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# An efficient one-pot synthesis of novel pyrazolophthalazinyl spirooxindoles

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**Abstract.** A simple and efficient method for the synthesis of novel pyrazolophthalazinyl spirooxindoles by L-proline catalysed one-pot three-component reaction is described.

**Keywords.** L-proline; pyrazolophthalazinyl spirooxindoles; three-component.

## 1. Introduction

Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to a final product in a one-pot procedure. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high-throughput generation of organic compounds.[1] In the past decade, there have been tremendous developments in three- and four-component reactions and efforts are still being made to find and develop new MCRs.[2] The indole template is generally recognized as an important structure in medicinal chemistry, and in particular, oxindoles that incorporate a quaternary stereogenic centre at C3 are attractive targets in organic synthesis because of their significant biological activities.[3] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids. For example, spirotryprostatin A, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly,[4] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (figure 1).[5] In addition to the naturally occurring pyrrolidino-spiro-3′-oxindoles, synthetic pyrrolino- and piperidino-spiro-3′-oxindoles have been shown to exhibit local anaesthetic properties. The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindoles have made them attractive synthetic targets (figure 1).

## 2. Experimental

### 2.1 *Materials and methods*

Malononitrile, isatin, $NH_2SO_3H$, $SnCl_2{\cdot}2H_2O$, $K_2CO_3$ and basic alumina were obtained from S.D. Fine Chemicals Indium(III) chloride, CAN, L-proline and phthalhydrazide were purchased from Aldrich. All melting points were uncorrected. IR spectra were recorded on a Perkin Elmer FT–IR spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in DMSO-$d_6$ using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz and Bruker spectrometer at 300 MHz and 75 MHz respectively. Mass spectra were recorded on a JEOL

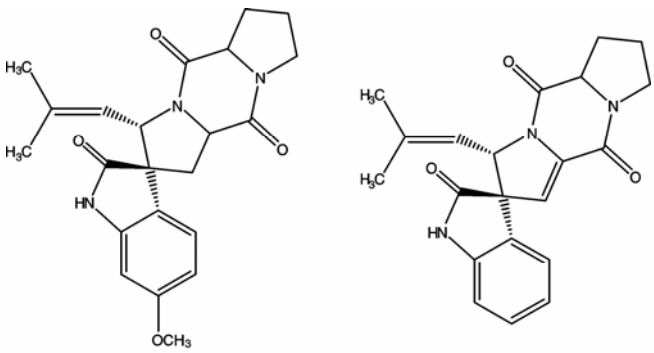
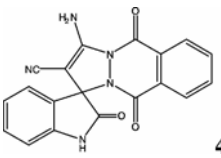
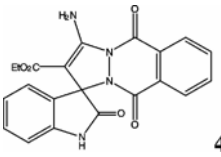
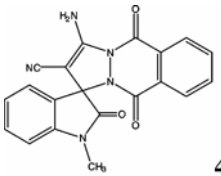
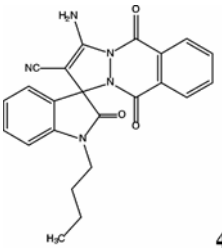
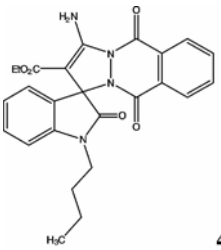
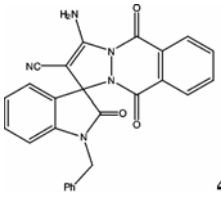
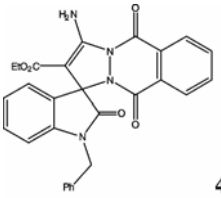
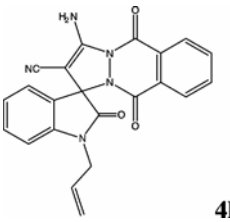



**Figure 1.** Representatives of spirooxindole-containing compounds.

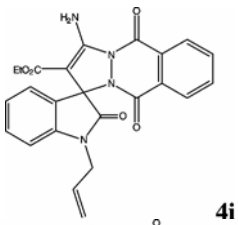
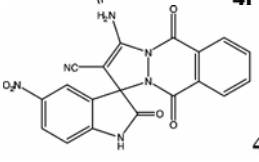
*For correspondence

**Table 1.** Synthesis of pyrazolophthalazinyl spiro-3′-oxindoles **4a–j**.

| Entry | R | R′ | X | Product (**4**) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | H | H | CN |  **4a** | 2.0 | 90 |
| 2 | H | H | $CO_2Et$ |  **4b** | 2.2 | 88 |
| 3 | $CH_3$ | H | CN |  **4c** | 2.0 | 92 |
| 4 | Butyl | H | CN |  **4d** | 2.2 | 91 |
| 5 | Butyl | H | $CO_2Et$ |  **4e** | 2.5 | 88 |
| 6 | Benzyl | H | CN |  **4f** | 2.0 | 92 |
| 7 | Benzyl | H | $CO_2Et$ |  **4g** | 2.2 | 90 |
| 8 | Allyl | H | CN |  **4h** | 2.2 | 87 |

(*Contd...*)

**Table 1.** (*Contd...*)

| Entry | R | R′ | X | Product (**4**) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 9 | Allyl | H | $CO_2Et$ |  **4i** | 2.5 | 86 |
| 10 | H | $NO_2$ | CN |  **4j** | 2.0 | 90 |

[a]Isolated yield

DX 303 HF spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyser. Analytical TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0·2 mm thickness (Macherey–Nagel, Germany).

### 2.2 *General procedure for the synthesis of pyrazolophthalazinyl spirooxindoles* (**4a–j**)

L-proline (20 mol%) was added to a stirred mixture of isatin (1 mmol), malononitrile (1 mmol) and phthalhydrazide (1 mmol) in ethanol (5 mL), and refluxed for the appropriate time (table 1). After complete conversion as indicated by TLC, water was added and the product was extracted with ethyl acetate (2 × 15 mL). The combined extracts were dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. The resulting product was recrystallized from ethanol to afford pure product (**4a–j**).

2.2a *3-Amino-5,10-dioxo spiro[(3′H)-indol-3′,1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1′H)-2′-one-2-carbonitrile* (**4a**) (table 1, entry 1): yellow solid. m.p.: 269–270°C. $\nu_{max}$ (KBr): 3439, 3350, 2209, 1756, 1678, 1653, 1465, 1364, 1257, 1163 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 6·90 (*d*, 1H, *J* = 7·65 Hz), 6·97 (*t*, 1H, *J* = 7·65 Hz), 7·27 (*t*, 1H, *J* = 7·6 Hz), 7·44 (*d*, 1H, *J* = 7·65 Hz), 7·96 (*m*, 3H), 8·25 (*d*, 1H, *J* = 7·65 Hz), 8·32 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable), 10·92 (*s*, 1H, NH, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 60·6, 70·3, 110·9, 114·9, 123·1, 125·2, 125·9, 127·5, 128·1, 128·3, 129·2, 131·0, 134·9, 135·6, 142·7, 152·2, 153·1, 156·9, 173·0. MS (*m/z*): 357 ($M^+$)· Anal. Calcd. For $C_{19}H_{11}N_5O_3$: C, 63·87; H, 3·10; N, 19·60%. Found: C, 63·83; H, 3·06; N, 19·55 %.

2.2b *Ethyl 3-amino-5,10-dioxo spiro[(3′H)-indol-3′,1-5,10-dihydro-1(H)-pyrazolo(1,2-b) phthalazin]-(1′H)-2′-one-2-carboxylate* (**4b**) (table 1, entry 2): yellow solid. m.p.: 284–286°C. $\nu_{max}$ (KBr): 3438, 3328, 1742, 1701, 1665, 1527, 1294, 1140 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 0·84 (*t*, 3H, *J* = 7·65 Hz), 3·81 (*m*, 2H), 6·80 (*d*, 1H, *J* = 7·65 Hz), 6·84 (*t*, 1H, *J* = 6·85 Hz), 7·18 (*t*, 1H, *J* = 7·65 Hz), 7·27 (*d*, 1H, *J* = 7·65 Hz), 7·52 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable), 7·94 (*m*, 3H), 8·25 (*d*, 1H, *J* = 9·15 Hz), 10·73 (*s*, 1H, NH, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 14·2, 59·3, 70·7, 81·3, 109·9, 122·2, 124·3, 127·3, 127·5, 128·0, 128·6, 129·1, 130·0, 134·7, 135·5, 143·9, 151·2, 152·6, 157·0, 163·7, 173·5. MS (*m/z*): 404 ($M^+$). Anal. Calcd. For $C_{21}H_{16}N_4O_5$: C, 62·37; H, 3·99; N, 13·85 %. Found: C, 62·28; H, 3·94; N, 13·78%.

2.2c *3-Amino-1′-methyl-5,10-dioxo spiro[(3′H)-indol-3′,1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1′H)-2′-one-2-carbonitrile* (**4c**) (table 1, entry 3): pale yellow solid. m.p.: 282–284°C. $\nu_{max}$ (KBr): 3453, 3327, 2197, 1728, 1664, 1611, 1472, 1371, 698 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 3·22 (*s*, 3H), 7·05 (*t*, 1H, *J* = 7·65 Hz), 7·11 (*d*, 1H, *J* = 7·65 Hz), 7·37 (*t*, 1H, *J* = 8·4 Hz), 7·51 (*d*, 1H, *J* = 6·9 Hz), 7·95 (*m*, 3H), 8·26 (*d*, 1H, *J* = 8·4 Hz), 8·37 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 27·3, 60·0, 69·9, 109·7, 114·9, 123·8, 124·9, 125·3, 127·5, 128·1, 128·3, 129·2, 131·2, 135·0, 135·6, 144·2, 152·4, 153·1, 156·8, 171·6.

MS (*m/z*): 371 ($M^+$). Anal. Calcd. for $C_{20}H_{13}N_5O_3$: C, 64·69; H, 3·53; N, 18·86%. Found: C, 64·63; H, 3·48; N, 18·81%.

2.2d *3-Amino-1'-butyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carbonitrile* (**4d**) (table 1, entry 4): pale yellow solid. m.p.: 222–223°C. $\nu_{max}$ (KBr): 3382, 3260, 2937, 2196, 1668, 1610, 1562, 1467, 1432, 1374, 1257, 1146 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 0·87 (*t*, 3H, *J* = 6·9 Hz), 1·33 (*m*, 2H), 1·59 (*m*, 2H), 3·70 (*m*, 2H), 7·03 (*t*, 1H, *J* = 7·65 Hz), 7·14 (*d*, 1H, *J* = 7·65 Hz), 7·35 (*t*, 1H, *J* = 7·6 Hz), 7·51 (*d*, 1H, *J* = 6·85 Hz), 7·94 (*t*, 2H, *J* = 7·6 Hz), 8·00 (*d*, 1H, *J* = 8·45 Hz), 8·26 (*d*, 1H, *J* = 7·6 Hz), 8·35 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 14·2, 19·8, 29·5, 60·4, 70·0, 109·9, 114·8, 123·5, 125·0, 125·4, 127·5, 128·1, 128·3, 129·2, 131·1, 134·9, 135·6, 143·5, 152·3, 153·1, 156·9, 171·4. MS (*m/z*): 413 ($M^+$). Anal. Calcd. for $C_{23}H_{19}N_5O_3$: C, 66·82; H, 4·63; N, 16·94%. Found: C, 66·93; H, 4·58; N, 16·88%.

2.2e *Ethyl 3-amino-1'-butyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carboxylate* (**4e**) (table 1, entry 5): pale yellow solid. m.p.: 258–260°C. $\nu_{max}$ (KBr): 3427, 3319, 2933, 1731, 1704, 1674, 1610, 1527, 1468, 1428, 1378, 1298, 1263, 1141, 757, 699 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 0·77 (*m*, 3H), 0·89 (*t*, 3H, *J* = 6·85 Hz), 1·37 (*m*, 2H), 1·60 (*m*, 2H), 3·67 (*t*, 2H, *J* = 7·65 Hz), 3·81 (*m*, 2H), 6·91 (*t*, 1H, *J* = 7·6 Hz), 7·02 (*d*, 1H, *J* = 8·4 Hz), 7·26 (*t*, 1H, *J* = 7·65 Hz), 7·33 (*d*, 1H, *J* = 7·65 Hz), 7·95 (*m*, 3H), 7·62 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable), 8·26 (*d*, 1H, *J* = 6·85 Hz). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 14·1, 14·3, 20·0, 29·7, 59·2, 70·1, 80·2, 108·8, 122·7, 124·1, 126·8, 127·6, 128·0, 128·6, 129·1, 130·2, 134·8, 135·5, 144·7, 151·4, 152·7, 157·2, 163·6, 171·8. MS (*m/z*): 460 ($M^+$). Anal. Calcd. for $C_{25}H_{24}N_4O_5$: C, 65·21; H, 5·25; N, 12·17%. Found: C, 65·27; H, 5·20; N, 12·12%.

2.2f *3-Amino-1'-benzyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carbonitrile* (**4f**) (table 1, entry 6): pale yellow solid. m.p.: 266°C. $\nu_{max}$ (KBr): 3373, 3258, 2197, 1666, 1611, 1468, 1371, 1163, 698 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 4·96 (ABq, 2H, *J* = 16·05 Hz), 6·87 (*d*, 1H, *J* = 8·4 Hz), 7·03 (*t*, 1H, *J* = 6·85 Hz), 7·26 (*d*, 2H, *J* = 6·9 Hz), 7·30 (*t*, 2H, *J* = 7·65 Hz), 7·42 (*d*, 2H, *J* = 7·6 Hz), 7·56 (*d*, 1H, *J* = 7·65 Hz), 7·97 (*m*, 2H), 8·05 (*d*, 1H, *J* = 6·85 Hz), 8·28 (*d*, 1H, *J* = 9·15 Hz), 8·41 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 44·0, 60·3, 70·0, 110·3, 115·0, 123·9, 125·1, 125·4, 127·5, 127·6, 128·0, 128·2, 129·1, 129·3, 131·0, 135·0, 135·6, 136·0, 143·1, 152·4, 153·2, 156·9, 171·8. MS (*m/z*): 447 ($M^+$). Anal. Calcd. for $C_{26}H_{17}N_5O_3$: C, 69·79; H, 3·83; N, 15·.65%. Found: C, 69·72; H, 3·78; N, 15·60%.

2.2g *Ethyl 3-amino-1'-benzyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carboxylate* (**4g**) (table 1, entry 7): pale yellow solid. m.p.: 290–291°C. $\nu_{max}$ (KBr): 3426, 3316, 1702, 1697, 1528, 1428, 1383, 1298, 1263, 1143, 700 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 0·65 (*m*, 3H), 3·40 (*m*, 2H), 4·88 (ABq, 2H, *J* = 16·05 Hz), 6·80 (*d*, 1H, *J* = 7·65 Hz), 6·91 (*t*, 1H, *J* = 7·65 Hz), 7·18 (*t*, 1H, *J* = 7·65 Hz), 7·26 (*t*, 1H, *J* = 6·85 Hz), 7·32 (*t*, 2H, *J* = 7·65 Hz), 7·38 (*d*, 1H, *J* = 7·65 Hz), 7·52 (*d*, 2H, *J* = 7·65 Hz), 7·96 (*m*, 3H), 8·15 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable), 8·28 (*d*, 1H, *J* = 9·15 Hz). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 14·3, 43·8, 56·6, 59·2, 70·2, 109·3, 123·1, 124·1, 127·6, 127·8, 127·9, 128·1, 128·9, 129·2, 130·0, 134·8, 135·6, 136·6, 144·4, 152·8, 157·1, 163·7, 172·3. MS (*m/z*): 494 ($M^+$). Anal. Calcd. for $C_{28}H_{22}N_4O_5$: C, 68·01; H, 4·48; N, 11·33%. Found: C, 67·95; H, 4·42; N, 11·28%.

2.2h *3-Amino-1'-allyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carbonitrile* (**4h**) (table 1, entry 8): pale yellow solid. m.p.: 276–277°C. $\nu_{max}$ (KBr): 3382, 3261, 2200, 1712, 1690, 1667, 1612, 1561, 1469, 1437, 1376, 1285, 1255, 1170, 698 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 4·34 (ABq, 2H, *J* = 13·0 Hz), 5·15 (*d*, 1H, *J* = 10·7 Hz), 5·31 (*d*, 1H, *J* = 16·8 Hz), 5·82 (*m*, 1H), 7·00 (*d*, 1H, *J* = 7·6 Hz), 7·06 (*t*, 1H, *J* = 7·65 Hz), 7·33 (*t*, 1H, *J* = 8·4 Hz), 7·53 (*d*, 1H, *J* = 7·65 Hz), 7·95 (*m*, 3H), 8·26 (*d*, 1H, *J* = 6·85 Hz), 8·37 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 42·6, 60·3, 70·0, 110·3, 114·9, 117·0, 123·8, 125·0, 125·3, 127·6, 128·1, 128·2, 129·2, 131·0, 131·6, 135·0, 135·6, 143·1, 152·3, 153·1, 156·9, 171·4. MS (*m/z*): 397 ($M^+$). Anal. Calcd. for $C_{22}H_{15}N_5O_3$: C, 66·49; H, 3·80; N, 17·62%. Found: C, 66·57; H, 3·75; N, 17·58%.

2.2i *Ethyl 3-amino-1′-allyl-5,10-dioxo spiro[(3′H)-indol-3′,1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1′H)-2′-one-2-carboxylate* **(4i)** (table 1, entry 9): pale yellow solid. m.p.: 254–256°C. $\nu_{max}$ (KBr): 3385, 3252, 1735, 1708, 1668, 1608, 1570, 1455, 1423, 1376, 1285, 1255, 1178, 692 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 0·80 (*s*, 3H), 3·79 (*q*, 2H, *J* = 6·9 Hz), 4·27 (ABq, 2H, *J* = 17·55 Hz), 5·18 (*d*, 1H, *J* = 9·95 Hz), 5·48 (*d*, 1H, *J* = 17·55 Hz), 5·82 (*m*, 1H), 6·91 (*t*, 1H, *J* = 7·6 Hz), 6·94 (*d*, 1H, *J* = 7·65 Hz), 7·25 (*t*, 1H, *J* = 7·65 Hz), 7·35 (*d*, 1H, *J* = 6·85 Hz), 7·86 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable), 7·95 (*t*, 2H, *J* = 7·65 Hz), 8·02 (*d*, 1H, *J* = 9·15 Hz), 8·27 (*d*, 1H, *J* = 7·9 Hz). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 14·4, 43·8, 59·4, 70·5, 79·7, 111·5, 117·9, 122·9, 124·2, 125·3, 127·1, 127·3, 127·9, 128·6, 130·1, 132·2, 134·8, 135·6, 152·8, 153·2, 157·1, 162·8, 171·8. MS (*m/z*): 444 ($M^+$). Anal. Calcd. for $C_{24}H_{20}N_4O_5$: C, 64·86; H, 4·54; N, 12·61%. Found: C, 64·75; H, 4·51; N, 12·55%.

2.2j *3-Amino-5′-nitro-5,10-dioxo spiro[(3′H)-indol-3′,1-5,10-dihydro-1(H)-pyrazolo (1,2-b)phthalazin]-(1′H)-2′-one-2-carboxylate* **(4j)** (table 1, entry 10): Yellow solid. m.p.: 280–282°C. $\nu_{max}$ (KBr): 3378, 3255, 2208, 1710, 1692, 1667, 1608, 1552, 1469, 1437, 1376, 1285, 1255, 1165, 698 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$, 500 MHz): $\delta$ 7·12 (*d*, 1H, *J* = 8·4 Hz), 7·96 (*m*, 3H), 8·24 (*m*, 2H), 8·44 (*br s*, 2H, $NH_2$, $D_2O$ exchangeable), 8·60 (*d*, 1H, *J* = 7·65 Hz), 11·65 (*s*, 1H, NH, $D_2O$ exchangeable). $^{13}C$ NMR (DMSO-$d_6$, 125 MHz): $\delta$ 64·0, 69·6, 111·2, 114·8, 121·6, 127·5, 128·0, 128·1, 129·5, 135·0, 135·6, 143·6, 148·7, 152·7, 153·1, 157·0, 173·7. MS (*m/z*): 402 ($M^+$). Anal. Calcd. for $C_{19}H_{10}N_6O_5$: C, 56·72; H, 2·51; N, 20·89%. Found: C, 56·80; H, 2·47; N, 20·82%.

## 3. Results and discussion

As part of our endeavour to discover new spirooxindoles of biocidal interest, and guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably, we investigated a three-component reaction of isatin with malononitrile and phthalhydrazide, in order to synthesize a new class of spirooxindoles with fused phthalazines. To the best of our knowledge, there have been no reports on the synthesis of pyrazolophthalazinyl spiro-3'-oxindoles. Heterocyclic fused phthalazines have been found effective for the inhibition of p38 MAP kinase,[6] selective binding of GABA receptor,[7] antianxiety drug,[8] antitumour agent,[9] high affinity ligands to the $\alpha_2\delta$ – 1 subunit of calcium channel.[10]

Recently, L-proline has been effectively used as a versatile organocatalyst in various organic transformations.[11] In an extension of our continuing efforts on the application of malononitrile based multicomponent reactions in heterocyclic synthesis and in the synthesis of spirooxindoles,[12] we report here a simple and efficient method for the synthesis of pyrazolophthalazinyl spiro-3'-oxindoles, through the three-component condensation of isatin, malononitrile and phthalhydrazide using L-proline as a catalyst (scheme 1).

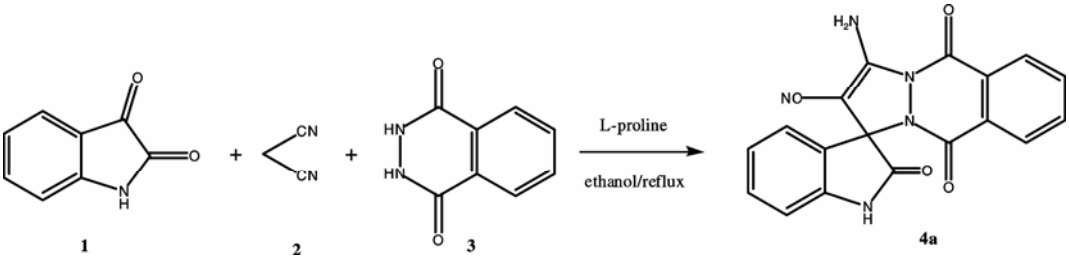
Initially, a model one-pot three-component reaction of isatin **1a** (1 mmol), malononitrile **2a** (1 mmol) and phthalhydrazide **3** (1 mmol) was investigated. Various catalysts, including $InCl_3$, CAN, $NH_2SO_3H$, $SnCl_2{\cdot}2H_2O$, L-proline, $K_2CO_3$ and basic alumina were screened in our model reaction (table 2). The best overall yield (90%) was obtained with L-proline in ethanol. Optimum results were obtained using 20 mol% of L-proline.

Table 1 summarizes our results on the one-pot reaction of various isatin derivatives and malononitrile/ethyl cyanoacetate with phthalhydrazide (scheme 2). All the completed reactions afforded the corresponding pyrazolophthalazinyl spiro-3′-oxindoles in good yields.

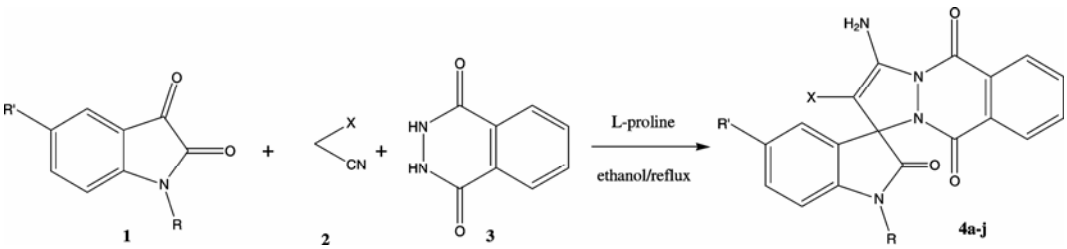
The structures of compounds **4a–j** were confirmed by IR, $^1H$ and $^{13}C$ NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **4a** displayed the molecular ion ($M^+$) peak at *m/z* 357. The $^1H$ NMR spectrum of **4a** exhibited a broad singlet at $\delta$ 8·32 ($D_2O$ exchangeable) due to $-NH_2$, a

**Table 2.** One-pot, three-component synthesis of **4a** using various catalysts.

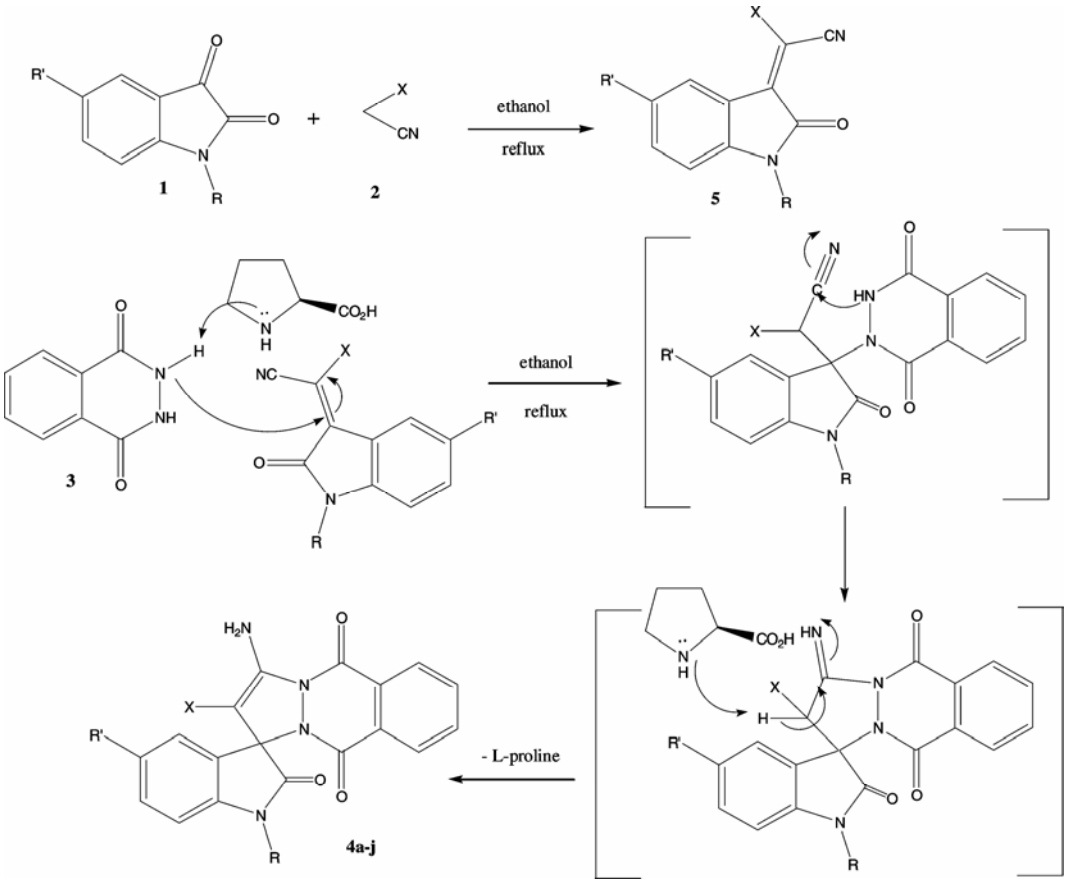
| Entry | Catalyst | Time (h) | Yield[a] (%) |
|---|---|---|---|
| 1 | No cat. | 24 | – |
| 2 | $InCl_3$ | 6 | 45 |
| 3 | CAN | 10 | – |
| 4 | $NH_2SO_3H$ | 9 | 10 |
| 5 | $SnCl_2{\cdot}2H_2O$ | 8 | 34 |
| 6 | L-proline | 2 | 90 |
| 7 | $K_2CO_3$ | 6 | 30 |
| 8 | Basic alumina | 6 | 20 |




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

singlet at $\delta$ 10·92 ($D_2O$ exchangeable) due to –NH isatin and aromatic protons in the range $\delta$ 6·90–8·25. Resonances at $\delta$ 70·3 (spiro carbon), $\delta$ 153·1 and 156·9 (–C=O groups of phthalazine) and $\delta$ 173·0 (isatin –C=O group) were observed in the $^{13}C$ NMR spectrum. Furthermore, the structure of **4b** was established by X-ray crystallographic analysis[13] (figure 2).

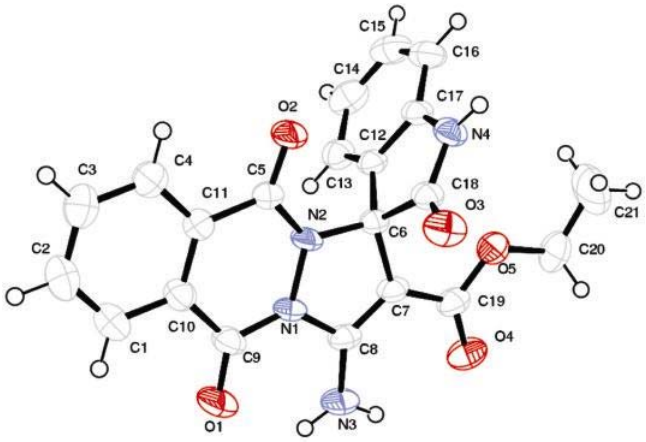



**Figure 2.** ORTEP diagram of compound **4b**.

A possible mechanism for the formation of **4a–j** is proposed in scheme 3. The process represents a typical cascade reaction in which the isatin **1** first condenses with malononitrile/ethyl cyanoacetate **2** to afford isatylidene malononitrile derivative **5**. This step can be regarded as a fast Knoevenagel addition. Then, the subsequent Michael type addition of the phthalhydrazide **3** to **5** followed by cyclization affords the corresponding product **4a–j**.

## 4. Conclusion

In conclusion, we have developed a simple and clean procedure for the synthesis of new pyrazolophthalazinyl spiro-3′-oxindoles starting from commercially available starting materials. The use of inexpensive and readily available L-proline has made this procedure simple, convenient and practical.

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13. Crystal structure of compound **4b** was deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 656685