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Synthesis of spiroimidazopyridineoxindole, spiropyridopyrimidineoxindole and spiropyridodiazepineoxindole derivatives based on heterocyclic ketene aminals *via* a four-component reaction†

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Here, we have described the synthesis of novel spiropyridineoxindole derivatives containing a pyridone ring *via* a four-component reaction between various diamines, 1,1-bis(methylthio)-2-nitroethylene, isatin derivatives and Meldrum's acid in the presence of *p*-toluenesulfonic acid. This protocol has some advantages such as the availability of starting materials, good yields, facile separation of products, the use of ethanol as an environmentally benign solvent and easy formation of three new bonds in one operation.

Introduction

The indole moiety is the most well-known heterocycle and a common and important feature of a variety of natural products and medicinal agents.[1] Furthermore, it has been reported that the addition of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[2]

Spirooxindoles are a key structural element in a wide range of natural products with biological activities.[3] They have attracted significant attention due to their useful pharmacological properties and biological activities including antimicrobial,[4] anti-tumor,[5] anti-tubercular,[6] anti-inflammatory,[7] anti-HIV,[8] anti-fungal,[9] the action as inhibitors of the human NK-1 receptor,[10] anti-cancer,[11] antibiotic,[12] and anti-malarial.[13]

Spirocyclic oxindoles containing a six-membered moiety, especially a six-membered piperidine structure at the C-3 position, have a wide spectrum of biological activities; examples include the non-peptidyl growth hormone secretagogue MK-0677 (ref. 14) and potent non-peptide MDM2 inhibitors,[15] which may have utility as anticancer agents (Fig. 1).

During the last years, there has been considerable interest in the synthesis of spirooxindoles fused in the 3-position from three-membered to seven-membered spiro-rings[16] and other fused heterocyclic compounds, which have multi-ring structures similar to spirooxindole dihydropyridines and spirooxindolepyrans.[17]

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In general, the synthesis of spirooxindole frameworks containing six-membered nitrogen rings has more limitations than that of five-membered heterocyclic moieties. In the last decade, synthetic methods for the generation of spiropyridineoxindoles *via* multicomponent reactions have been abundantly developed.[18] Previous approaches for producing these structures relied on utilizing isatin, various C–H acids and a wide variety of different enamines as starting materials. Among these strategies, similar cases in which ketene aminals have been used as enamines are reported here (Fig. 2).

In 2015, a green approach to the synthesis of the spirooxindole derivative **A** was described in water in the presence of
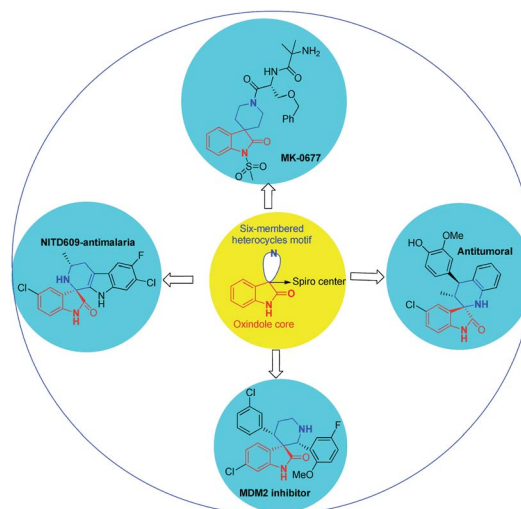

Fig. 1 Bioactive and medicinally important compounds containing a spiropyridineoxindole skeleton.

a catalytic amount of NaCl by using ethylcyanoacetate and heterocyclic ketene aminals.[19] In 2014, another reaction was reported using benzoylacetonitrile and 2-(nitromethylene)imidazoline in ethanol and trimethylamine, which led to the corresponding product **B**.[20]

In 2013, a method was developed using a mixture of ethyl trifluoroacetate, HKA and different isatins in the presence of piperidine in ethanol to give product **C**.[21] In 2019, the four-component reaction of various amines and nitroketene dithioacetal with isatin and barbituric acid derivatives in water afforded spirooxindole **D**.[22]

As a part of our program on the study of developing new multi-component reactions for the synthesis of heterocyclic compounds, we report the efficient synthesis of novel spiroimidazopyridineoxindole, spiropyridopyrimidineoxindole and spiropyridodiazepineoxindole structures *via* a one-pot, four-component reaction of nitro ketene aminals derived from the addition of various 1,*n*-diamines to 1,1-bis(methylthio)-2-nitroethylene, isatin and its derivatives and Meldrum's acid in the presence of *p*-TSA. To the best of our knowledge, these structures have not been synthesized so far and there are no reports on the preparation of spirooxindoles from Meldrum's acid.

Results and discussion

We prepared the spiropyridineoxindole derivative **5** *via* one-pot four-component condensation of diamine **1**, 1,1-bis(methylthio)-2-nitroethylene **2**, isatin **3** and Meldrum's acid **4** in the presence of *p*-TSA catalyst in ethanol under reflux conditions (Scheme 1). The reaction was completed after 0.15–6 h to afford the corresponding heterocyclic systems **5a–j** in moderate to good yields (69–87%).

For our initial investigation, the reaction of diamine **1a** (1 mmol), dithioacetal **2** (1 mmol), isatin **3a** (1 mmol) and Meldrum's acid **4** (20% mmol) was considered as the model reaction. The effects of various catalysts, solvents and temperatures were monitored (Table 1). These results indicated that the best reaction conditions for the synthesis of spirooxindole **5a** were obtained in ethanol as the solvent and by using *p*-TSA as the
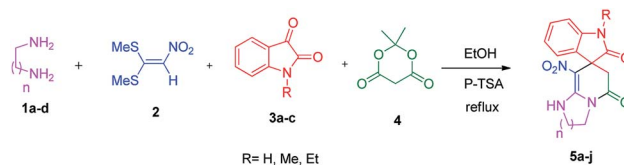
Scheme 1 Synthetic scheme for the generation of products 5a–j.

catalyst at reflux conditions. This procedure provided the highest yield of 87% and the shortest reaction time (Table 1, entry 7).

We explored the scope of this reaction by varying the structures of diamine **1a–d** and isatin **3a–c** components. The reaction proceeded to afford a series of spiropyridineoxindole derivatives **5a–j** in 66–87% yields. The results are summarized in Table 2. This reaction was performed with other derivatives of isatin (*N*-benzyl and *N*-butyl isatin) under the same conditions but did not result in the product. Additionally, the reaction of *N*-ethyl isatin with 1,2-diaminopropane and 1,3-diaminopropane did not produce a product. Also, when 1,2-diaminocyclohexane was used for the synthesis of ketene aminal, no reaction occurred. We also tried using 1,2-diaminophenyl and aromatic amines in the reaction conditions. All the reactions were very slow and did not result in the desired products. The structures of compounds **5a–j** were deduced from their mass, IR, ^1H NMR, and ^{13}C NMR spectroscopic data (ESI†).

The ^1H and ^{13}C NMR spectra of the crude products clearly indicate the formation of the suggested products **5a–j**. As a representative case, the key signals of the ^1H and ^{13}C NMR chemical shifts for 8-nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3′-indoline]-2′,5(6*H*)-dione **5a** are shown in the ESI.†

The ^1H NMR spectrum of **5a** shows the two NH groups (δ 9.57, 10.55 ppm) that are exchangeable with D_2O. The two protons of methylene appear at δ 2.36 and 3.04 ppm as two doublets. Four protons of the aromatic ring can be observed at δ 6.81–7.20 ppm as four doublets. The ^1H-decoupled ^{13}C NMR spectrum of **5a** indicates 14 distinct resonances in accordance with the desired structure. The characteristic signal of the carbon of the CH_2 group is seen at δ 41.8 ppm. The carbon of the spiro center appears at δ 49.5 ppm. The two signals at δ 105.6 and 153.6 ppm are related to C–NO_2 and C=C–NH, respectively. The two carbonyl groups appear at δ 165.6 and 177.6 ppm.

The mass spectrum of **5a** displays a molecular-ion peak at *m*/*z* 300, which is in agreement with the proposed structure. The IR spectrum of **5a** shows broad absorption bands due to NH at 3327^{-1}, stretching vibrations of the CH_2 groups at 2920^{-1}, strong absorption bands of carbonyl groups at 1725^{-1} and 1683^{-1} and absorption bands at 1480^{-1} and 1369 cm^{-1} related to NO_2.

A plausible mechanism for the formation of spiropyridineoxindole **5** is depicted in Scheme 2. On the basis of the well-established chemistry of 1,1-bis(methylthio)-2-nitroethylene, initially, the addition of diamine **1** to 1,1-bis(methylthio)-2-nitroethylene **2** leads to the formation of ketene aminal **6**. The second step involves the condensation of isatin **3** with Meldrum's acid **4** in the presence of *p*-
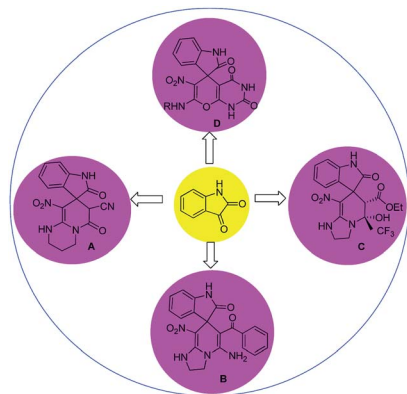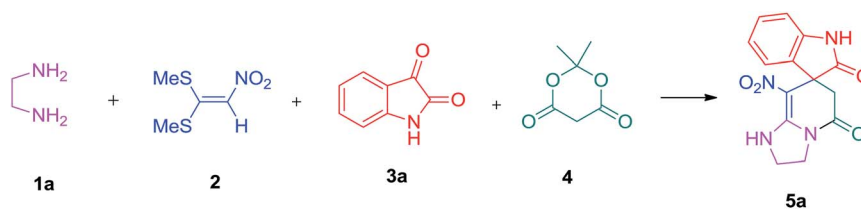

Fig. 2 Summary of previous works of spiropyridineoxindole synthesis.

Table 1 Optimization of reaction conditions for the synthesis of **5a**[a]

Entry	Solvent	Catalyst (mol%)	Time (h)	Temp. (°C)	Yield[b] (%)
1	EtOH	NEt$_3$	1	80	75
2	EtOH	Piperidine	24	80	None
3	EtOH	—	5	r.t	60
4	H$_2$O/EtOH (1 : 1, v/v)	—	6	80	65
5	H$_2$O/EtOH (3 : 1, v/v)	—	7	80	40
6	EtOH	*p*-TSA	24	r.t	Trace
7	**EtOH**	***p*-TSA**	**0.15**	**80**	**87**

[a] The reaction was performed using **1a**, **2**, **3a**, **4** (1 mmol), catalyst (0.2 mmol), and solvent (10 mL). [b] Isolated yield based on **5a**.

toluenesulfonic acid to afford the Knoevenagel product **7**. Then, the Michael addition of the ketene aminal **6** to adduct **7** affords the intermediate **8**; it undergoes subsequent imine–enamine tautomerization, followed by intramolecular cyclization *via* the nucleophilic addition of –NH to the carbonyl group. Subsequently, one equivalent of CO$_2$ and acetone are removed from intermediate **9** to give the corresponding product **5** (Scheme 2).

Experimental

Materials

Meldrum's acid, 1,1-bis(methylthio)-2-nitro ethylene, diamines, various isatin derivatives, *p*-toluenesulfonic acid and solvents were purchased from Sigma-Aldrich and used as received without further purification. Melting points (mp) were determined with an electrothermal 9100 apparatus. Infrared (IR) spectra were recorded on a Bruker Tensor 27 spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker DRX-300 Avance instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) with CDCl$_3$ and DMSO as solvents. Chemical shifts were expressed in parts per million (ppm) relative to internal TMS, and the coupling constant (*J*) was reported in hertz (Hz). All of the compounds were analyzed for mass data using Agilent 5975C VL MSD with a Triple-Axis Detector operating at an ionization potential of 70 eV.

General procedure for the synthesis of 8-nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3′-indoline]-2′,5(6*H*)-dione (5a)

A mixture of ethylene diamine (66 mL, 1 mmol), 1,1-bis(methylthio)-2-nitroethylene (0.165 g, 1 mmol) and 10 mL EtOH in a 50 mL flask was refluxed for 6 h. After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane, 1 : 1), isatin (0.147 g, 1 mmol), Meldrum's acid (0.144 g, 1 mmol) and *p*-toluenesulfonic acid (0.03 g, 0.2 mmol) were added to the reaction mixture, and it was stirred under reflux for 0.15 h. The progress of the reaction was monitored by TLC using ethyl

acetate–*n*-hexane (1 : 1) as an eluent. After reaction completion, the precipitated product was collected by filtration and washed with EtOH to give the pure product **5a** in 87% yield.

8-Nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3′-indoline]-2′,5(6*H*)-dione (5a). Light gray powder; yield: 0.26 g, (87%); mp: 310–312 °C; IR (KBr) ($\bar{v}_{max}$/cm^{-1}): 3327 (NH), 2920 (CH$_2$), 1725, 1683 (2C=O), 1632 (C=C), 1480 and 1369 (NO$_2$), 1277 (C–N); ^{1}H NMR (300 MHz, DMSO): δ = 2.36 (1H, d, $^2J_{HH}$ = 16 Hz, CH$_2$CO), 3.03 (1H, d, $^2J_{HH}$ = 16 Hz, CH$_2$CO), 3.78–3.83 (2H, m, CH$_2$NH), 3.90–4.06 (2H, m, CH$_2$N), 6.82 (1H, d, $^3J_{HH}$ = 7.8 Hz, ArH), 6.88 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.11–7.20 (2H, m, ArH), 9.57 (1H, br, NHCH$_2$), 10.55 (1H, s, NH–C=O); ^{13}C NMR (75 MHz, DMSO-d_6); δ = 41.8 (CH$_2$CO), 43.2 (CH$_2$NH), 44.3 (CH$_2$N), 49.5 (C$_{spiro}$), 105.6 (C–NO$_2$), 110.1, 121.9, 122.7, 129.0 (4CH of Ar), 131.9, 142.1 (C–Ar), 153.6 (C=C–NO$_2$), 165.6 (NH–C=O), 177.6 (CH$_2$–C=O); MS (EI, 70 eV): *m/z* (%) = 300 (56) [M]$^+$, 254 (69), 239 (100), 225 (24), 198 (27), 155 (14), 69 (3), 44 (20). Anal. calcd for C$_{14}$H$_{12}$N$_4$O$_4$ (300.27): C, 56; H, 4.03; N, 18.66. Found C, 56.3; H, 4.2; N, 18.50.

1′-Methyl-8-nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3′-indoline]-2′,5(6*H*)-dione (5b). White powder; yield: 0.27 g, (85%) mp: 328–330 °C; IR (KBr) ($\bar{v}_{max}$/cm^{-1}): 3334 (NH), 2886 (CH$_3$), 1711, 1636 (2C=O), 1488 and 1326 (NO$_2$), 1157 (C–N); ^{1}H NMR (300 MHz, DMSO): δ = 2.17 (1H, d, $^2J_{HH}$ = 20 Hz, CH$_2$CO), 3.04 (1H, d, $^2J_{HH}$ = 20 Hz, CH$_2$CO), 3.21 (3H, s, CH$_3$), 3.67–3.78 (2H, m, CH$_2$NH), 3.90–4.07 (2H, m, CH$_2$N), 6.82–6.98 (2H, m, ArH), 7.11–7.30 (2H, m, ArH), 9.8 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6); δ = 26.9 (N–CH$_3$), 41.5 (CH$_2$CO), 43.3 (CH$_2$NH), 44.3 (CH$_2$N), 49.1 (C$_{spiro}$), 105.5 (C–NO$_2$), 109.0, 122.4, 122.6, 129.1 (4CH of Ar), 131.1, 143.6 (C–Ar), 153.6 (C=C–NO$_2$), 165.5 (NMe–C=O), 175.9 (CH$_2$–C=O); MS (EI, 70 eV): *m/z* (%) = 314 (82) [M]$^+$, 269 (12.5), 253 (100), 225 (17), 169 (12), 130 (13), 44 (14). Anal. calcd for C$_{15}$H$_{14}$N$_4$O$_4$ (314.30): C, 57.32; H, 4.4; N, 17.83. Found C, 57.6; H, 4.1; N, 18.60.

1′-Ethyl-8-nitro-2,3-dihydro-1*H*-spiro[imidazo[1,2-*a*]pyridine-7,3′-indoline]-2′,5(6*H*)-dione (5c). White powder; yield: 0.23 g,
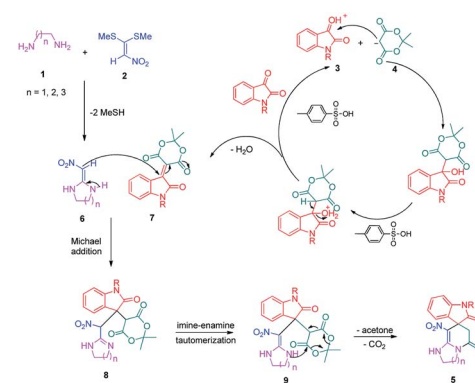
Table 2   Compounds **5a–j**[a]

Entry	Diamine		R	Product		Time (h)	Yield[b] (%)
1		**1a**	H	**5a**		0.15	87
2		**1a**	Me	**5b**		2	85
3		**1a**	Et	**5c**		0.5	70
4		**1b**	Me	**5d**		3	73
5		**1b**	H	**5e**		3	83
6		**1c**	Me	**5f**		5	75
7		**1c**	Et	**5g**		6	69
8		**1c**	H	**5h**		5	72

Table 2   (Contd.)

Entry	Diamine		R	Product		Time (h)	Yield[b] (%)
9		**1d**	H	**5i**		4	80
10		**1d**	Me	**5j**		3	76

[a] The reaction conditions include **1**, **2**, **3**, **4** (1 mmol), catalyst (0.2 mmol), and ethanol (10 mL). [b] Yields refer to the isolated pure products.

Scheme 2   Proposed mechanism for the formation of the product **5a**.

(70%); mp: 321–323 °C; IR (KBr) ($\bar{v}_{max}$/cm^{-1}): 3335 (NH), 2925, 2856 (C–H), 1711, 1636 (2C=O), 1487 and 1369 (NO$_2$), 1158 (C–N); ^{1}H NMR (300 MHz, DMSO): δ = 1.11 (3H, t, $^3J_{HH}$ = 6.9 Hz, CH$_3$), 2.30 (1H, d, $^2J_{HH}$ = 15.9 Hz, CH$_2$CO), 3.05 (1H, d, $^2J_{HH}$ = 15.9 Hz, CH$_2$CO), 3.62–3.71 (2H, m, CH$_2$NH), 3.77 (2H, q, $^3J_{HH}$ = 6.9 Hz, CH$_3$–CH$_2$–N), 3.83–4.07 (2H, m, CH$_2$N), 6.83 (1H, t, J_{HH} = 7.8 Hz, ArH), 6.93 (1H, d, J_{HH} = 7.5 Hz, ArH), 7.19 (1H, d, J_{HH} = 7.8 Hz, ArH), 7.27 (1H, t, J_{HH} = 7.5 Hz, ArH), 9.75 (1H, br, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.4 (CH$_3$), 34.8 (CH$_3$–CH$_2$N), 41.5 (CH$_2$C=O), 43.2 (CH$_2$NH), 44.3 (CH$_2$N), 49.0 (C$_{spiro}$), 105.53 (C–NO$_2$), 109.1, 122.4, 122.7, 129.1 (4CH of Ar), 131.2, 142.5 (C–Ar), 153.5 (C=C–NO$_2$), 165.5 (N–C=O), 175.5 (CH$_2$–C=O); MS (EI, 70 eV): m/z (%) = 328 (100) [M]$^+$, 282 (38), 267 (72), 239 (98), 224 (22), 197 (20), 158 (15), 44 (21). Anal. calcd for C$_{16}$H$_{16}$N$_4$O$_4$ (328.32): C, 50.53; H, 4.91; N, 17.06. Found C, 50.1; H, 4.6; N, 17.30.

1-Methyl-9′-nitro-1′,2′,3′,4′-tetrahydrospiro[indoline-3,8′-pyrido[1,2-a]pyrimidine]-2,6′(7′H)-dione (5d). White powder; yield:

0.24 g, (73%); mp: 318–320 °C; IR (KBr) ($\bar{\upsilon}_{max}/cm^{-1}$): 3412 (NH), 3032 (C–H of Ar), 2921 (CH$_3$), 1716, 1619 (2C=O), 1496 and 1323 (NO$_2$), 1151 (C–N); ^{1}H NMR (300 MHz, DMSO): δ = 1.95–2.09 (2H, m, CH$_2$), 2.34 (1H, d, $^2J_{HH}$ = 15.3 Hz, CH$_2$CO), 3.13 (1H, d, $^2J_{HH}$ = 15.3 Hz, CH$_2$CO), 3.14 (3H, s, N–Me), 3.52–3.59 (2H, m, CH$_2$NH), 3.72–3.78 (1H, m, CH$_2$N), 3.88–3.95 (1H, m, CH$_2$N), 6.94 (1H, t, J_{HH} = 7.2 Hz, ArH), 7.01 (1H, d, J_{HH} = 7.8 Hz, ArH), 7.09 (1H, d, J_{HH} = 7.2 Hz, ArH), 7.28 (1H, t, J_{HH} = 7.8 Hz, ArH), 11.50 (1H, s, NH); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.0 (CH$_2$), 26.9 (N–CH$_3$), 39.2 (CH$_2$–C=O), 39.5 (CH$_2$NH), 40.3 (CH$_2$N), 48.0 (C$_{spiro}$), 107.8 (C–NO$_2$), 108.6, 121.8, 122.6, 129.1 (4CH of Ar), 129.3, 143.4 (C–Ar), 152.7 (C=C–NO$_2$), 166.4 (NMe–C=O), 175.9 (CH$_2$–C=O). Anal. calcd for C$_{16}$H$_{16}$N$_4$O$_4$ (328.33): C, 58.53; H, 4.91; N, 17.06. Found C, 58.9; H, 4.5; N, 17.20.

9′-Nitro-1′,2′,3′,4′-tetrahydrospiro[indoline-3,8′-pyrido[1,2-a]pyrimidine]-2,6′(7′H)-dione (5e). White powder; yield: 0.26 g, (82%); mp 327–329 °C; ^{1}H NMR (300 MHz, DMSO): δ = 1.90–2.05 (2H, m, CH$_2$), 2.61 (1H, d, $^2J_{HH}$ = 16.5 Hz, CH$_2$CO), 3.29 (1H, d, $^2J_{HH}$ = 16.5 Hz, CH$_2$CO), 3.38–3.52 (4H, m, CH$_2$N), 6.85–6.90 (3H, m, ArH), 7.15–7.21 (1H, m, ArH), 9.35 (1H, br, NH), 10.18 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.8 (CH$_2$), 34.7 (CH$_2$CO), 37.7 (CH$_2$NH), 39.9 (CH$_2$N), 49.8 (C$_{spiro}$), 106.1 (C–NO$_2$), 116.5, 120.2, 122.6, 126.1 (4CH of Ar), 129.3, 139.5 (C–Ar), 153.0 (C=C–NO$_2$), 167.7 (N–C=O), 174.1 (CH$_2$–C=O); MS (EI, 70 eV): m/z (%) = 314 (46) [M]$^+$, 268 (100), 57 (41), 236 (31), 83 (30), 185 (20), 155 (19), 211 (14). Anal. calcd for C$_{15}$H$_{14}$N$_4$O$_4$ (314.30): C, 57.32; H, 4.49; N, 17.83. Found C, 57.5; H, 4.1; N, 17.50.

1-Methyl-10′-nitro-2′,3′,4′,5′-tetrahydro-1′H-spiro[indoline-3,9′-pyrido[1,2-a][1,3]diazepine]-2,7′(8′H)-dione (5f). Light pink powder; yield: 0.25 g, (75%); mp: 300–302 °C; ^{1}H NMR (300 MHz, DMSO): δ = 1.78–2.10 (4H, m, 2CH$_2$), 2.31 (1H, d, $^2J_{HH}$ = 15.3 Hz, CH$_2$CO), 3.13 (3H, s, N–CH$_3$), 3.31 (1H, d, $^2J_{HH}$ = 15.3 Hz, CH$_2$CO), 3.64–3.84 (3H, m, 2CH$_2$–N), 4.41–4.50 (1H, m, CH$_2$N), 6.88–7.03 (3H, m, ArH), 7.26–7.31 (1H, m, ArH), 11.32 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 24.2, 24.5 (2CH$_2$), 27.0 (N–CH$_3$), 41.4 (CH$_2$CO), 45.1 (CH$_2$NH), 45.7 (CH$_2$N), 48.0 (C$_{spiro}$), 109.2 (C–NO$_2$), 111.3, 122.4, 122.6 (4CH of Ar), 129.3, 143.7 (C–Ar), 158.5 (C=C–NO$_2$), 167.8 (N–C=O), 175.5 (CH$_2$–C=O). Anal. calcd for C$_{15}$H$_{14}$N$_4$O$_4$ (324.35): C, 59.64; H, 5.30; N, 16.37. Found C, 59.4; H, 5.6; N, 16.10.

1-Ethyl-10′-nitro-2′,3′,4′,5′-tetrahydro-1′H-spiro[indoline-3,9′-pyrido[1,2-a][1,3]diazepine]-2,7′(8′H)-dione (5g). Light pink powder; yield: 0.25 g, (69%); mp: 302–304 °C; ^{1}H NMR (300 MHz, DMSO): δ = 1.13 (3H, t, J_{HH} = 6.9, N–CH$_2$–CH$_3$), 1.79–1.83 (3H, m, CH$_2$), 2.03–2.19 (1H, m, CH$_2$), 2.26 (1H, d, $^2J_{HH}$ = 15.3 Hz, CH$_2$CO), 3.32 (2H, m, N–CH$_2$–CH$_3$), 3.62–3.77 (4H, m, CH$_2$N), 4.41–4.50 (1H, m, CH$_2$N), 6.88–6.96 (2H, m, ArH), 7.06 (1H, d, J_{HH} = 7.8 Hz, ArH), 7.28 (1H, t, J_{HH} = 7.5 Hz, ArH), 11.32 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.1 (N–CH$_2$–CH$_3$), 24.2, 24.6 (2CH$_2$), 34.8 (N–CH$_2$–CH$_3$), 41.4 (CH$_2$CO), 45.1 (CH$_2$NH), 45.7 (CH$_2$N), 47.9 (C$_{spiro}$), 109.1 (C–NO$_2$), 111.3, 122.4, 122.6, 129.3, (4CH of Ar), 129.5, 142.6 (C–Ar), 158.5 (C=C–NO$_2$), 167.8 (N–C=O), 175.1 (CH$_2$–C=O). Anal. calcd for C$_{18}$H$_{20}$N$_4$O$_4$ (356.38): C, 60.66; H, 5.66; N, 15.7. Found C, 60.9; H, 5.3; N, 15.50.

The integrals in the ^{1}H NMR spectrum of **5h** and the particular carbon signals in the ^{13}C NMR spectrum represent two structures that cannot be separated. The spectral information is given for one structure (**A**):

10′-nitro-2′,3′,4′,5′-tetrahydro-1′H-spiro[indoline-3,9′-pyrido[1,2-a][1,3]diazepine]-2,7′(8′H)-dione (5h). Pink powder; yield: 0.24 g, (72%); mp: 315–317 °C; ^{1}H NMR (300 MHz, DMSO): δ = 1.00–1.05, 1.85–1.94 (4H, m, 2CH$_2$), 2.33 (1H, d, $^2J_{HH}$ = 16.2 Hz, CH$_2$CO), 3.27–3.32 (2H, m, 2CH$_2$NH), 3.44 (1H, d, $^2J_{HH}$ = 16.2 Hz, CH$_2$CO), 3.76–3.84 (2H, m, CH$_2$N), 6.79–7.20 (4H, m, ArH), 9.99 (1H, s, NH), 10.20 (1H, br, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.8, 26.8 (2CH$_2$), 35.7 (CH$_2$NH), 36.6 (CH$_2$N), 42.2 (CH$_2$CO), 49.9 (C$_{spiro}$), 107.2 (C–NO$_2$), 116.1, 120.1, 122.6, 125.6 (4CH of Ar), 128.3, 139.4 (C–Ar), 158.1 (C=C–NO$_2$), 167.6 (N–C=O), 175.0 (CH$_2$–C=O).

The presence of two chiral centers in **5i** and **5j** compounds led to four isomers: (3R,3′S), (3S,3′S) and their enantiomers. The ^{1}H NMR and ^{13}C NMR spectra also confirmed the existence of two types of diastereoisomers.

3-Methyl-8-nitro-2,3-dihydro-1H-spiro[imidazo[1,2-a]pyridine-7,3′-indoline]-2′,5(6H)-dione (5i). White powder; yield: 0.25 g, (80%); mp: 301–303 °C; ^{1}H NMR (300 MHz, DMSO): δ = 1.31–1.50 (3H, m, CH$_3$), 2.32–2.48 (2H, m, CH$_2$CO), 2.91–3.68 (2H, m, CH$_2$NH), 3.95–4.61 (1H, m, CHMe), 6.81–6.89 (2H, m, ArH), 7.04–9.91 (2H, m, ArH), 9.91 (1H, br, NH), 10.51 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.4 (NH–C–CH$_3$), 41.8 (CH$_2$CO), 49.3 (C$_{spiro}$), 49.8 (CH$_2$NH), 52.3 (CHMe), 105.3 (C–NO$_2$), 110.0, 121.9, 122.6, 128.8 (4CH of Ar), 131.9, 142.1 (C–Ar), 152.9 (C=C–NO$_2$), 165.6 (N–C=O), 177.6 (CH$_2$–C=O); MS (EI, 70 eV): m/z (%) = 314 (82) [M]$^+$, 314 (59), 269 (25), 253 (100), 240 (30), 212 (33), 155 (24), 41 (25). Anal. calcd for C$_{15}$H$_{14}$N$_4$O$_4$ (314.1): C, 57.32; H, 4.49; N, 17.83.

1′,3-Dimethyl-8-nitro-2,3-dihydro-1H-spiro[imidazo[1,2-a]pyridine-7,3′-indoline]-2′,5(6H)-dione (5j). White powder; yield: 0.25 g, (76%); mp: 278–280 °C; ^{1}H NMR (300 MHz, DMSO): δ = 1.34–1.40 (3H, m, CH$_3$), 2.30–2.39 (1H, m, CH$_2$CO), 3.01–3.11 (1H, m, CH$_2$CO), 3.16 (3H, s, N–CH$_3$), 3.40–3.63 (2H, m, CH$_2$NH), 3.90–4.35 (1H, m, CHMe), 6.93–7.03 (2H, m, ArH), 7.17 (1H, t, $^3J_{HH}$ = 6.9 Hz, ArH), 7.29 (1H, t, $^3J_{HH}$ = 7.8 Hz, ArH), 9.82 (1H, br, NH), 9.95 (1H, br, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.1 (C–CH$_3$), 26.9 (N–CH$_3$), 41.6 (CH$_2$CO), 49.2 (C$_{spiro}$), 49.9 (CH$_2$NH), 52.3 (CHMe), 105.2 (C–NO$_2$), 109.05, 122.4, 122.6, 129.1 (4CH of Ar), 131.0, 143.6 (C–Ar), 152.8 (C=C–NO$_2$), 165.7 (N–C=O), 175.9 (CH$_2$–C=O). Anal. calcd for C$_{16}$H$_{16}$N$_4$O$_4$ (328.32): C, 58.53; H, 4.91; N, 17.06. Found C, 58.2; H, 4.6; N, 17.30.

Conclusion

We designed a novel and convenient procedure for the synthesis of three new classes of spiropyridineoxindoles with fused heterocyclic compounds (imidazole, pyrimidine and diazepine) in good yields *via* a four-component reaction among 1,1-bis(methylthio)-2-nitroethylene, various aliphatic diamines, Meldrum's acid and isatin derivatives using a catalytic amount of *p*-TSA. The present process has several important features including mild and facile reaction conditions, easy accessibility of reactants, a simple workup procedure, the use of ethanol as a solvent, short reaction times, and good-to-high yields. These

structures having both indole and fused-pyridine moieties, which are some of the most typical privileged scaffolds, are completely new and there is no other report on their synthesis.

Conflicts of interest

The authors declare no competing financial interest.

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