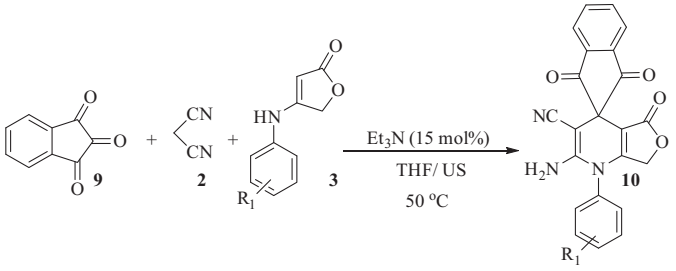
2.3.14. 2-Amino-1′,3′,5-trioxo-1-p-tolyl-1′,3′,5,7-tetrahydro-1H-spiro[furo[3,4-b]pyridine-4,2′-indene]-3-carbonitrile (10c)

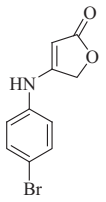
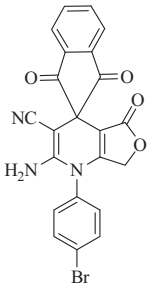
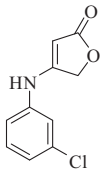
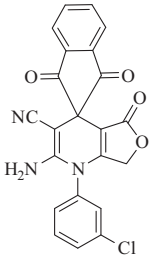
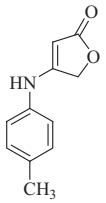
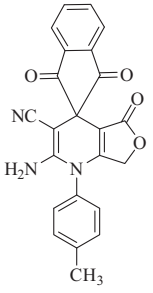
Yellow powder (0.309 g, 78%). mp > 300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3360, 2188, 1738, 1691. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_{ppm}: 2.39 (3H, s, CH_3), 4.74 (2H, s, OCH_2), 6.69 (2H, s, NH_2), 7.42–8.07 (8H, m, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ_{ppm}: 21.8, 58.7, 62.0, 66.7, 99.4, 110.3, 119.9, 123.6, 125.8, 129.7, 131.6, 134.9, 141.0, 153.4, 160.4, 172.3, 180.1. Anal. Calcd for $C_{23}H_{15}N_3O_4$: C, 69.52; H, 3.80; N, 10. 57%; Found C, 69.57; H, 3.74; N, 10.62%. Ms: *m/z* 397.

3. Results and discussion

Anilinolactones and associated compounds possessing the structural unit are versatile synthetic intermediates in organic chemistry that combine the ambient nucleophilicity of enamine and the electrophilicity of enones. They are commonly applied in

Table 4
Synthesis of 2-amino-1′,3′,5-trioxo-1-phenyl-1′,3′,5,7-tetrahydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,2′-indene]-3-carbonitrile derivatives **10**.[a]



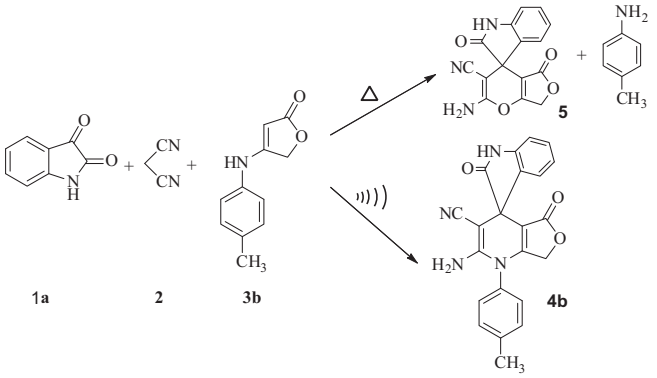
Anilinolactone **3**	Product **10**	Time (h)/yields (%)[b]
	 **10a**	2/75
	 **10b**	3/72
	 **10c**	2/78

[a] Reaction conditions: ninhydrine **9** (1 mmol), malononitrile **2** (1 mmol), and anilinolactones **3** (1 mmol); Et_3N (15 mol%); THF (5 ml), at 50 °C, under ultrasound conditions.
[b] Isolated yields.

Table 5
Screening on the reaction conditions for the synthesis of **4b**.[a]

Entry	Media	Catalyst (20 mol%)	Product	Yield (%)[b]
1	H_2O[c]	*p*-TSA	**5**	75
2	H_2O[c]	Et_3N	**5**	63
3	EtOH[c]	*p*-TSA	**5**	66
4	EtOH[c]	Et_3N	**5**	58
5	CH_3COOH[c]	Et_3N	**5**	49
6	CH_3CN[c]	Et_3N	**5**	42
7	THF[c]	Et_3N	**5**	48
8	THF[d]	Et_3N	**4b**	88
9	THF[d]	Pyridine	**4b**	63
10	CH_3COOH[d]	*p*-TSA	**4b**	52
11	CH_3CN[d]	*p*-TSA	**4b**	48
12	THF[d]	Alum	–	–
13	EtOH[c]	Pyridine	**5**	54
14	CH_3CN[c]	Pyridine	**5**	45
15	CH_3CN[d]	Pyridine	**4b**	53
16	EtOH[c]	CF_3COOH	**5**	64

[a] Reaction conditions: isatine **1a** (1 mmol), malononitrile **2** (1 mmol), and anilinolactones **3b** (1 mmol); catalyst (20 mol%); solvent (5 ml).
[b] Isolated yields.
[c] Classical heating conditions (8 h, reflux).
[d] Ultrasonic irradiation conditions (3 h, 50 °C).



Scheme 3. Model reaction of isatin **(1a)**, malononitrile **(2)** and 4-(4-methylphenylamino) furan-2(3*H*)-one **(3b)** under heating and ultrasonic conditions.

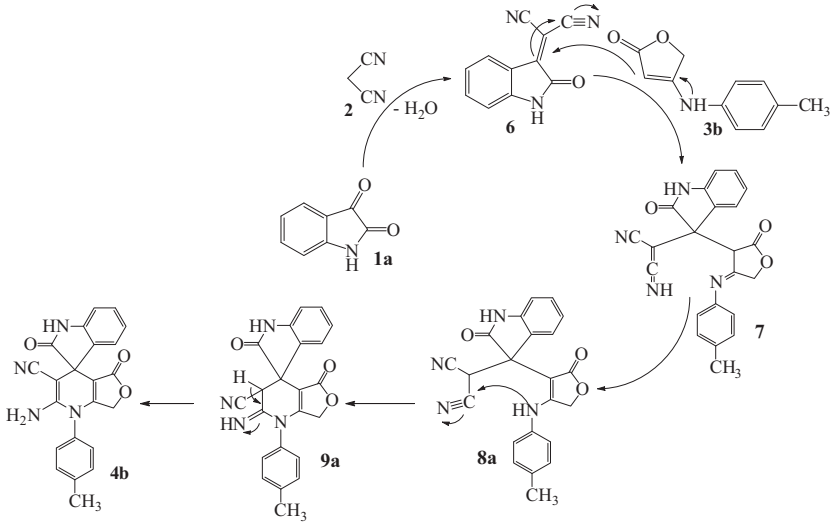
the preparation of heterocyclic compounds [29–30]. Regarding to importance of heterocycles containing spirooxindole structures, we have planned an ultrasonic assisted, one-pot, three component condensation reaction of isatins, malononitrile, and anilinolactones in order to synthesis of novel 1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitriles. To attain this goal, at first, the anilinolactones were prepared from the condensation reaction of tetronic acid with various anilines. As shown in Scheme 1, when tetronic acid was reacted with an equimolar amount of various anilines in 1,4-dioxane at room temperature, the corresponding products were obtained in excellent yields, appropriate reaction times, and high purity [31].

The choice of an appropriate reaction conditions is of crucial importance for a successful synthesis. Initially, the three component reaction of isatin **1a**, malononitrile **2**, and 4-(4-methylphenylamino) furan-2(3*H*)-one **3b** as a simple model substrate under ultrasonic conditions in the presence of Et_3N as inexpensive and available catalyst in THF at 50 °C was investigated to establish the feasibility of the strategy and optimize the reaction conditions toward synthesis of **4b** as target product (Scheme 2).

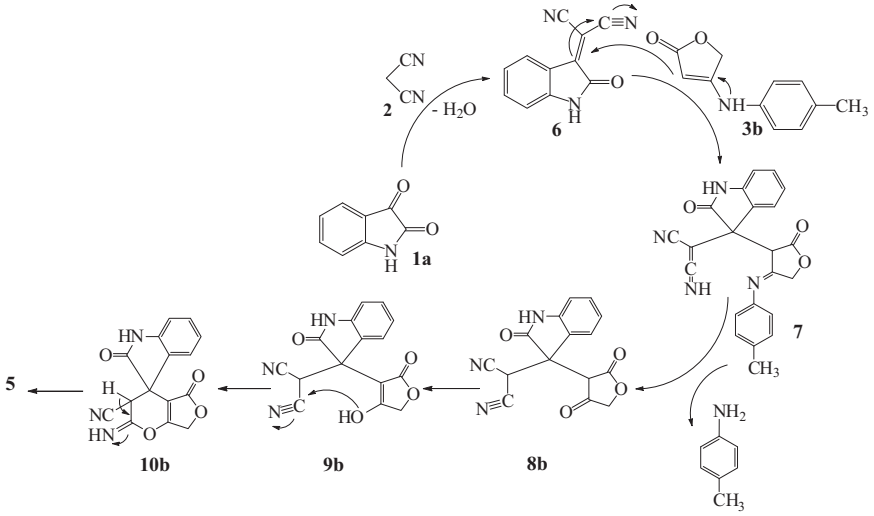
To study the effect of catalyst amount, the reactions were carried out in the presence of different amount of Et_3N ranging from 10–20 mol%. It was found that when increasing the amount of the Et_3N from 10 to 15, and 20 mol%, the yields increased from 72 to 88 and 88%, respectively. It was found that 15 mol% Et_3N in THF is sufficient to push this reaction forward. More amounts of the Et_3N did not improve the yields. When this reaction was carried out without Et_3N, the yield of the expected product was very low (<30%). Also, different solvents were screened in the model reaction. It was found that the reaction using THF after 3 h resulted in higher yield (Table 1).

To optimize the reaction temperature, we also performed several experiments at 25, 40, 45, 50 and 55 °C under ultrasonic irradiation in THF. As can be seen from Table 2, the most suitable reaction temperatures are 50 and 55 °C under ultrasonic irradiation. Thus 50 °C was chosen as appropriate temperature for the synthesis of these spirooxindole derivatives.

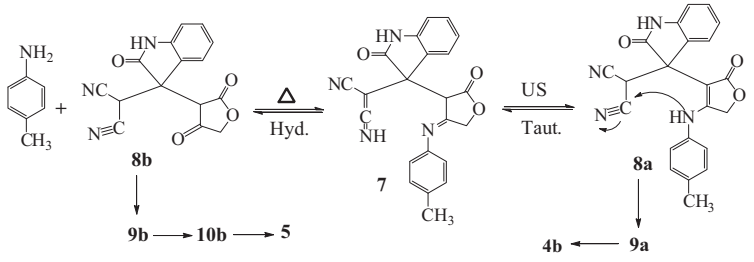
Encouraged by this success, we extended this reaction by a series of isatins **1a–c**, and malononitrile **2** with a range of anilinolactones **3a–g** under optimized conditions and corresponding



Scheme 4. Proposed mechanism for the synthesis of **4b** under ultrasonic conditions.



Scheme 5. Proposed mechanism for the synthesis of **5** under heating conditions.



Scheme 6. The conversion of intermediate **7** under heating and ultrasonic conditions.

spiro[furo-pyridine-indoline]-3-carbonitriles **4a–l** were synthesized in high yields. The results are summarized in Table 3.

To further explore the potential of this protocol for spirooxindole synthesis, we investigated the reaction of malononitrile **2** and anilinolactones **3** with ninhydrin **9**, and ralated 2-amino-1′,3′,5-trioxo-1-phenyl-1′,3′,5,7-tetrahydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,2′-indene]-3 carbonitrile derivatives **10a–c** were obtained in high yields under the same reaction conditions (Table 4).

In order to investigate the effects of ultrasonic irradiation and to evaluate and compare conventional heating with ultrasound assisted method, we continued our efforts in different conditions such as different catalysts and various media on model reaction. The results were listed in Table 5. As can be seen in Table 5, surprisingly, it was found that in the conventional heating, a different product **5** was produced instead of **4b** (Scheme 3). After purification, the structure of product **5** was characterized based on Mass, ^{1}H NMR, and ^{13}C NMR spectroscopic data. In the ^{1}H NMR spectrum of product, the signal at δ = 10.70 ppm indicates the presence of –NH proton of oxindole ring (D_2O exchangeable), the NH_2 protons resonated at δ = 7.70 ppm with two integral values

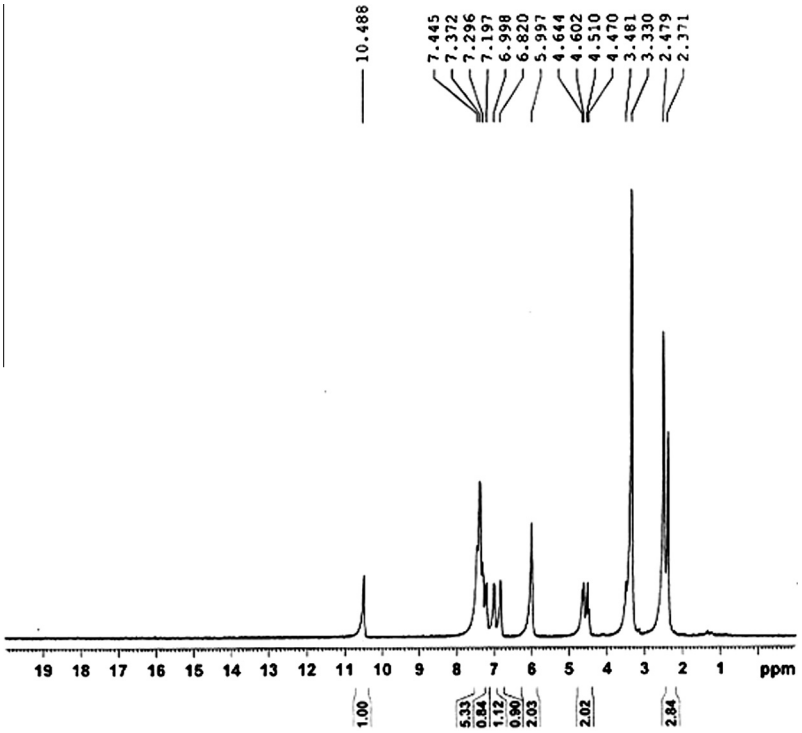


Fig. 2. ^{1}H NMR spectra of 2-amino-2′,5-dioxo-1-*p*-tolyl-5,7-dihydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3 carbonitrile **4b**.

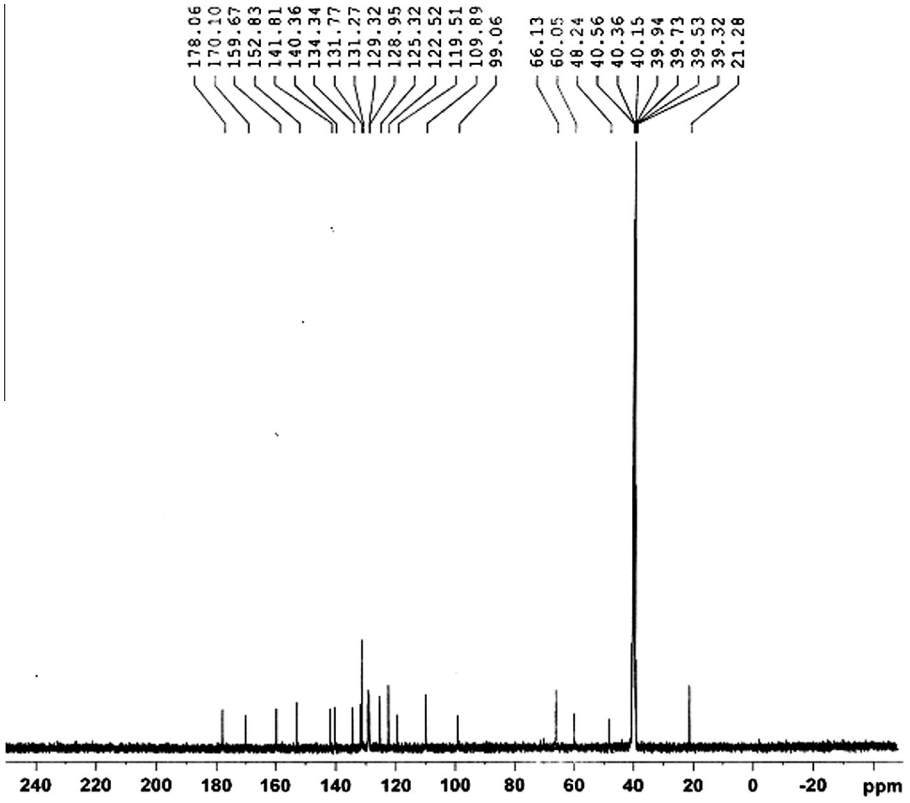


Fig. 3. ^{13}C NMR spectra of 2-amino-2′,5-dioxo-1-*p*-tolyl-5,7-dihydro-1*H*-spiro[furo[3,4-*b*]pyridine-4,3′-indoline]-3-carbonitrile **4b**.

(exchangeable with D_2O), the aromatic protons exhibited multiplet in the region δ = 6.85–7.26 ppm with four integral values, the signals around δ = 5.06–5.21 ppm with two integral values are assigned to the protons of OCH_2 of tetronic acid. The ^{13}C NMR spectrum showed 15 distinct signals; also the mass spectrum of product displayed the molecular ion peak at *m/z*: 295.

Ultrasound enhanced the rate of a reaction and, consequently, reduced energy consumption. The chemical and physical effects of ultrasound derive primarily from acoustic cavitation, which includes formation, growth and collapse of the cavity. The driving force for the increased efficiency of spirooxindoles formation by ultrasound is due to the increase in the temperature related to the formation of hot spots; and due to increase in the reactant contact surface area through cavitations phenomenon.[27b,c].

Based on the studied parallel articles [32–34] a reasonable possibility is shown in Scheme 4. Compound **4b** could be synthesized *via* domino reactions of Knoevenagel condensation, Michael addition, and a cyclocondensation in which the isatin **1a** can be firstly condensed with malononitrile **2** to afford isatylidene malononitrile **6** under ultrasonic irradiation**.** This step was regarded to a fast Knoevenagel condensation reaction. Then, compound **6** is attacked *via* Michael type addition of 4-(4-methylphenylamino)furan-2(3*H*)-one **3b** to give the intermediate **7**.

When the model reaction (isatin **1a**, malononitrile **2**, and 4-(4-methylphenylamino) furan-2(3*H*)-one **3b**) was carried out under conventional heating, the imine group of intermediate **7** was hydrolyzed to **8b**. Thereupon, the product **5** was obtained and aromatic amine as a leaving group removed from intermediate **7** (Scheme 5).

On the basis of our knowledge, the intermediate **7** can be underwent two different competitive routes; (a) equilibrium tautomerization to intermediate **8a**, followed by nucleophilic attack of amine tautomer to cyanide group and cyclization to **9a**, then to form **4b** as target product, (b) equilibrium hydrolysis of the imine group to **8b,** followed to convert **9b** and **10b**, then to form **5** as product (Scheme 6). In sonication, the implosive collapse of the cavitations period of the sound waves generates the bubbles at localized sites in the liquid phase. When the bubbles burst, it results in high temperature and high pressure which facilitate the equilibrium tautomerization of **7** to intermediate **8a**. Also, it was accelerated the intramolecular cyclization reaction of **8a,** through providing the high activation energy of this reaction, to afford the product **4b** and thus there is any chance for hydrolysis of **7** to **8b**. While in the absence of ultrasound, with decrease the rate of tautomerization and cyclization, the **7** was hydrolyzed to **8b** that led to compound **5**.

The structure of product **4b** has been confirmed by physical and spectroscopic data such as; IR, ^{1}H NMR, and ^{13}C NMR. In the IR spectrum of this compound revealed broad absorption bands at 3180–3425 cm^{-1} assigned to the NH_2 group, the stretching frequency of –CN is formed in the region $\nu = 2185\ cm^{-1}$, the absorption bands at 1721 and 1682 cm^{-1} corresponding to two carbonyls of the amide and ester confirmed the presence of this structure. In the ^{1}H NMR spectrum, the signal at $\delta = 10.48$ ppm indicates the presence of –NH proton of oxindole ring (D_2O exchangeable), the aromatic protons exhibited multiplet in the region $\delta = 6.82–7.44$ ppm with eight integral values, the $–NH_2$ protons resonated at $\delta = 5.99$ ppm with two integral values (exchangeable with D_2O), the signals around $\delta = 4.47–4.64$ ppm with two integral values are assigned to the protons of $–OCH_2$ of tetronic acid, and the signal at $\delta = 2.37$ ppm indicates the presence of $–CH_3$ protons (Fig. 2). The ^{13}C NMR spectrum showed 20 distinct signals (Fig. 3).

4. Conclusion

In this work, we have developed one-pot and efficient three component procedures for a convenient and mild synthesis of novel spirooxindole derivatives. Prominent among the advantages of these new methods are operational simplicity, high yields in short reaction times and easy work-up procedures employed. Most importantly of all, in this research, it was observed that in ultrasonic reaction conditions novel 1*H*-spiro[furo[3,4-*b*]pyridine-4, 3′-indoline]-3-carbonitriles were produced, while in classical heating conditions surprisingly 2-amino-2′, 5-dioxo-5,7-dihydrospiro[furo[3,4-*b*]pyran-4,3′-indoline]-3-carbonitriles were obtained.

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