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ORIGINAL PAPER

L-Proline: an efficient catalyst for the synthesis of new spirooxindoles

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Abstract L-Proline was found to be a versatile organocatalyst for the synthesis of new spirooxindole derivatives in good yields under mild reaction conditions using 1-propanol as a solvent.

Keywords L-Proline · Spirooxindole · Isatin · Multi-component · Organocatalyst

Introduction

Indole and indoline fragments are important moieties of a large number of natural products and medicinal agents [1], and some indolines, spiro-annulated with heterocycles in the 3-position, have shown high biological activity [2, 3]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [4, 5]. Therefore, a number of methods have been reported for the preparation of spirooxindole-fused heterocycles [6–18].

In recent years, the use of L-proline in different organic reactions has drawn much interest because of its experimental simplicity, ease of handling, cost effectiveness, and excellent solubility in water and organic solvents. L-Proline is a very efficient catalyst in transformations such as enamine-based direct catalytic asymmetric aldol condensation [19, 20], α-amination reaction [21], Mannich reaction [22, 23], Diels–Alder reaction [24], Michael addition [25], and as excellent promoter for copper-catalyzed coupling reactions [26]. Proline has also been used as a catalyst for two-carbon homologation and in various one-pot multicomponent reactions [27–32]. More recently, proline has been used in the synthesis of spirooxindoles [33].

As part of our program aimed at developing new methodologies for the preparation of heterocyclic compounds [34–37], we very recently reported several novel syntheses of spirooxindoles via isatin-based multicomponent reactions [38–42]. Herein, we describe new multicomponent reactions leading to spirooxindoles and fused heterocycles using L-proline as an organocatalyst.

Results and discussion

First, to achieve suitable conditions for the synthesis of spirooxindoles, we tested the reaction of 1,3-indandione (**1**), isatin (**2a**), and 3-aminocrotononitrile (**3a**) as a simple model system in different solvents with or without the presence of various catalysts (Table 1). As can be seen in Table 1, the best result was obtained with 20 mol% of L-proline as the catalyst in refluxing 1-propanol (entry 4). Using less catalyst resulted in lower yields, whereas higher amounts of catalyst did not affect reaction times and yields (significantly) (Table 1). When this reaction was carried out without L-proline or with other catalysts such as $ZnCl_2$, *para*-toluenesulfonic acid (*p*-TSA), HOAc, Et_3N, K_2CO_3, and KOH the yield of the expected product was low (Table 1). In the presence of piperidine or $LiClO_4$ as catalyst the product was obtained in moderate yield. To delineate the best solvent, the reaction was investigated in various solvents. Table 1 demonstrates that 1-propanol was the best choice of solvent and the use of L-proline in refluxing 1-propanol improved the reaction rate and the product yield.

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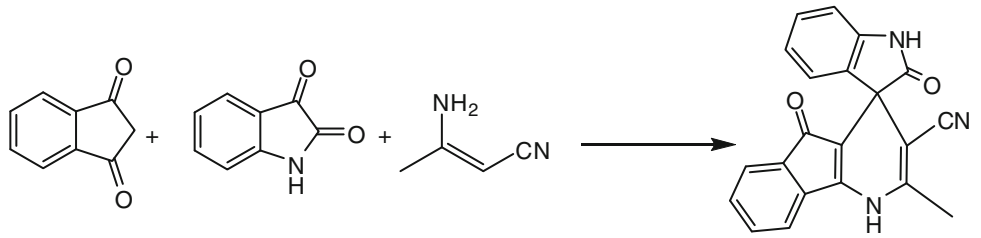
Table 1 Effect of reaction conditions



1 **2a** **3a** **4a**

Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)
1	1-Propanol	None	24	<30
2	1-Propanol	L-Proline (10)	10	44
3	1-Propanol	L-Proline (15)	10	66
4	1-Propanol	L-Proline (20)	10	81
5	1-Propanol	L-Proline (25)	10	82
6	H_2O	L-Proline (20)	10	<30
7	CH_3CN	L-Proline (20)	10	43
8	THF	L-Proline (20)	10	54
9	EtOH	L-Proline (20)	10	63
10	1-Propanol	*p*-TSA (20)	10	57
11	1-Propanol	$LiClO_4$ (20)	10	67
12	1-Propanol	$ZnCl_2$ (20)	10	<30
13	1-Propanol	HOAc (20)	10	48
14	1-Propanol	Et_3N (20)	10	56
15	1-Propanol	Piperidine (20)	10	65
16	1-Propanol	K_2CO_3	10	<30
17	1-Propanol	KOH	10	47

Indandione (1 mmol), isatin (1 mmol), and aminocrotonitrile (1 mmol) at reflux

THF tetrahydrofuran

Encouraged by this success, a variety of isatins and enamines were employed under similar conditions to evaluate the substrate scope of this reaction. The corresponding spiro[indeno[1,2-*b*]pyridine-indoline] derivatives **4a**–**4n** were selectively synthesized by the one-pot, three-component condensation of 1,3-indandione (**1**), isatins **2a**–**2e**, and enamines **3a**–**3c** in good yields. The results are summarized in Table 2.

Although the mechanism of this reaction has not been studied experimentally, the proposed mechanism is described in Scheme 1.

The ^{1}H NMR spectra of the crude products indicated the formation of spirooxindoles **4**. Compounds **4** are stable solids whose structures were established by IR, NMR spectroscopy, and elemental analysis.

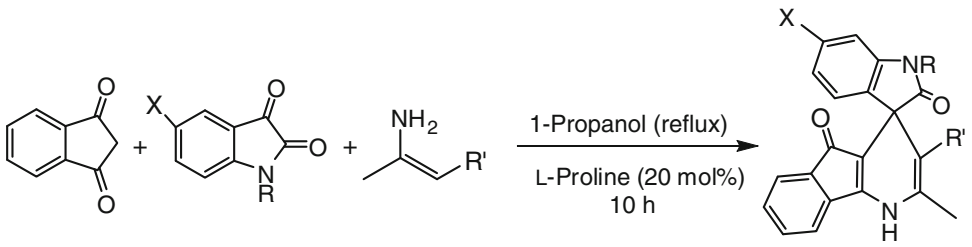
This three-component method is simple, interesting, convenient, and acceptable and because of the availability of various isatins and enamines, it should be applicable to synthesis of libraries with high diversity. In addition, the work-up of these very clean reactions is simple, involving only a filtration and simple washing step with EtOH.

As expected, when the isatin **2** was replaced by acenaphthylene-1,2-dione (**5**), spiro[acenaphthylene-indeno [1,2-*b*]pyridine] derivatives **6** were obtained in good yields under the same reaction conditions (Scheme 2).

To further explore the potential of this protocol for spirooxindole synthesis, we investigated the reaction of malononitrile (**7**) and isatins **2** with enamines **3** and obtained spiro[indoline-3,4′-pyridine] derivatives **8** in good yields under the same reaction conditions (Table 3). To investigate the effect of L-proline on the enantioselectivity of the reactions, the optical rotation ($[\alpha]_D^{25}$) for selected products **4a**, **4c**, **4m**, **8a**, **8c**, and **6a** was measured and low optical rotation (<5%) was observed.

Under similar conditions in the absence of 1,3-indandione or malononitrile, aminocrotonitrile and isatins gave

Table 2 Synthesis of spiro[indeno[1,2-*b*]pyridine-indoline] derivatives **4**



Product	R	X	R′	Yield (%)
4a	H	H	CN	81
4b	Me	H	CN	78
4c	H	Br	CN	82
4d	H	NO_2	CN	86
4e	H	H	COOMe	79
4f	Me	H	COOMe	83
4g	H	NO_2	COOMe	80
4h	Et	H	COOMe	85
4i	Me	NO_2	COOMe	78
4j	H	H	COOEt	84
4k	Me	H	COOEt	82
4l	H	NO_2	COOEt	80
4m	Et	H	COOEt	82
4n	Me	NO_2	COOEt	87

spiro[indoline-3,4′-pyridine] derivatives **9** in 73–84% yields (Table 4).

In conclusion, we have developed efficient straightforward procedures for the synthesis of spirooxindole derivatives of potential synthetic and biological interest by a one-pot, three-component methodology using L-proline as an organocatalyst.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. Chemicals were purchased from Fluka or Merck and used as received.

General procedure for the preparation of spirooxindoles

A mixture of 1,3-indandione or malononitrile (1 mmol), isatin (1 mmol), enamine (1 mmol), and L-proline (20 mol%) in 5 cm^3 refluxing 1-propanol was stirred for 10 h. After completion the reaction mixture was filtered and the precipitate washed with 10 cm^3 EtOH and air-dried to provide the pure products.

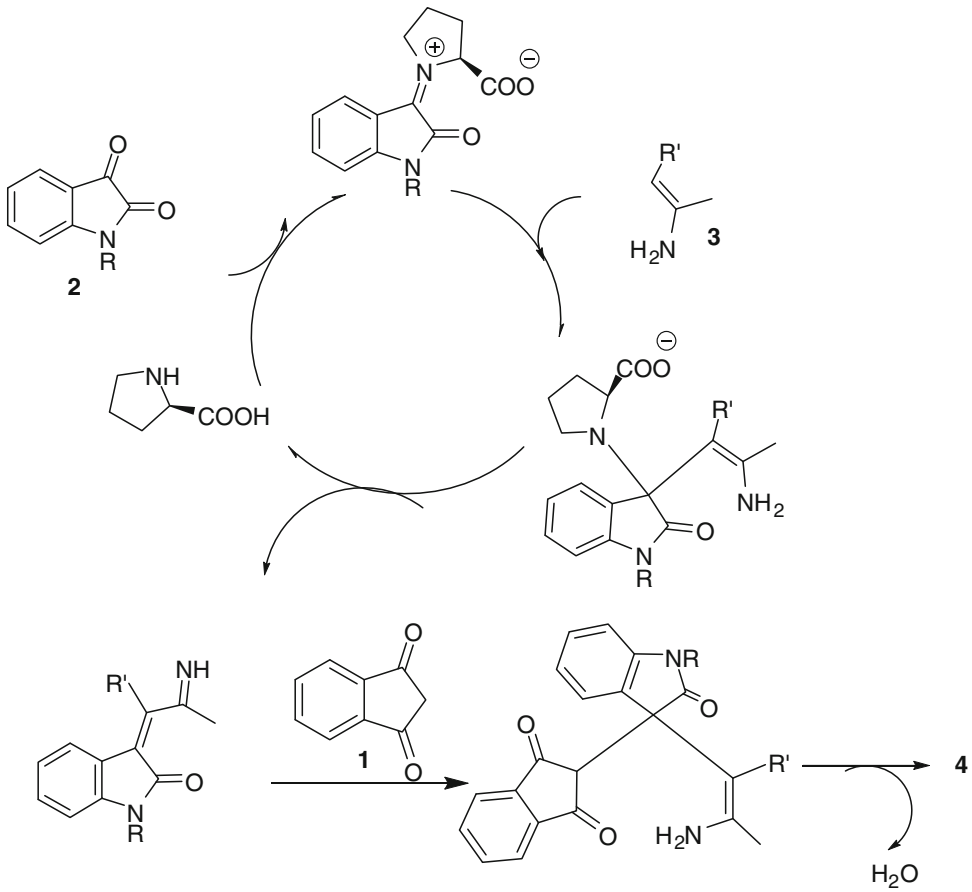
1,1′,2′,5-Tetrahydro-2-methyl-2′,5-dioxospiro-[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carbonitrile (**4a**, $C_{21}H_{13}N_3O_2$)

Orange powder (81%); m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 3,296, 3,225, 3,040, 2,189, 1,704, 1,659 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.29 (3H, s, CH_3), 6.86–7.62 (8H, m, H–Ar), 10.60 (1H, s, NH), 10.92 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.7, 49.4, 87.7, 104.7, 109.9, 117.6, 120.2, 121.4, 122.7, 125.2, 129.6, 131.2, 132.8, 132.9, 134.4, 136.1, 141.7, 149.3, 154.9, 177.8, 190.1 ppm.

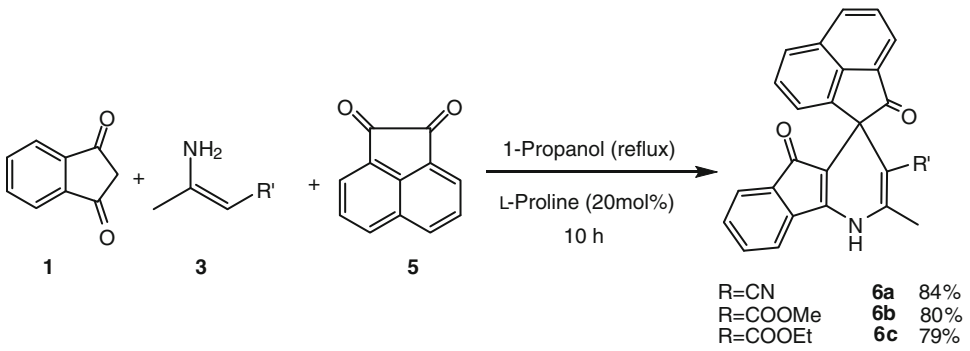
1,1′,2′,5-Tetrahydro-1′,2-dimethyl-2′,5-dioxospiro-[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carbonitrile (**4b**, $C_{22}H_{15}N_3O_2$)

Orange powder (78%); m.p.: >300 °C; IR (KBr): $\bar{\nu}$ = 3,225, 3,043, 2,187, 1,701, 1,664 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.30 (3H, s, CH_3), 3.19 (3H, s, CH_3), 7.01–7.65 (8H, m, H–Ar), 11.02 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.7, 26.9, 49.1, 87.3,

Scheme 1



Scheme 2



104.6, 108.9, 117.5, 120.4, 121.4, 123.4, 124.9, 129.7, 131.3, 132.8, 132.9, 133.5, 136.0, 143.2, 149.6, 154.9, 176.2, 190.0 ppm.

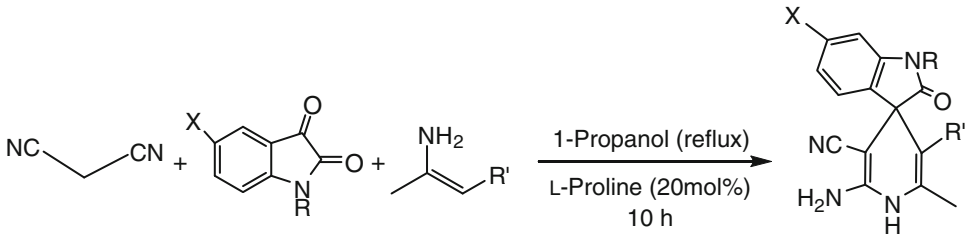
6′-Bromo-1,1′,2′,5-tetrahydro-2-methyl-2′,5-dioxospiro-[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carbonitrile (**4c**, $C_{21}H_{12}BrN_3O_2$)

Brown powder (82%); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,301, 3,220, 3,027, 2,196, 1,705, 1,660 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.29 (3H, s, CH_3), 6.83–7.66 (7H, m, H–Ar), 10.80 (1H, s, NH), 11.03 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.8, 49.7, 86.9, 104.2, 112.0, 114.4, 117.6, 120.5, 121.5, 128.2, 131.4, 132.4, 132.8, 132.9, 136.1, 136.5, 141.1, 149.9, 155.2, 177.5, 190.2 ppm.

1,1′,2′,5-Tetrahydro-2-methyl-6′-nitro-2′,5-dioxospiro-[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carbonitrile (**4d**, $C_{21}H_{12}N_4O_4$)

Orange powder (86%); m.p.: 297 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,306, 3,218, 3,019, 1,704, 1,669 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.32 (3H, s, CH_3), 7.10–8.24 (7H, m, H–Ar), 11.14 (1H, s, NH), 11.39 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.7, 49.8, 86.6, 104.5, 112.3, 114.4, 118.2, 120.8, 122.3, 128.7, 131.5,

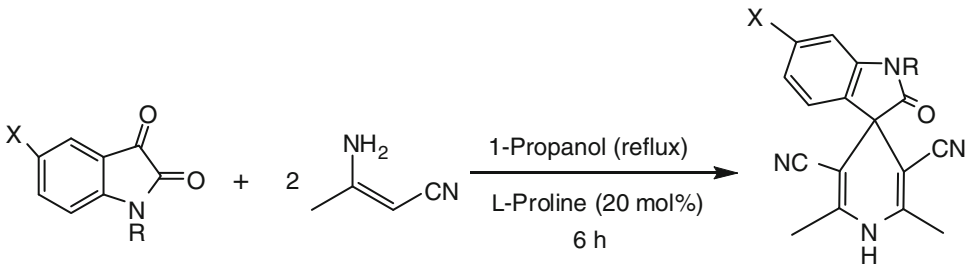
Table 3 Synthesis of spiro[indoline-3,4′-pyridine] derivatives **8**



7 **2** **3** **8a-8g**

Product	R	X	R′	Yield (%)
8a	H	H	CN	77
8b	Me	H	CN	76
8c	H	Br	CN	80
8d	H	NO_2	CN	81
8e	H	H	COOMe	75
8f	Me	H	COOMe	77
8g	H	Br	COOMe	79

Table 4 Synthesis of spiro[indoline-3,4′-pyridine] derivatives **9**



2 **3** **9a-9e**

Product	R	X	Yield (%)
9a	H	H	80
9b	Me	H	78
9c	Et	H	73
9d	H	Br	82
9e	H	NO_2	84

132.4, 132.9, 133.4, 136.9, 136.7, 141.8, 151.3, 155.1, 177.9, 190.3 ppm.

Methyl 1,1′,2′,5-tetrahydro-2-methyl-2′,5-dioxospiro[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4e**, $C_{22}H_{16}N_2O_4$)

Red powder (79%); m.p.: >300 °C; IR (KBr): $\overline{v}$ = 3,247, 3,153, 1,697, 1,674, 1,641 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.42 (3H, s, CH_3), 3.30 (3H, s, OCH_3), 6.74–7.65 (8H, m, H–Ar), 10.28 (1H, s, NH), 10.37 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.7, 50.0, 51.1, 105.8, 107.1, 109.0, 120.0, 121.0, 121.6, 123.7, 128.3, 130.9, 132.4, 133.4, 135.9, 136.8, 142.7, 146.9, 154.0, 166.6, 179.9, 189.6 ppm.

Methyl 1,1′,2′,5-tetrahydro-1′,2-dimethyl-2′,5-dioxospiro-[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4f**, $C_{23}H_{18}N_2O_4$)

Brown powder (83%); m.p.: >300 °C; IR (KBr): $\overline{v}$ = 3,252, 1,701, 1,674, 1,654 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6):

$\delta = 2.43$ (3H, s, CH_3), 3.15 (3H, s, NCH_3), 3.27 (3H, s, OCH_3), 6.88–7.65 (8H, m, H–Ar), 10.43 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 19.7, 26.7, 49.4, 51.3, 105.4, 107.0, 107.9, 120.1, 121.0, 122.4, 123.5, 128.5, 131.0, 132.5, 133.4, 135.9, 136.0, 144.1, 147.5, 154.0, 166.5, 178.4, 189.6$ ppm.

Methyl 1,1′,2′,5-tetrahydro-2-methyl-6′-nitro-2′,5-dioxo-spiro[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4g**, $C_{22}H_{15}N_3O_6$)
Red powder (80%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}179$, 3,221, 1,712, 1,674, 1,641 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.29$ (3H, s, CH_3), 3.36 (3H, s, OCH_3), 6.97–8.13 (7H, m, H–Ar), 10.59 (1H, s, NH), 11.08 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.0, 50.1, 51.4, 104.4, 109.1, 119.2, 120.5, 121.2, 125.8, 126.0, 128.6, 129.4, 131.2, 132.6, 133.2, 135.8, 137.8, 142.4, 148.9, 149.4, 166.4, 180.5$ ppm.

Methyl 1′-ethyl-1,1′,2′,5-tetrahydro-2-methyl-2′,5-dioxo-spiro[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4h**, $C_{24}H_{20}N_2O_4$)
Orange powder (85%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}247$, 1,695, 1,679 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.22$ (3H, t, $^3J_{HH} = 6.9$ Hz, CH_3), 2.44 (3H, s, CH_3), 3.26 (3H, s, OCH_3), 3.72 (2H, q, $^3J_{HH} = 6.9$ Hz, NCH_2), 6.88–7.65 (8H, m, H–Ar), 10.42 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 12.7, 19.7, 34.6, 49.4, 51.1, 105.3, 107.1, 107.9, 120.1, 121.0, 122.1, 123.7, 128.4, 130.9, 132.4, 133.4, 135.9, 136.2, 143.0, 147.5, 154.0, 166.5, 177.7, 189.6$ ppm.

Methyl 1,1′,2′,5-tetrahydro-1′,2-dimethyl-6′-nitro-2′,5-dioxo-spiro[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4i**, $C_{23}H_{17}N_3O_6$)
Orange powder (78%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}153$, 1,685, 1,648 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.48$ (3H, s, CH_3), 3.27 (3H, s, NCH_3), 3.34 (3H, s, OCH_3), 7.17–8.23 (7H, m, H–Ar), 10.65 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.0, 27.1, 49.4, 51.6, 104.0, 108.1, 118.8, 120.6, 121.3, 126.1, 131.2, 132.7, 133.2, 137.0, 143.0, 149.3, 150.2, 154.6, 166.3, 179.1$ ppm.

Ethyl 1,1′,2′,5-tetrahydro-2-methyl-2′,5-dioxospiro-[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4j**, $C_{23}H_{18}N_2O_4$)
Red powder (84%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}211$, 3,158, 1,680, 1,638, 1,617 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.81$ (3H, t, $^3J_{HH} = 6.3$ Hz, CH_3), 2.42 (3H, s, CH_3), 3.72–3.74 (2H, m, OCH_2), 6.73–7.64 (8H, m, H–Ar), 10.29 (1H, s, NH), 10.38 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.5, 19.5, 49.9, 57.3, 59.9, 105.6, 107.1, 109.0, 119.9, 121.0, 121.6, 123.8, 128.2, 130.9, 132.4, 133.4, 135.9, 137.0, 142.8, 147.0, 154.0, 166.1, 180.0, 189.7$ ppm.

Ethyl 1,1′,2′,5-tetrahydro-1′,2-dimethyl-2′,5-dioxo-spiro-[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4k**, $C_{24}H_{20}N_2O_4$)
Red powder (82%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}164$, 1,680, 1,647, 1,610 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.74$ (3H, t, $^3J_{HH} = 6.9$ Hz, CH_3), 2.45 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 3.68–3.73 (2H, m, OCH_2), 6.87–7.65 (8H, m, H–Ar), 10.44 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.8, 19.6, 26.6, 49.4, 59.8, 105.0, 107.1, 107.8, 120.1, 121.0, 122.4, 123.5, 128.4, 130.9, 132.4, 133.4, 135.9, 136.2, 144.2, 147.7, 153.9, 165.9, 178.3, 189.6$ ppm.

Ethyl 1,1′,2′,5-tetrahydro-2-methyl-6′-nitro-2′,5-dioxo-spiro[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4l**, $C_{23}H_{17}N_3O_6$)
Red powder (80%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}247$, 3,169, 1,711, 1,680, 1,643 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.87$ (3H, t, $^3J_{HH} = 6.9$ Hz, CH_3), 2.55 (3H, s, CH_3), 3.79 (2H, q, $^3J_{HH} = 6.9$ Hz, OCH_2), 6.97–8.16 (7H, m, H–Ar), 10.60 (1H, s, NH), 11.10 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.9, 19.9, 49.4, 60.2, 103.6, 105.8, 108.1, 118.8, 120.5, 121.3, 126.1, 131.2, 132.7, 133.2, 135.8, 137.1, 143.0, 149.6, 150.2, 154.5, 165.6, 179.1, 189.7$ ppm.

Ethyl 1′-ethyl-1,1′,2′,5-tetrahydro-2-methyl-2′,5-dioxo-spiro[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4m**, $C_{25}H_{22}N_2O_4$)
Red powder (82%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}153$, 1,711, 1,674, 1,643 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.72$ (3H, t, $^3J_{HH} = 6.9$ Hz, CH_3), 1.23 (3H, t, $^3J_{HH} = 6.3$ Hz, CH_3), 2.44 (3H, s, CH_3), 3.57–3.68 (2H, m, NCH_2), 3.70–3.78 (2H, m, OCH_2), 6.88–7.65 (8H, m, H–Ar), 10.41 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 12.6, 13.7, 19.6, 49.5, 59.7, 105.1, 107.1, 107.9, 120.0, 121.0, 122.1, 123.6, 128.4, 130.9, 132.4, 133.4, 135.9, 136.3, 143.2, 147.6, 153.9, 165.9, 177.7, 189.6$ ppm.

Ethyl 1,1′,2′,5-tetrahydro-1′,2-dimethyl-6′-nitro-2′,5-dioxo-spiro[4H-indeno[1,2-b]pyridine-4,3′-[3H]indole]-3-carboxylate (**4n**, $C_{24}H_{19}N_3O_6$)
Orange powder (87%); m.p.: >300 °C; IR (KBr): $\overline{\nu} = 3{,}174$, 1,695, 1,648 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.80$ (3H, t, $^3J_{HH} = 6.9$ Hz, CH_3), 2.51 (3H, s, CH_3), 3.26 (3H, s, NCH_3), 3.76 (2H, q, $^3J_{HH} = 6.9$ Hz, OCH_2), 7.17–8.26 (7H, m, H–Ar), 10.66 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 13.6, 19.9, 27.0, 49.4, 60.2, 103.6, 105.8, 108.1, 118.8, 120.5, 121.2, 126.1, 131.2, 132.6, 133.2, 135.7, 137.1, 143.0, 149.6, 150.2, 154.5, 165.6, 179.1, 189.7$ ppm.

1,1′,2,5′-Tetrahydro-2′-methyl-2,5′-dioxospiro-[acenaphthylene-1(2H),4′-[4H]indeno[1,2-b]-pyridine]-3′-carbonitrile (**6a**, $C_{25}H_{14}N_2O_2$)
Red powder (84%); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,177, 2,221, 1,715, 1,649 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.96 (3H, s, CH_3), 7.01–8.02 (10H, m, H–Ar), 10.41 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.3, 54.9, 87.5, 108.8, 119.4, 120.2, 120.6, 120.7, 124.5, 128.7, 129.1, 129.7, 130.5, 130.9, 132.2, 133.2, 134.8, 136.1, 140.3, 145.5, 145.9, 154.2, 189.8, 197.1, 204.6 ppm.

Methyl 1,1′,2,5′-tetrahydro-2′-methyl-2,5′-dioxospiro-[acenaphthylene-1(2H),4′-[4H]indeno[1,2-b]-pyridine]-3′-carboxylate (**6b**, $C_{26}H_{17}NO_4$)
Red powder (80%); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,226, 1,690, 1,643 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.97 (3H, s, CH_3), 3.37 (3H, s, OCH_3), 7.03–8.20 (10H, m, H–Ar), 10.48 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.6, 50.9, 54.4, 106.7, 108.5, 120.1, 120.5, 120.9, 121.0, 124.7, 128.7, 129.1, 129.3, 129.8, 130.9, 132.5, 133.1, 134.1, 136.0, 140.6, 145.4, 147.3, 154.1, 166.7, 189.9, 205.3 ppm.

Ethyl 1,1′,2,5′-tetrahydro-2′-methyl-2,5′-dioxospiro-[acenaphthylene-1(2H),4′-[4H]indeno[1,2-b]-pyridine]-3′-carboxylate (**6c**, $C_{27}H_{19}NO_4$)
Red powder (79%); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,221, 1,701, 1,680, 1,638 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 0.11 (3H, t, $^3J_{HH}$ = 6.9 Hz, CH_3), 2.49 (3H, s, CH_3), 3.33–3.36 (3H, m, CH_2),7.28–8.19 (10H, m, H–Ar), 10.52 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.8, 19.5, 54.4, 59.6, 106.3, 108.6, 120.1, 120.5, 120.9, 121.2, 124.6, 128.7, 129.2, 129.9, 131.0, 132.5, 133.2, 134.2, 136.0, 140.9, 145.5, 147.5, 154.0, 166.0, 190.0, 205.4 ppm.

2′-Amino-1,2-dihydro-6′-methyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile
(**8a**, $C_{15}H_{11}N_5O$)
White powder (77%); m.p.: 260 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,341, 3,218, 2,219, 2,215, 1,680 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.24 (3H, s, CH_3), 6.88–7.32 (4H, m, H–Ar), 7.52 (2H, bs, NH_2), 10.78 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.1, 49.7, 54.2, 88.3, 110.6, 115.5, 117.6, 123.3, 125.5, 130.4, 131.7, 141.8, 159.8, 162.2, 176.9 ppm.

2′-Amino-1,2-dihydro-1,6′-dimethyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile
(**8b**, $C_{16}H_{13}N_5O$)
White powder (76%); m.p.: 230 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,340, 3,210, 2,223, 1,680 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.25 (3H, s, CH_3), 3.32 (3H, s, CH_3), 7.11–7.43 (4H, m, H–Ar), 7.54 (2H, bs, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.2, 27.0, 49.3, 53.9, 88.1, 109.6, 115.3, 117.4, 124.0, 125.3, 130.6, 130.9, 143.3, 159.9, 162.5, 175.3 ppm.

2′-Amino-6-bromo-1,2-dihydro-6′-methyl-2-oxospiro-[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile
(**8c**, $C_{15}H_{10}BrN_5O$)
Cream powder (80%); m.p.: 295 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,342, 3,214, 3,114, 2,229, 2,216, 1,656 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.23 (3H, s, CH_3), 3.37 (3H, s, OCH_3), 7.21–7.58 (4H, m, H–Ar), 7.63 (2H, bs, NH_2), 10.91 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.2, 49.9, 53.7, 87.4, 112.6, 114.9, 115.5, 117.7, 128.6, 133.3, 134.1, 141.1, 159.8, 162.7, 176.6 ppm.

2′-Amino-1,2-dihydro-6′-methyl-6-nitro-2-oxospiro-[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile
(**8d**, $C_{15}H_{10}BrN_5O$)
Green powder (81%); m.p.: 260 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,348, 3,221, 3,119, 2,226, 2,219, 1,664 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.24 (3H, s, CH_3), 7.12 (1H, bs, H–Ar), 7.69 (2H, bs, NH_2), 8.26–8.38 (2H, m, H–Ar), 11.52 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.3, 49.9, 53.0, 86.6, 111.1, 115.4, 117.4, 121.8, 127.6, 132.7, 143.6, 148.1, 159.9, 163.3, 177.6 ppm.

Methyl 6′-amino-5′-cyano-1,2-dihydro-2′-methyl-2-oxospiro-[3H-indole-3,4′(1′H)-pyridine]-3′-carboxylate
(**8e**, $C_{16}H_{14}N_4O_3$)
Cream powder (75%); m.p.: 271 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,335, 3,223, 3,122, 2,221, 1,711, 1,664 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.21 (3H, s, CH_3), 3.75 (3H, s, CH_3), 7.10–7.34 (4H, m, H–Ar), 7.65 (2H, bs, NH_2), 11.51 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.0, 49.9, 51.3, 52.4, 89.2, 115.5, 117.7, 120.3, 125.6, 132.1, 144.2, 147.3, 159.7, 164.8, 176.4, 189.5 ppm.

Methyl 6′-amino-5′-cyano-1,2-dihydro-1,2′-dimethyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′-carboxylate
(**8f**, $C_{17}H_{16}N_4O_3$)
White powder (77%); m.p.: 273 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,335, 3,234, 2,221, 1,715, 1,660 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.21 (3H, s, CH_3), 3.31 (3H, s, CH_3), 3.73 (3H, s, CH_3), 7.12–743 (4H, m, H–Ar), 7.71 (2H, bs, NH_2), 11.57 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.1, 36.6, 49.7, 51.4, 53.1, 89.8, 115.1, 116.5, 121.3, 125.6, 132.4, 144.0, 147.9, 158.5, 163.9, 176.7, 188.9 ppm.

Methyl 6′-amino-6-bromo-5′-cyano-1,2-dihydro-2′-methyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-5′-carboxylate
(**8g**, $C_{16}H_{13}BrN_4O_3$)
Cream powder (79%); m.p.: 297 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,330, 3,216, 3,128, 2,222, 1,716, 1,673 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.23 (3H, s, CH_3), 3.77 (3H, s, CH_3), 7.13–7.38 (3H, m, H–Ar), 7.56 (2H, bs,

NH_2), 11.61 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.3, 49.7, 51.6, 53.3, 90.1, 114.5, 116.8, 121.4, 125.9, 133.3, 145.1, 146.3, 159.6, 165.1, 176.8, 188.9 ppm.

1,2-Dihydro-2′,6′-dimethyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile (**9a**, $C_{16}H_{12}N_4O$)
Cream powder (80%); m.p.: 278 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,265, 3,198, 3,028, 2,186, 1,676 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.08 (6H, s, $2CH_3$), 6.85–7.27 (4H, m, H–Ar), 9.94 (1H, bs, NH), 10.64 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.3, 51.6, 81.6, 110.4, 117.8, 123.3, 125.9, 130.3, 134.3, 141.0, 148.8, 177.7 ppm.

1,2-Dihydro-1,2′,6′-trimethyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile (**9b**, $C_{17}H_{14}N_4O$)
White powder (78%); m.p.: 264 °C (dec.); IR (KBr): $\overline{\nu}$ = 3,205, 3,011, 2,194, 1,671 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.08 (6H, s, $2CH_3$), 3.68 (3H, s, CH_3), 7.05–7.31 (4H, m, H–Ar), 9.96 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.0, 35.2, 51.4, 81.2, 109.8, 117.3, 122.9, 125.0, 131.3, 132.7, 141.6, 148.1, 176.1 ppm.

1-Ethyl-1,2-dihydro-2′,6′-dimethyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile (**9c**, $C_{18}H_{16}N_4O$)
White powder (73%); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,210, 3,021, 2,199, 1,665 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.13 (3H, t, $^3J_{HH}$ = 6.1 Hz, CH_3), 2.09 (6H, s, $2CH_3$), 3.73 (2H, q, $^3J_{HH}$ = 6.1 Hz, CH_2), 7.12–7.41 (4H, m, H–Ar), 9.99 (1H, bs, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.7, 18.3, 34.9, 51.1, 81.4, 109.4, 117.6, 123.8, 125.8, 130.5, 133.8, 141.3, 148.9, 175.7 ppm.

6-Bromo-1,2-dihydro-2′,6′-dimethyl-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile
(**9d**, $C_{16}H_{11}BrN_4O$)
Cream powder (82%); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,273, 3,187, 3,018, 2,181, 1,666 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.09 (6H, s, $2CH_3$), 6.87–7.32 (3H, m, H–Ar), 9.98 (1H, s, NH), 10.78 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.1, 51.9, 81.5, 110.1, 116.9, 121.0, 126.8, 134.7, 144.1, 146.9, 149.7, 177.0 ppm.

1,2-Dihydro-2′,6′-dimethyl-6-nitro-2-oxospiro[3H-indole-3,4′(1′H)-pyridine]-3′,5′-dicarbonitrile
(**9e**, $C_{16}H_{11}N_5O_3$)
Yellow powder (84%); m.p.: >300 °C; IR (KBr): $\overline{\nu}$ = 3,311, 3,210, 3,017, 2,195, 1,671 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.11 (6H, s, $2CH_3$), 7.12 (1H, d, $^3J_{HH}$ = 9.3 Hz, H–Ar), 8.25–8.28 (2H, m, H–Ar), 10.13 (1H, s, NH), 11.42 (1H, s, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.5, 52.0, 80.2, 110.9, 117.6, 121.8, 127.7, 134.8, 143.6, 147.3, 149.8, 178.2 ppm.

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