Indium Trichloride Catalysed Domino Reactions of Isatin: A Facile Access to the Synthesis of Spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-one Derivatives

Nataraj Poomathi, Jayabal Kamalraja, Sivakalai Mayakrishnan, D. Muralidharan, Paramasivan T. Perumal*

Organic Chemistry Division, CSIR-Central Leather Research Institute, Adyar, Chennai 6000 20, India
Fax +91(44)24911589; E-mail: ptperumal@gmail.com

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Abstract: A versatile high-yielding indium trichloride mediated one-pot regioselective synthesis of spiroxindoles via domino one-pot, three-component reaction of isatins, pyrazoles, and (*E*-)-*N*-methyl-1-(methylthio)-2-nitroethenamine is described. This reaction presumably occurs via domino Knoevenagel condensation–Michael addition–intramolecular O-cyclization sequence. The salient features of the methodology are its clean reaction conditions, the eco-friendly medium, low cost, easy isolation, and excellent yields without column chromatographic purification.

Key words: domino reaction, spiroxindole, indium trichloride, Michael addition, regioselective synthesis

Multicomponent reactions (MCR) are chemical transformations in which three or more starting materials combine together via a one-pot procedure to give a final complex product. Such reactions have emerged as powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry for their facileness and efficiency as well as their economy and ecology in organic synthesis.[1] In the past decade, there have been tremendous developments in three- and four-component reactions and significant efforts are made to develop new MCR.[2]

The spiroxindole system is the core structure of many pharmacological agents, natural alkaloids,[3] and their derivatives and occupies a special place in organic and medicinal chemistry because these compounds are well-known as microtubule assembly inhibitors (spirotryprostatin A and B),[4] muscarinic M1, and serotonin receptor modulators (pteropodine and isopteropodine),[5] and non-peptidyl growth-hormone secretagogues (MK-0677).[6] Considerable attention has been focused on the development of new methodologies to synthesize novel spiroxindole ring systems because of their interesting biological and pharmacological properties, such as vasodilatory, hypoglycemic, anti-inflammatory, analgesic, and antipyretic activities.[7] Some indole and oxindoles that were fused with different heterocycles have recently received attention due to their useful biological properties.[8] These fused heterocyclic systems seem to be promising candidates for biological responses since they incorporate both indole and other heterocycles moieties simultaneously.

Recently, the synthetic utility of indium(III) Lewis acids in organic synthesis[9–11] has received great attention due to their relatively low toxicity, their stability in air and water at ambient temperature, and the fact that they can be handled safely without any apparent toxicity.

Guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biological profile remarkably, we continued our work on the synthesis of novel heterocycles[12] employing domino protocols. Recently, Shestopalov et al.[13] reported the synthesis of spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-ones via one-pot, two-step reaction of isatin, hydrazine, malanonitile, and β-keto ester catalyzed by Et_3N.

Considering the above reports, the development of new and simple synthetic methods for the efficient preparation of the spiroxindoles will be a beneficial and interesting challenge as a part of our research study, which aims to develop new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds.[14] In this paper, we report a rapid, one-pot synthesis of spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-one derivatives through domino Knoevenagel condensation–Michael addition–intramolecular O-cyclization sequence of reactions in a single step with improved efficiency allowing the rapid isolation of products. In addition, we describe the optimum reaction conditions in terms of rate and yield.

Initial reaction was carried out with isatin **1**, pyrazole **2**, and (*E*-)-*N*-methyl-1-(methylthio)-2-nitroethanamine (NMSM, **3**) leading to the formation of spiroxindole **4a** (Scheme 1). This reaction was chosen as model reaction to investigate the feasibility of the strategy and to optimize the reaction conditions (Table 1). To begin with, the reaction was performed in the absence of base in ethanol which failed to yield the product even after eight hours either at ambient temperature or reflux conditions. When this reaction was tested in the presence of bases such as pyridine, pyrrolidine, piperidine, L-proline, DBU, K_2CO_3, Na_2CO_3, NaOH, and DMAP in refluxing ethanol traces of **4a** were obtained at longer reaction time, but in the presence of DABCO, **4a** was obtained in 70% yield at three hours.

The feasibility of the reaction was further examined with various Lewis acids, such as $SnCl_2{\cdot}2H_2O$, $PTSA{\cdot}H_2O$, $FeCl_3$, $In(OTf)_3$, $AlCl_3$, and $BiCl_3$ in refluxing ethanol but these Lewis acids could not promote the reaction efficiently even after prolonged reaction times (Table 1). In the presence of indium trichloride in ethanol, **4a** was ob-

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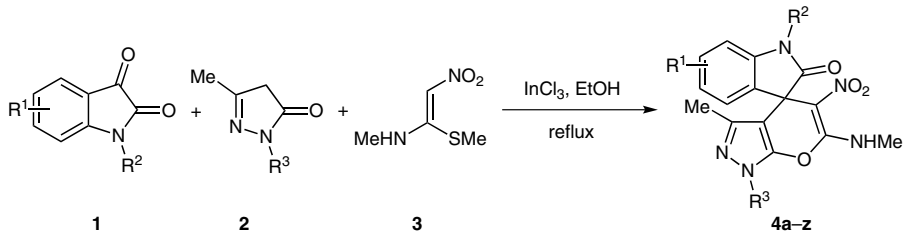


Scheme 1 Synthesis of spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-one derivatives **4a**–**z**

tained in 94% yield (Table 1, entry 12). Subsequently, in effect of solvents (EtOH, MEOH, and MeCN) and catalyst loading, 5 mol%, 10 mol%, 15 mol%, 20 mol%, and 25 mol% of indium trichloride were tested, respectively.

Table 1 Optimization of the Reaction Conditions

Entry	Catalyst (mol%)	Time (h)	Yield (%)[a,b]			
			MeOH	EtOH	MeCN	Neat
1	$InCl_3$ (20)	10	70	92	50	30
2	$SnCl_2·2H_2O$ (20)	10	10	25	15	10
3	$PTSA·H_2O$ (20)	10	20	10	10	trace
4	$BiCl_3$ (20)	10	15	10	trace	trace
5	$AlCl_3$ (20)	10	20	30	10	30
6	$FeCl_3$ (20)	10	25	5	trace	12
7	$In(OTf)_3$ (20)	10	20	10	20	35
8	$InCl_3$ (15)	10	50	80	45	30
9	$InCl_3$ (10)	10	45	60	30	20
10	$InCl_3$ (5)	10	30	40	25	15
11	$InCl_3$ (25)	10	70	92	45	25
12	$InCl_3$ (20)	7	72	94	52	35
13	$InCl_3$ (20)	5	65	85	40	20
14	$InCl_3$ (20)	3	65	70	35	15

[a] The reaction was performed with isatin **1** (1 mmol), pyrazole **2** (1 mmol), NMSM (**3**, 1 mmol), catalyst, reflux.
[b] Isolated yields.

The results summarized in Table 1 show that 20 mol% loading of indium trichloride was optimal. Higher amounts of indium trichloride did not lead to significant change in the reaction yields (Table 1, entry 11). From the data in Table 1, ethanol was found to be the ideal solvent for the domino reaction which afforded the maximum yield of **4a** (94%, Table 1, entry 12). From the above results, indium trichloride emerged as the ideal choice of Lewis acid for these domino reactions. Further, the product was precipitated in the reaction vessel and hence no column chromatographic purification was required. After completion of the reaction the product was filtered and washed with ethanol to obtain pure **4a**.

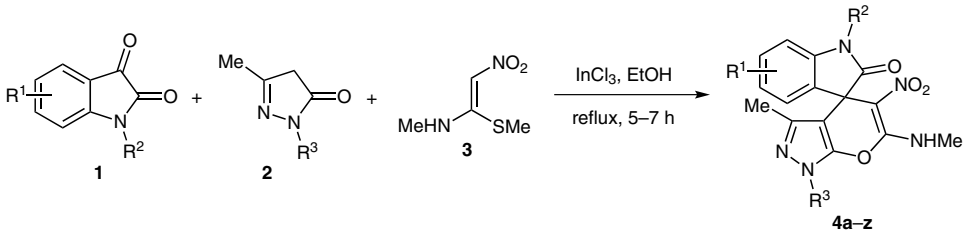
The optimal conditions thus established were then applied to the synthesis of novel spiroxindoles via the one-pot, three-component domino reaction of isatin **1**, pyrazole **2**, and NMSM (**3**), respectively (Table 2). A total of 26 novel spiroxindoles were synthesized[15] in excellent yields. To the best of our knowledge, there is no report on the synthesis of spiroxindoles through the MCR of isatin, pyrazole, and NMSM. Therefore, such a synthesis can be considered as a powerful and practical method for the preparation of a new class of pyrazoles and NMSM-fused isatin heterocyclic derivatives.

On the basis of the above results a plausible mechanism for the formation of spiroxindole is proposed in Scheme 2. The first step is the Knoevenagel condensation between active methylene compound **2** and spiroxindole **1** that leads to the adduct **5**, which acts as a Michael acceptor.

The adduct **5** immediately undergoes Michael-type addition with NMSM (**3**) to generate the open-chain intermediate **6**. The intermediate **6** undergoes intramolecular O-cyclization via path I to give compound **6** with elimination of MeSH. The intermediate **6** may exist in another tautomeric form **6′** which could undergo N-cyclization via path II to give compound **4′**. During our investigations, we did not observe even traces of **4′** and only **4** was obtained exclusively, suggesting O-cyclization through route I, making the protocol highly chemo and regioselective. The scope of the reaction was further studied with various isatin derivatives under optimized conditions. All the reactions proceeded smoothly to provide spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-one derivatives **4a**–**z** in good yields (80–94%). The results are summarized in Table 2. The structures of the products were identified by their FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic and mass spectrometric data. Furthermore, the structure was finally ascertained by single-crystal X-ray diffraction data (Figure 1).[16] Compound **4b** (CCDC-964326, Figure 1) crystallized in the monoclinic space group *P*2(1)/*c* with the following unit cell parameters $a = 10.7871(18)$ Å, $\alpha = 90°$, $b = 20.851(3)$ Å, $\beta = 99.028(5)°$, $c = 8.0231(13)$ Å, $\gamma = 90°$.

In summary, we have demonstrated a simple and efficient route for the one-pot, three-component synthesis of spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-one derivatives regioselectively in almost quantitative yields using readily available starting materials. It is noteworthy that this domino reaction results in the formation of three new

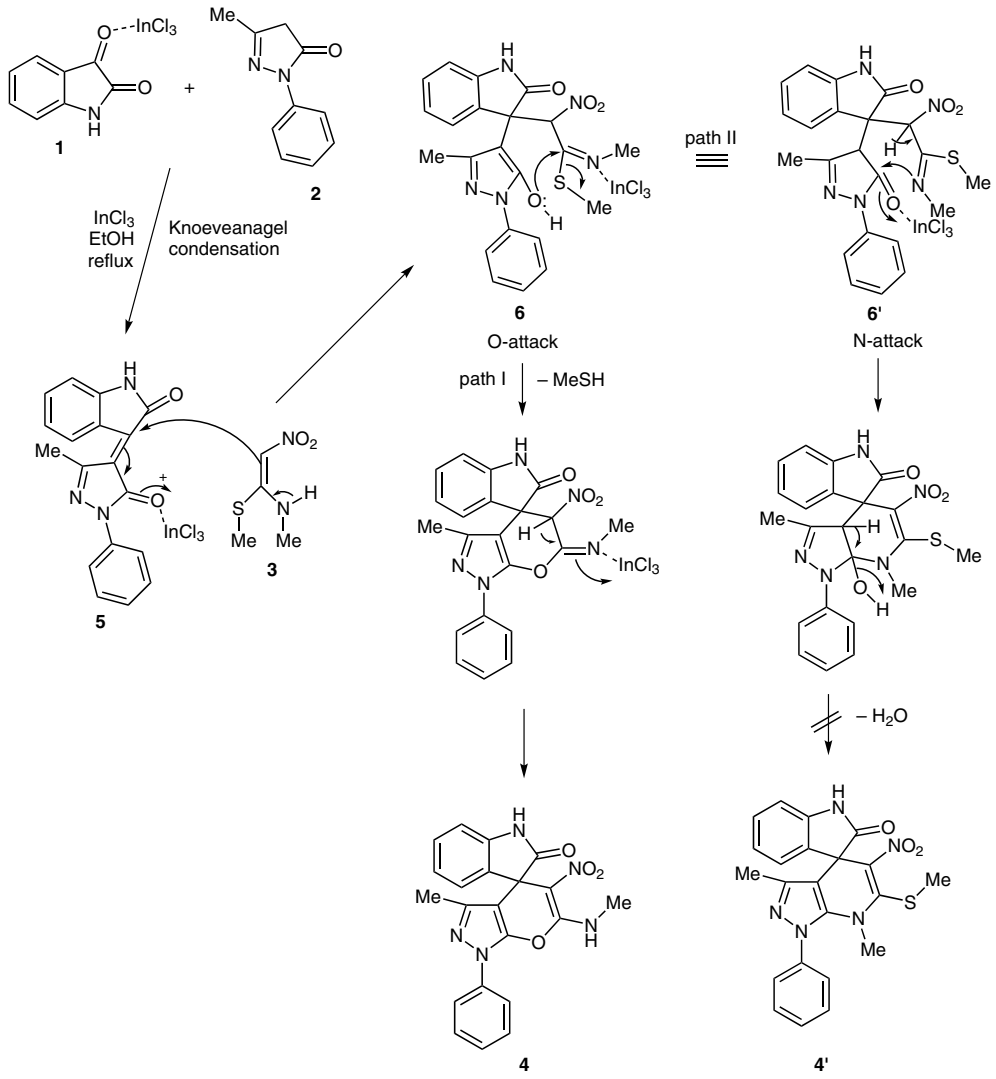
Table 2 Synthesis of Spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-one Derivatives by One-Pot, Three-Component Reactions



Entry	R^1	R^2	R^3	Time (h)	Yield (%)[a–c]	Product **4**
1	H	H	Ph	6	94	**4a**
2	Cl	H	Ph	7	90	**4b**
3	Br	H	Ph	5.5	92	**4c**
4	NO_2	H	Ph	6.5	88	**4d**
5	Me	H	Ph	6	85	**4e**
6	H	Me	Ph	7	89	**4f**
7	H	Et	Ph	7	84	**4g**
8	H	All	Ph	6.5	86	**4h**
9	H	propargyl	Ph	7	90	**4i**
10	H	Bn	Ph	5	93	**4j**
11	F	H	Ph	6	80	**4k**
12	Cl	Me	Ph	7	85	**4l**
13	Cl	propargyl	Ph	6.5	89	**4m**
14	Cl	Et	Ph	6	84	**4n**
15	NO_2	Et	Ph	7	91	**4o**
16	Cl	Bn	Ph	5	87	**4p**
17	H	H	H	6	90	**4q**
18	Cl	H	H	5	92	**4r**
19	NO_2	H	H	6.5	89	**4s**
20	Me	H	H	5	94	**4t**
21	H	propargyl	H	5.5	93	**4u**
22	Cl	Me	H	5	92	**4v**
23	H	Et	H	6	88	**4w**
24	Cl	propargyl	H	5	92	**4x**
25	Br	propargyl	H	7	88	**4y**
26	Br	Bn	H	5.5	90	**4z**

[a] The reaction was performed with isatin **1** (1 mmol), pyrazole **2** (1 mmol), NMSM (**3**, 1 mmol), $InCl_3$ (0.20 mmol), EtOH (3 mL), reflux.
[b] Reaction progress was followed by TLC analysis.
[c] Yields of isolated products.

bonds (two C–C and one C–O) in a single operation. The significant features of this method are simple practical workup, high yields of the products, operational simplicity, and no column chromatographic purification as the product is obtained in pure form just by filtration. Further investigations pertaining to the synthesis of several other novel heterocycles using (*E*)-*N*-methyl-1-(methylthio)-2-nitroethanamine are currently in progress in our lab.



Scheme 2 Proposed mechanism for the domino reaction

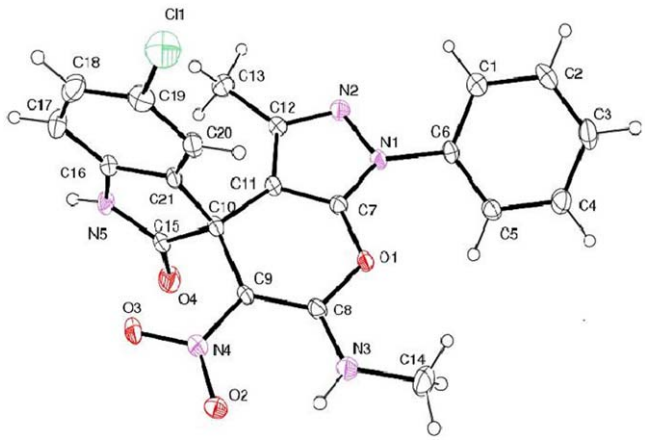


Figure 1 The molecular structure of **4b**

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(15) **General Procedure for the Preparation of Spiro(indoline-3,4′-pyrano[2,3-*c*]pyrazol)-2-one Derivatives by a One-Pot, Three-Component Reaction of Isatin, Pyrazole, and NMSM**

A mixture of isatin **1** (1 mmol), pyrazole **2** (1 mmol), NMSM (**3**, 1 mmol), and $InCl_3$ (0.20 mmol) in EtOH (3 mL) were charged in a 25 mL round-bottomed flask, and the mixture was heated at reflux. The resulting solution was stirred for 5–7 h. The consumption of the starting material was monitored by TLC. The precipitated solid was filtered, washed with EtOH (5–7 mL), and dried under vacuum to obtain pure **4a**–**z** in good yields (80–94%). The identities of products **4a**–**z** were confirmed by FTIR, NMR, and ESI-Mass, giving good agreement with the assigned structures.

Compound **4a**: white solid, 94%; mp 275–278 °C. IR (KBr): ν = 3356, 2344, 1725, 1652, 1130, 1068, 924.91, 753.0 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.78 (br S, 1 H, NH), 10.75–10.76 (d, 1 H, *J* = 4.96 Hz, NH), 7.75–7.77 (d, 2 H, *J* = 8.04 Hz, ArH), 7.53–7.57 (t, 2 H, *J* = 7.78 Hz, ArH), 7.36–7.40 (t, 1 H, *J* = 7.38 Hz, ArH), 720–7.24(t, 1 H, *J* = 7.64 Hz, ArH), 7.13–7.15 (d, 1 H, *J* = 7.28 Hz, ArH), 6.91–6.95 (t, 2 H, *J* = 7.62 Hz, ArH), 3.20–3.21 (d, 3 H, *J* = 4.72 Hz, $NHCH_3$), 1.63 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.5, 159.5, 144.6, 142.9, 142.9, 137.2, 132.1, 130.0, 128.8, 127.5, 123.6, 122.4, 121.1, 109.7, 107.5, 98.3, 50.0, 36, 29, 15, 12.0 ppm. ESI-MS: *m/z* = 404.07 $[M + 1]^+$.

Compound **4q**: white solid, 90%; mp >350 °C. IR (KBr): ν = 3275, 1708, 1647, 1467, 1355, 1171, 1054, 1020, 921, 738 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.5 (br s, 1 H, NH), 10.7 (br s, 1 H, NH), 10.6 (s, 1 H, NH), 7.15–7.19 (t, 1 H, *J* = 7.52 Hz, ArH), 6.90–7.00 (d, 1 H, *J* = 7.36 Hz, ArH), 6.87–6.90 (t, 2 H, *J* = 6.72 Hz, ArH), 3.17 (br s, 3 H, $NHCH_3$), 1.61 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.8, 160.5, 153.7, 142.7, 136.0, 132.7, 128.5, 123.6, 122.36, 109.60, 107.35, 96.70, 49.54, 28.90, 9.36 ppm. ESI-MS: *m/z* = 328.50 $[M + 1]^+$.

(16) Crystallographic data for compound **4b** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC-964326. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)762911 or e-mail: deposit@ccdc.cam.ac.uk].

