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An environmentally benign approach for the synthesis of 3,3′-pyrrolidonyl spirooxindole derivatives *via* a cascade Knoevenagel–Michael–cyclization multicomponent reaction†

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A series of 3,3′-pyrrolidonyl spirooxindole derivatives have been synthesized in good yields from the cascade Knoevenagel–Michael–cyclization multicomponent reaction of isatin, malononitrile and α-isothiocyanato imide in the presence of a catalytic amount of triethylamine ''on water'' assisted with ultrasonic irradiation. The advantages of this method include high efficiency, mild reaction conditions and environmentally benign reagents. The current process provides a simple and green method for creating diversity-oriented syntheses of this intriguing class of compounds with potential biological activities.

Introduction

3,3′-Pyrrolidonyl spirooxindoles are structural motifs frequently formed in numerous natural products and significant biologically active compounds.[1] Many 3,3′-pyrrolidonyl spirooxindoles, such as coerulescine,[2] horsfiline,[3] elacomine,[4] and rychnophylline[1b] show interesting biological activities (Fig. 1). Consequently, approaches towards the efficient synthesis of these molecules have received considerable attention.[5] Many of the known strategies have resulted in a different class of spirocycle oxindole fused pyrrolidines that are showing promise as biologically active compounds.[6] In this context, searching for creative procedures that could achieve high reactivity for the construction of structurally diverse spirocycle oxindoles is still challenging.

The growing importance of green chemistry has highlighted the search for transformations that are capable of promoting two or more distinct transformations sequentially in one pot with eco-friendly conditions or under aqueous conditions.[7] In this respect, one of the most promising approaches is to perform organic reactions in aqueous media under mild conditions.

α-Isothiocyanato derivatives are highly attractive nucleophilic reagents for a number of cascade reactions and multicomponent reactions.[8] Their α-protons are readily removed by bases to generate nucleophilic anions. The resulting reaction intermediates are subsequently trapped by the appropriate electron-deficient olefins to provide cyclic products. In continuation of our work on the multi-component synthesis of heterocyclic compounds,[9] we designed a unique synthetic route to privileged heterocyclic scaffolds of medicinal relevance that combine the synthetic efficiency of multi-component protocols with the environmental benefit of using water as a reaction medium. This reaction was achieved by reacting isatin **1**, malononitrile **2** and α-isothiocyanato imide **3** as starting materials ''on water'' assisted with ultrasonic irradiation.

Results and discussion

We initiated our studies by evaluating the reaction between *N*-methyl substituted isatin **1a**, malononitrile **2**, and α-isothiocyanato imide **3** using Et_3N as the catalyst in toluene at room temperature (Table 1). We found that the reaction proceeded smoothly and afforded the desired product in high yield (Table 1, entry 1). Further seeking insight into the origin of the rate of acceleration in this reaction, the results show that polar protic solvents accelerate the reaction. The observed reaction rates are in the following order: isopropyl alcohol ≈ THF > CH_2Cl_2 > diethyl ether > toluene (Table 1, entries 2–5).

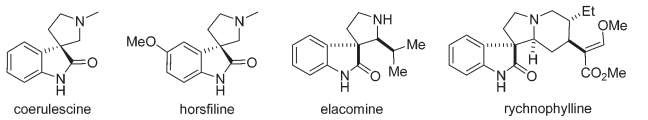

Fig. 1 Representative examples of bioactive 3,3′-pyrrolidinyl-spirooxindoles.

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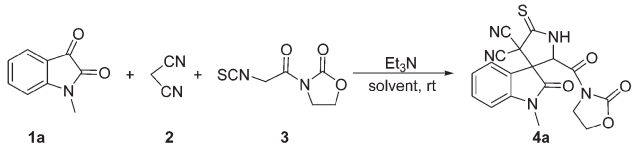
Table 1 Screening of reaction conditions[a]

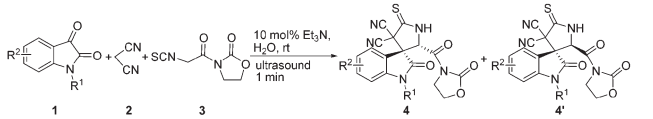


1a 2 3 4a

Entry	Solvent	Volume (mL)	TEA (mol%)	Time (h)	Yield (%)[b]
1	$PhCH_3$	3	15	9.0	95
2	Et_2O	3	15	8.5	98
3	CH_2Cl_2	3	15	5.5	98
4	THF	3	15	0.8	98
5	$(CH_3)_2CHOH$	3	15	0.8	98
6	$(CH_3)_2CHOH$–H_2O	3[c]	15	0.8	98
7	$(CH_3)_2CHOH$–H_2O	3[d]	15	0.8	98
8	H_2O	5	15	24	98
9	H_2O[e]	5	15	1.0	98
10	H_2O[e]	5	30	1.0	98
11	H_2O[e]	5	50	0.6	98
12	H_2O[e]	5	100	0.3	98
13	H_2O[e]	5	10	1.1	98
14	H_2O[e]	5	5	1.5	98

[a] Reaction conditions: A solution of **1a** (0.3 mmol), TEA, and malononitrile **2** (0.3 mmol) in the right amount of solvent was stirred at room temperature. After the reaction was completed (monitored by TLC), α-isothiocyanato imide **3** (0.33 mmol) was added and the mixture was further stirred at room temperature. [b] After purification by column chromatography. [c] $V_{(CH_3)_2CHOH}/V_{H_2O}$ = 1 : 1. [d] $V_{(CH_3)_2CHOH}/V_{H_2O}$ = 1 : 2. [e] Sonication irradiation 1 min.

Table 2 Substrate scope of the cascade Knoevenagel–Michael–cyclization multicomponent reactions[a]



1 2 3 4 4'

Entry	1	R^1	R^2	Time (h)	Yield (%)[b]	*Threo* : *erythro* ratio[c]
1	**1a**	CH_3	H	1.1	98	51 : 49
2	**1b**	CH_3	5-CH_3	1.5	98	55 : 45
3	**1c**	CH_3	5-NO_2	24	91	64 : 36
4	**1d**	CH_3	5-Br	7	98	51 : 49
5	**1e**	CH_3	5-Cl	8	98	56 : 44
6	**1f**	CH_3	7-CH_3	5	98	51 : 49
7	**1g**	H	H	8	95	51 : 49
8	**1h**	H	5-CH_3	10	98	55 : 45
9	**1i**	H	5-OCH_3	3	93	52 : 48
10	**1j**	H	5-NO_2	30	83	51 : 49
11	**1k**	H	5-Br	25	85	51 : 49
12	**1l**	H	5-Cl	25	81	63 : 37
13	**1m**	H	6-OCH_3	10	98	61 : 39
14	**1n**	H	7-CH_3	7	91	62 : 38
15[d]	**1o**	Bn	H	72	68	67 : 33
16	**1p**	Ac	H	72	<10	—

[a] All reactions were carried out with isatin **1** (0.3 mmol), malononitrile **2** (0.3 mmol) and Et_3N (0.03 mmol) in H_2O (5.0 mL) at room temperature. After the reaction was completed (monitored by TLC), α-isothiocyanato imide **3** (0.33 mmol) was added and the mixture was sonicated at room temperature for 1 min in an ultrasound bath. [b] After purification by column chromatography. [c] *Threo*/*erythro* ratio was determined by ^{1}H NMR spectra of crude product. [d] 30 mol% Et_3N has been employed.

This trend suggests that hydrogen bonding and dipolar effects may be important for rate acceleration.[10]

Remarkably, with the use of aqueous isopropyl alcohol solutions, the reaction proceeded efficiently and afforded excellent yields (Table 1, entries 6,7). This observation encouraged us to exclude organic solvents from the reaction mixture. Interestingly, by using pure water as a solvent the reaction proceeded very well and obtained the desired product **4a** with an excellent yield (Table 1, entry 8). Sonication enables the rapid dispersion of solids on the water surface allowing for better contact between water and the reactants. The use of ultrasound as a means of accelerating reactions is an important technique and one which is rapidly developing for green processes.[11] In order to accelerate the rate of this reaction, we proceeded with the reaction assisted with ultrasonic irradiation. A large rate acceleration was observed in the reaction (Table 1, entry 9).

Subsequently, with Et_3N as the catalyst, different catalyst loadings were studied (Table 1, entries 10–14). Finally, it was observed that the reaction was able to proceed to completion in 66 min with 10 mol% Et_3N affording product **4a** as a mixture of two diastereoisomers in a 98% yield (Table 1, entry 13). Thus, the optimal reaction conditions for this transformation were determined to be 0.3 mmol isatin **1**, 0.3 mmol malononitrile **2**, 0.33 mmol α-isothiocyanato imide **3**, 10 mol% Et_3N in 5 mL H_2O as solvent at room temperature with ultrasonic irradiation.

Having established the optimal reaction parameters, we then examined the generality of this reaction (Table 2). It is shown that structurally varied isatin derivatives **1** can efficiently engage in the reaction (Table 2, entries 1–14). High yields (81–98%) were obtained, irrespective of the differences in electronic and steric properties of the substituents appending to the aromatic rings of the oxindole framework. Notably, the reaction proceeded slowly when electron-withdrawing substituents were at the 5-position on the aromatic ring (Table 2, entry 3 and entries 10–12). It appears that the *N*-protecting group in the oxindole is critical for achieving a high yield. Masking of the "*N*" (*e.g.*, Bn, entry 15) led to a dramatic decrease of the yield (68%). When *N*-acetyl protected isatin **1p** was employed as the substrate the reaction proceeded exclusively in lower yields (<10%) despite a long reaction time (Table 2, entry 16). The diastereomeric ratio of product was determined by ^{1}H NMR spectroscopy of the crude product. In order to determine the structure of the products, a single crystal X-ray diffraction study of **4b** was performed.[12] The molecular structure of **4b** is shown in Fig. 2, and the structure showed that the relative configuration of the main product was assigned as *threo*.

The mechanism of this multicomponent cascade reaction is proposed as shown in Scheme 1. The first step involves the Knoevenagel reaction of isatin **1** with malononitrile **2** to form a

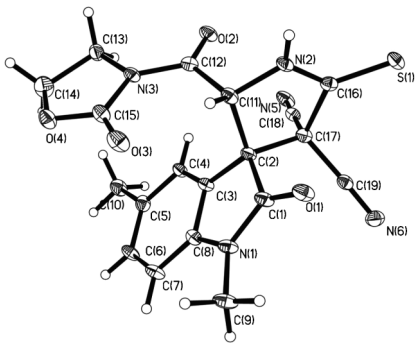
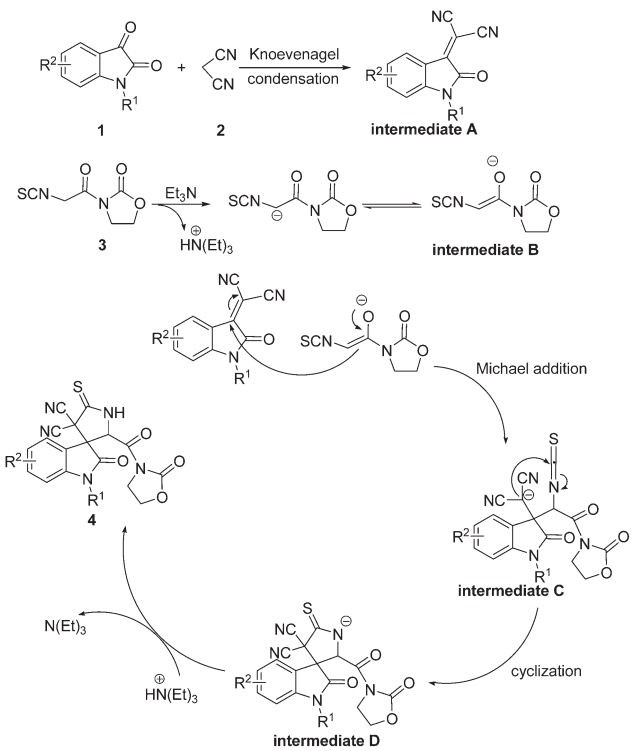


Fig. 2 X-ray crystal structure of **4b**.

dicyanoalkene intermediate A. The next step is the Michael addition of the Knoevenagel adduct with α-isothiocyanato imide **3** which is initiated by Et_3N to form the enolate intermediate B, resulting in intermediate C. The intermediate C undergoes an intramolecular cyclization reaction to afford the product **4** through the intermediate D. Overall, this three-component cascade transformation leads to the generation of three C–C bonds.

Conclusions

We have developed a versatile new method for the room-temperature synthesis of functionalized 3,3′-pyrrolidonyl spirooxindoles "on water" assisted with ultrasonic irradiation. The reaction has been shown to display relatively good functional group tolerance, high yields, and product isolation is very straightforward. The power of this straightforward process is highlighted by its extremely high efficiency in synthesizing the spirooxindole skeleton in one single operation. Further studies into expanding the application of this strategy to synthesize more promising candidates for drug discovery as well as the biological evaluation of these compounds are currently underway.



Scheme 1 Plausible reaction mechanism.

Experimental section

Solvents were dried and distilled prior to use according to standard methods. Unless otherwise indicated, all materials were obtained from commercial sources, and used as purchased without dehydration. Flash column chromatography was performed on silica gel (particle size 10–40 μm, Ocean Chemical Factory of Qingdao, China). ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO on Bruker AV 400 MHz spectrometers, TMS served as the internal standard (δ = 0 ppm). Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet) and coupling constant in Hertz (Hz). The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Mass spectra were recorded on a LCQ advantage spectrometer as shown in the ESI.† HR-MS was recorded on APEXII and ZAB-HS spectrometers. Melting points were determined on a T-4 melting point apparatus (uncorrected).

Typical reaction procedure for the synthesis of 3,3′-pyrrolidinyl-spirooxindole

A solution of isatin **1** (0.3 mmol), TEA (0.03 mmol) and malononitrile **2** (0.3 mmol) in 5 ml H_2O was stirred at room temperature. After the reaction was completed (monitored by TLC), α-isothiocyanato imide **3** (0.33 mmol) was added and the mixture was sonicated for 1 min in an ultrasound bath, then further stirred at room temperature. After the complete consumption of the dicyanoalkene, as indicated by TLC (ethyl acetate–hexane = 3 : 1), the solvent was evaporated. The residue was purified by column chromatography over silica gel (ethyl acetate–hexane = 3 : 1) to afford the product as a colorless powder.

1-Methyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4a**: white solid. mp 151–153 °C; ^{1}H NMR (300 MHz, DMSO): δ 12.33 (br, 1H), 7.26–7.62 (m, 4H), 5.77 (s, 1H), 4.15–4.66 (dt, J = 7.8 Hz, J = 4.2 Hz, 4H), 3.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 187.31, 173.07, 166.94, 154.19, 145.87, 133.13, 125.61, 124.25, 119.59, 112.05, 111.47, 66.76, 64.73, 57.87, 43.22, 31.86, 28.10. HRMS calculated $[M + Na]^+$ for $C_{18}H_{13}N_5O_4SNa$: 418.0580, found: 418.0583.

Minor diastereoisomer **4a′**: ^{1}H NMR (300 MHz, DMSO): δ 12.33 (br, 1H), 7.13–7.25 (m, 4H), 5.63 (s, 1H), 3.85–4.11 (dt, J = 7.8 Hz, J = 4.2 Hz, 4H), 3.20 (s, 3H). ^{13}C NMR (101 MHz,

DMSO): δ 187.31, 169.38, 165.79, 155.41, 144.20, 132.67, 126.88, 124.88, 123.68, 112.05, 111.32, 68.75, 65.08, 59.15, 43.69, 31.86, 28.10.

1,5-Dimethyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4b**: white solid. mp 165–168 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.30 (br, 1H), 7.16–7.45 (m, 3H), 5.79 (s, 1H), 4.13–4.59 (dt, *J* = 8.0 Hz, *J* = 4.0 Hz, 4H), 3.23 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.50, 171.71, 165.69, 152.94, 142.40, 132.33, 132.20, 124.63, 122.89, 110.67, 110.35, 110.06, 65.17, 63.53, 56.53, 55.81, 42.08, 26.90, 20.59. HRMS calculated [M + Na]$^+$ for $C_{19}H_{15}N_5O_4SNa$: 432.0737, found: 432.0740.

Minor diastereoisomer **4b′**: ^{1}H NMR (400 MHz, DMSO): δ 12.30 (br, 1H), 7.00–7.15 (m, 3H), 5.64 (s, 1H), 3.83–4.08 (dt, *J* = 8.0 Hz, *J* = 4.0 Hz, 4H), 3.17 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.84, 168.02, 164.51, 154.16, 140.76, 132.82, 131.79, 125.53, 118.35, 110.77, 109.94, 109.22, 67.14, 63.88, 57.89, 56.11, 42.48, 30.63, 20.70.

1-Methyl-5-nitro-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4c**: white solid; mp 161–163 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.53 (br, 1H), 8.03–8.57 (m, 3H), 5.89 (s, 1H), 4.26–4.62 (dt, *J* = 7.8 Hz, *J* = 4.0 Hz, 4H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 185.94, 168.85, 163.95, 154.24, 148.91, 142.96, 128.50, 119.58, 118.79, 110.67, 108.74, 66.88, 64.10, 57.43, 42.49, 30.63, 27.48. HRMS calculated [M + Na]$^+$ for $C_{18}H_{12}N_6O_6SNa$: 463.0431, found: 463.0435.

Minor diastereoisomer **4c′**: ^{1}H NMR (400 MHz, DMSO): δ 12.53 (br, 1H), 7.42–7.88 (m, 3H), 5.83 (s, 1H), 3.91–4.23 (dt, *J* = 7.8 Hz, *J* = 4.0 Hz, 4H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 185.94, 172.22, 165.54, 153.33, 150.36, 142.83, 128.78, 125.39, 119.44, 110.86, 110.05, 65.37, 63.97, 55.72, 42.23, 30.63, 27.48.

5-Bromo-1-methyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4d**: white solid; mp 173–175 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.40 (br, 1H), 7.35–7.87 (m, 3H), 5.77 (s, 1H), 4.25–4.63 (dt, *J* = 7.7 Hz, *J* = 4.0 Hz, 4H), 3.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.17, 167.87, 164.19, 154.20, 142.52, 134.35, 126.86, 125.57, 114.92, 112.54, 110.53, 108.92, 66.88, 63.98, 57.72, 42.48, 30.66, 27.08. HRMS calculated [M + Na]$^+$ for $C_{18}H_{12}BrN_5O_4SNa$: 495.9686, found: 495.9689.

Minor diastereoisomer **4d′**: ^{1}H NMR (400 MHz, DMSO): δ 12.40 (br, 1H), 7.15–7.33 (m, 3H), 5.79 (s, 1H), 3.73–4.05 (dt, *J* = 7.7 Hz, *J* = 4.0 Hz, 4H), 3.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.07, 171.28, 165.62, 153.06, 144.22, 134.78, 127.15, 120.54, 114.15, 112.25, 110.45, 110.17, 65.34, 63.80, 56.10, 42.22, 30.66, 27.12.

5-Chloro-1-methyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4e**: white solid; mp 158–161 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.40 (br, 1H), 7.34–7.78 (m, 3H), 5.77 (s, 1H), 4.24–4.59 (dt, *J* = 8.2 Hz, *J* = 4.2 Hz, 4H), 3.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.18, 167.95, 164.21, 154.21, 142.11, 131.50, 127.35, 126.82, 122.94, 111.81, 110.18, 66.87, 63.99, 57.77, 55.96, 42.48, 27.10. HRMS calculated [M + Na]$^+$ for $C_{18}H_{12}ClN_5O_4S$: 452.0191, found: 452.0195.

Minor diastereoisomer **4e′**: ^{1}H NMR (400 MHz, DMSO): δ 12.40 (br, 1H), 7.11–7.31 (m, 3H), 5.79 (s, 1H), 3.75–4.07 (dt, *J* = 8.2 Hz, *J* = 4.2 Hz, 4H), 3.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.06, 171.38, 165.60, 153.09, 143.80, 131.93, 126.84, 124.08, 112.08, 110.45, 108.93, 65.33, 63.79, 56.18, 55.57, 42.23, 27.14.

1,7-Dimethyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4f**: white solid; mp 166–168 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.33 (br, 1H), 7.13–7.36 (m, 3H), 5.75 (s, 1H), 4.13–4.61 (dt, *J* = 7.8 Hz, *J* = 4.0 Hz, 4H), 3.50 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.92, 168.70, 164.60, 154.21, 140.71, 135.01, 123.62, 122.81, 121.41, 120.18, 110.30, 109.24, 67.41, 63.91, 57.44, 42.48, 30.64, 29.89, 18.32. HRMS calculated [M + Na]$^+$ for $C_{19}H_{15}N_5O_4SNa$: 432.0737, found: 432.0741.

Minor diastereoisomer **4f′**: ^{1}H NMR (400 MHz, DMSO): δ 12.33 (br, 1H), 6.85–7.11 (m, 3H), 5.60 (s, 1H), 3.76–4.08 (dt, *J* = 7.8 Hz, *J* = 4.0 Hz, 4H), 3.44 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.50, 172.57, 165.71, 152.96, 142.43, 135.48, 126.25, 122.25, 121.47, 118.75, 110.85, 110.67, 65.38, 63.51, 56.10, 42.02, 30.64, 30.03, 18.40.

2-Oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4g**: white solid; mp 171–173 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.30 (br, 1H), 11.51 (s, 1H), 7.17–7.55 (m, 4H), 5.81 (s, 1H), 4.26–4.60 (dt, *J* = 7.9 Hz, *J* = 4.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.81, 173.51, 165.76, 152.96, 141.70, 131.88, 124.67, 123.00, 122.73, 122.32, 118.94, 110.99, 64.94, 63.87, 56.80, 42.04, 30.65. HRMS calculated [M + Na]$^+$ for $C_{17}H_{11}N_5O_4SNa$: 404.0424, found: 404.0428.

Minor diastereoisomer **4g′**: ^{1}H NMR (400 MHz, DMSO): δ 12.30 (br, 1H), 11.32 (s, 1H), 6.93–7.17 (m, 4H), 5.67 (s, 1H), 3.74–4.60 (dt, *J* = 7.9 Hz, *J* = 4.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.58, 169.64, 164.51, 154.19, 143.44, 131.44, 126.29, 123.00, 122.73, 122.32, 118.94, 111.09, 66.88, 63.87, 58.36, 42.44, 30.65.

5-Methyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4h**: white solid; mp 175–178 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.26 (br, 1H), 11.41 (s, 1H), 6.98–7.38 (m, 3H), 5.81 (s, 1H), 4.17–4.59 (dt, *J* = 8.0 Hz, *J* = 4.2 Hz, 4H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.63, 173.45, 165.81, 152.91, 141.03, 132.16, 131.77, 124.81, 123.05, 110.83, 109.32, 64.92, 63.48, 56.77, 55.77, 42.10, 20.59. HRMS calculated [M + Na]$^+$ for $C_{18}H_{13}N_5O_4SNa$: 418.0580, found: 418.0582.

Minor diastereoisomer **4h′**: ^{1}H NMR (400 MHz, DMSO): δ 12.26 (s, 1H), 11.21 (s, 1H), 6.85–6.98 (m, 3H), 5.66 (s, 1H), 3.68–4.17 (dt, *J* = 8.0 Hz, *J* = 4.2 Hz, 4H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.79, 169.63, 164.53, 154.14, 139.32,

131.97, 131.77, 126.29, 119.04, 110.83, 110.39, 66.88, 63.83, 58.44, 56.41, 42.43, 20.71.

5-Methoxy-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4i**: white solid; mp 173–175 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.29 (s, 1H), 11.15 (s, 1H), 7.01–7.16 (m, 3H), 5.72 (s, 1H), 4.23–4.57 (dt, J = 7.8 Hz, J = 4.2 Hz, 4H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.70, 169.49, 164.46, 155.25, 154.13, 134.92, 127.14, 115.48, 111.62, 110.90, 110.37, 110.05, 66.75, 63.84, 58.72, 55.56, 42.43, 30.62. HRMS calculated $[M + Na]^+$ for $C_{18}H_{13}N_5O_5S$: 434.0530, found: 434.0532.

Minor diastereoisomer **4i′**: ^{1}H NMR (400 MHz, DMSO): δ 12.29 (s, 1H), 11.36 (s, 1H), 6.65–7.01 (m, 3H), 5.83 (s, 1H), 3.86–4.23 (dt, J = 7.8 Hz, J = 4.2 Hz, 4H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.57, 173.33, 165.89, 154.78, 152.95, 136.57, 120.02, 116.02, 111.76, 111.22, 110.74, 109.28, 64.96, 63.54, 56.90, 55.78, 42.26, 30.62.

5-Nitro-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4j**: white solid; mp 193–195 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.46 (br, 1H), 12.09 (s, 1H), 8.03–8.49 (m, 3H), 5.93 (s, 1H), 4.17–4.62 (dt, J = 7.6 Hz, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 185.71, 173.80, 163.92, 154.21, 148.12, 142.53, 128.47, 119.97, 119.22, 111.44, 110.48, 108.84, 66.65, 64.04, 58.11, 42.44, 30.61. HRMS calculated $[M - H]^-$ for $C_{17}H_{10}N_6O_6S$: 425.0305, found: 425.0305.

Minor diastereoisomer **4j′**: ^{1}H NMR (400 MHz, DMSO): δ 12.46 (br, 1H), 12.30 (s, 1H), 7.11–8.03 (m, 3H), 5.86 (s, 1H), 3.65–4.17 (dt, J = 7.6 Hz, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.04, 170.35, 165.64, 153.30, 149.64, 142.32, 128.74, 126.05, 120.10, 111.44, 110.39, 110.05, 65.11, 63.90, 56.06, 42.23, 30.61.

5-Bromo-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4k**: white solid; mp 158–160 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.34 (s, 1H), 11.49 (s, 1H), 7.31–7.77 (m, 3H), 5.80 (s, 1H), 4.28–4.59 (dt, J = 7.8 Hz, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.10, 172.98, 165.73, 154.18, 141.23, 134.29, 127.11, 125.81, 113.24, 113.02, 110.55, 110.21, 66.66, 64.11, 56.42, 42.23, 30.65. HRMS calculated $[M + Na]^+$ for $C_{17}H_{10}BrN_5O_4S$: 481.9529, found: 481.9535.

Minor diastereoisomer **4k′**: ^{1}H NMR (400 MHz, DMSO): δ 12.34 (s, 1H), 11.73 (s, 1H), 6.95–7.27 (m, 3H), 5.82 (s, 1H), 3.75–4.09 (dt, J = 7.8 Hz, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.20, 169.44, 164.22, 153.03, 143.00, 134.70, 127.96, 121.28, 114.14, 113.31, 110.64, 109.03, 65.10, 63.74, 58.34, 42.44, 30.65.

5-Chloro-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4l**: white solid; mp 163–165 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.35 (s, 1H), 11.74 (s, 1H), 7.20–7.63 (m, 3H), 5.83 (s, 1H), 4.19–4.59 (dt, J = 8.0 Hz, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.18, 173.10, 165.70, 153.06, 142.59, 131.89, 126.58, 124.30, 120.94, 112.80, 110.55, 109.03, 65.06, 63.74, 59.73, 42.24, 14.05. HRMS calculated $[M + Na]^+$ for $C_{17}H_{10}ClN_5O_4SNa$: 438.0034, found: 438.0039.

Minor diastereoisomer **4l′**: ^{1}H NMR (400 MHz, DMSO): δ 12.35 (s, 1H), 11.50 (s, 1H), 7.01–7.24 (m, 3H), 5.81 (s, 1H), 3.81–4.15 (dt, J = 8.0 Hz, J = 4.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.10, 169.54, 164.22, 154.19, 140.84, 131.46, 127.59, 126.03, 123.15, 112.60, 110.64, 110.21, 66.63, 63.95, 56.49, 42.44, 20.73.

6-Methoxy-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4m**: white solid; mp 143–145 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.22 (s, 1H), 11.46 (s, 1H), 6.70–7.20 (m, 3H), 5.79 (s, 1H), 4.23–4.58 (dt, J = 7.8 Hz, J = 4.2 Hz, 4H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.72, 174.09, 165.89, 161.97, 152.96, 144.94, 125.75, 111.09, 110.28, 107.61, 97.51, 67.13, 64.76, 64.11, 55.46, 42.06, 30.61. HRMS calculated $[M + Na]^+$ for $C_{18}H_{13}N_5O_5SNa$: 434.0530, found: 434.0532.

Minor diastereoisomer **4m′**: ^{1}H NMR (400 MHz, DMSO): δ 12.22 (s, 1H), 11.46 (s, 1H), 6.35–6.68 (m, 3H), 5.63 (s, 1H), 3.86–4.21(dt, J = 7.8 Hz, J = 4.2 Hz, 4H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.85, 170.21, 164.50, 161.74, 154.14, 143.19, 123.85, 111.09, 110.46, 107.94, 97.51, 64.11, 63.82, 58.33, 56.79, 42.43, 29.53.

7-Methyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4n**: white solid; mp 148–151 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.25 (s, 1H), 11.53 (s, 1H), 7.07–7.34 (m, 3H), 5.81 (s, 1H), 4.15–4.56 (dt, J = 7.6 Hz, J = 4.2 Hz, 4H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.69, 174.04, 165.81, 152.92, 142.03, 133.07, 122.19, 121.93, 120.57, 118.63, 111.07, 110.68, 64.97, 63.45, 57.01, 42.04, 30.64, 16.44. HRMS calculated $[M + Na]^+$ for $C_{18}H_{13}N_5O_4SNa$: 418.0580, found: 418.0579.

Minor diastereoisomer **4n′**: ^{1}H NMR (400 MHz, DMSO): δ 12.25 (s, 1H), 11.36 (s, 1H), 6.98–7.05 (m, 3H), 5.66 (s, 1H), 3.88–4.11 (dt, J = 7.6 Hz, J = 4.2 Hz, 4H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 186.88, 170.12, 164.54, 154.17, 140.31, 132.66, 126.01, 122.97, 120.52, 119.92, 110.36, 109.31, 66.95, 63.85, 58.62, 42.43, 30.64, 16.38.

1-Benzyl-2-oxo-2′-(2-oxooxazolidine-3-carbonyl)-5′-thioxospiro[indoline-3,3′-pyrrolidine]-4′,4′-dicarbonitrile

Major diastereoisomer **4o**: white solid; mp 218–221 °C; ^{1}H NMR (400 MHz, DMSO): δ 12.36 (br, 1H), 7.03–7.55 (m, 9H), 5.89 (s, 1H), 5.16 (d, J = 16 Hz, 2H), 4.15–4.66 (dt, J = 7.8 Hz, J = 4.2 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.94, 172.48, 166.12, 153.44, 144.34, 135.36, 132.44, 129.03, 128.17, 127.86, 125.11, 123.71, 118.72, 111.35, 111.08, 65.60, 64.05, 57.06, 56.26, 44.13, 42.56. HRMS calculated $[M + Na]^+$ for $C_{24}H_{17}N_5O_4SNa$: 494.0893, found: 494.0897.

Minor diastereoisomer **4o′**: ^{1}H NMR (400 MHz, DMSO): δ 12.36 (br, 1H), 7.03–7.55 (m, 9H), 5.78 (s, 1H), 4.90 (d, J = 16 Hz, 2H), 3.81–4.08 (dt, J = 7.8 Hz, J = 4.2 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 186.94, 168.81, 164.84, 154.69, 142.67, 135.65, 132.01, 129.10, 127.65, 125.76, 124.35, 123.22, 118.72, 111.48, 111.20, 67.30, 64.45, 58.53, 57.00, 44.13, 42.95.

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Notes and references

1 For reviews of 3,3′-pyrrolidinyl-spirooxindole natural products, see: (*a*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*b*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209.

2 W. T. Wei, C. X. Chen, R. J. Lu, J. J. Wang, X. J. Zhang and M. Yan, *Org. Biomol. Chem.*, 2012, **10**, 5245.

3 A. Jossang, P. Jossang, H. A. Hadi, T. Sevenet and B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527.

4 C. Pellegrini, M. Weber and H. J. Borschberg, *Helv. Chim. Acta*, 1996, **79**, 151.

5 For selected recent examples, see: (*a*) B. Tan, N. R. Candeias and C. F. Barbas III, *J. Am. Chem. Soc.*, 2011, **133**, 4672; (*b*) B. Tan, N. R. Candeias and C. F. Barbas III, *Nat. Chem.*, 2011, **3**, 473; (*c*) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735; (*d*) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7200; (*e*) X. H. Chen, Q. Wei, S. W. Luo, H. Xiao and L. Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819; (*f*) B. M. Trost, N. Cramer and S. M. Silverman, *J. Am. Chem. Soc.*, 2007, **129**, 12396.

6 Some examples of the synthesis of spirocyclic oxindoles fused with pyrrolidines, see: (*a*) H. C. Malinakova and L. S. Liebeskind, *Org. Lett.*, 2000, **2**, 4083; (*b*) L. E. Overman and M. D. Rosen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4596; (*c*) P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666; (*d*) T. Onishi, P. R. Sebahar and R. M. Williams, *Org. Lett.*, 2003, **5**, 3135; (*e*) C. Chen, X.-D. Li, C. S. Neumann, M. M.-C. Lo and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2005, **44**, 2249; (*f*) B. M. Trost and M. K. Brennan, *Org. Lett.*, 2006, **8**, 2027.

7 (*a*) R. T. Baker and W. Tumas, *Science*, 1999, **284**, 1477; (*b*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998; (*c*) P. Anastas and T. Williamson, *Green Chemistry, Frontiers in Benign Chemical Synthesis and Procedures*, Oxford Science Publications, Oxford, 1998; (*d*) S. Kobayashi and K. Manabe, *Acc. Chem. Res.*, 2002, **35**, 209; (*e*) U. K. Lindström, *Chem. Rev.*, 2002, **102**, 2751; (*f*) C. J. Li, *Chem. Rev.*, 2005, **105**, 3095; (*g*) U. M. Lindstrom, *Organic Reactions in Water*, Blackwell Publishing, Oxford, UK, 2007; (*h*) V. K. Ahluwalia and R. S. Varma, *Green Solvents for Organic Synthesis*, Alpha Science International, Abingdon, UK, 2009; (*i*) C. J. Li, *Chem. Rev.*, 1993, **93**, 2023.

8 For selected examples, see: (*a*) X. X. Jiang, Y. M. Cao, Y.Q. Wang, L. P. Liu, F. F. Shen and R. Wang, *J. Am. Chem. Soc.*, 2010, **132**, 15328; (*b*) Y. Y. Han, W. B. Chen, W. Y. Han, Z. J. Wu, X. M. Zhang and W. C. Yuan, *Org. Lett.*, 2012, **14**, 490; (*c*) X. L. Liu, W. Y. Han, X. M. Zhang and W. C. Yuan, *Org. Lett.*, 2013, **15**, 1245.

9 Y. Y. Wang, H. T. Yang, J. P. Yu, Z. W. Miao and R. Y. Chen, *Adv. Synth. Catal.*, 2009, **351**, 3057.

10 (*a*) A. Rodgman and G. F. Wright, *J. Org. Chem.*, 1953, **18**, 465; (*b*) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275.

11 (*a*) P. Cintas and J. L. Luche, *Green Chem.*, 1999, **1**, 115; (*b*) T. J. Mason and J. P. Lorimer, *Applied Sonochemistry*, Wiley-VCH, Weinheim, 2002.

12 Crystallographic data for the structural analysis of compound **4b** has been deposited at the Cambridge Crystallographic Data Centre as No. CCDC 939641. These data can be obtained free of charge by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk.

