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# An Efficient One-Pot Multicomponent Synthesis of Spirooxindole Derivatives

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**ABSTRACT**

*The development of efficient and versatile catalytic system for one-pot multicomponent reaction is one of the active ongoing research areas for further improvement towards milder reaction conditions. In this context, we report here in Boron trifluoride diethyl ether ($BF_3$-$Et_2O$) as a convenient and readily available catalyst for the synthesis of spirooxindole derivatives in satisfactory yields. This new protocol has the advantages of environmental friendliness, higher yields, shorter reaction times, low cost, and convenient operation.*

**Keywords**: Multicomponent reactions; Multi-step synthesis; Spirooxindoles; $BF_3$-$Et_2O$; Isatin

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## INTRODUCTION

Multicomponent reactions (MCRs) allow the formation of several bonds in one-step and easy operation to offer rapid access to drug-like molecules with greater efficiency, lower costs and atom economy [1] that are among the major challenges in organic synthesis in recent years. Consequently, synthetic strategies consisting MCRs, in which three or more reagents are brought together in a one-pot version, have emerged as a uniquely powerful tool in accessing novel and structurally complex products from easily available and simple starting materials. Taking into account the high reactivity [2] and easy its availability, isatin and its derivatives have been used as key building blocks in many different and elegant MCRs for the synthesis of various heterocyclic and spiro-heterocyclic products [3] among which we can find spirooxindole derivatives which possess variety of biological activities such as antibacterial and antifungal activities [4]. Furthermore, the spirooxindole structure is animportant pharmacophore in medicinal chemistry [5], hence, there has been significant interest in developing new methods for the construction of spirooxindoles from researchers working in both synthetic and medicinal chemistry [6-9].

In continuation of our investigation and development towards MCRs for the preparation of heterocyclic compounds [10,11], and considering the interesting biological properties and complex architecture of spirocyclic oxindoles, we wish to report, herein, the synthesis of series of spirooxindole derivatives, via the three-component reaction of isatin, malononitrile or cyanoacetic esters, and 1,3-dicarbonyl compounds in the presence of $BF_3$-$Et_2O$ as a novel and efficient catalyst.

## EXPERIMENTAL SECTION

### Materials and Reagents

All products are known compounds and were characterized by comparison of their physical and spectroscopic data with those of authentic samples. Melting points were measured using a fine control Electro thermal capillary apparatus and are uncorrected. IR spectra were obtained as KBr pellets with a Shimadzu FT IR-8201 PC spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded in DMSO-$d_6$ and/or $CDCl_3$ on a Bruker Avance DPX spectrometer. Chemical shifts (δ) are reported in ppm and *J* values in hertz (Hz).

**General Procedure for the Synthesis of Spirooxindol Derivatives (4a-i)**

A mixture of isatin derivative (1.0 mmol), malononitrile or ethyl cyanoacetate (2a-b) (1.0 mmol), 1,3 diketone (3a-b) (1.0 mmol) and $BF_3$. $Et_2O$ (10 mol%) in $H_2O$/EtOH (10 ml, 1/1) was stirred at 80°C for an appropriate time. Upon completion of the reaction as indicated by TLC (3:2; EtOAc: pet. ether), the reaction mixture was allowed to cool to room temperature, poured upon ice cold water and stirred for 10 minutes. The solid formed was filtered off and washed with water and cold ethanol to afford the desired products (4), which were purified by recrystallization from ethanol. The structures of all the prepared products were unambiguously established on the basis of their spectral analysis (IR, $^1$H&$^{13}$C NMR) and melting points (Figure 1).

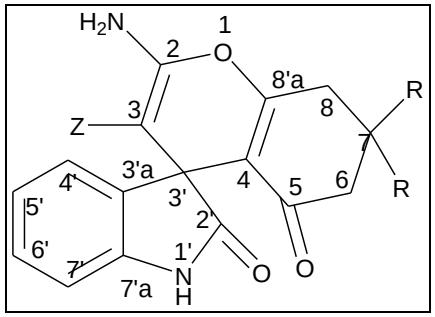



**Figure 1: Spirooxindol derivative**

**2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4a)**:

White solid; yield: 95%; mp: › 300°C (lit. 307-308°C); IR cm$^{-1}$: 3359 (NH), 3155 ($NH_2$), 2256 (CN), 1733 (CO); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 1.00 (s, 3H, $CH_3$), 1.02 (s, 3H, $CH_3$), 2.05 (d, *J* = 16.1 Hz, 1H, $CH_AH_B$), 2.17 (d, *J* = 15.8 Hz, 1H, $CH_AH_B$), 2.50 (s, 2H, $CH_2$), 6.79 (d, *J* = 7.6 Hz, 1H, CH aromatic), 6.85 (d, *J* = 7.3 Hz, 1H, CH aromatic), 6.93 (t, *J* = 6.2 Hz, 1H, CH aromatic), 7.11 (t, *J* = 6.8 Hz, 1H, CH aromatic), 7.00 (s, 2H, $NH_2$), 10.35 (s, 1H, NH); $^{13}$C NMR (62.9 MHz, DMSO-$d_6$-$CDCl_3$): δ 25.7 ($CH_3$), 26.5 ($CH_3$), 30.4 (C-7), 48.7 (C-8, C-3'), 56.2 (C-3), 107.8 (C-4), 118.40 (CN), 120.00, 121.4, 126.54, 132.80, 140.53 (C-7'a), 157.30 (C-8a), 162.36 (C-2), 176.70 (C=O, amide), 193.10 (C=O).

**2-amino-7-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4b):**

White solid, yield: 82% ; mp: 296-298°C (lit. 291-293°C); IR cm$^{-1}$: 3309 (NH), 3139 ($NH_2$), 2252 (CN), 1720 (CO); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 1.00 (s, 3H, $CH_3$), 1.09 (s, 3H, $CH_3$), 2.05 (d, 1H, *J* = 16.2 Hz ,$CH_ACH_B$), 2.18 (d, 1H, *J* = 16.1 Hz, *C*$H_ACH_B$), 2.40-2.52 (m, 2H, $CH_2$), 6.66 (s, 2H, $NH_2$), 6.81-7.12 (m, 3H, CH aromatic), 10.60 (s, 1H, NH).

**2-amino-5-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4c):**

White solid; yield: 64%; mp: 290-292°C (lit. 293-295°C); IR cm$^{-1}$: 3371 (NH), 3155.3 ($NH_2$), 2191 (CN), 1724 (CO); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 1.00 (s, 3H, $CH_3$) 1.01 (s, 3H, $CH_3$), 2.10 (s, 2H, $CH_2$), 2.40-2.6.0 (m, 2H, $CH_2$), 6.78 (d, *J* = 8.2 Hz, 1H, CH aromatic), 6.92 (s, 1H, CH aromatic), 7.00 (s, 2H, $NH_2$), 7.10 (dd, *J* = 1.3, 8.0 Hz), 10.50 (s , 1H, NH)**.**

**2-amino-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4d):**

White solid; yield: 67%; mp: › 300°C (lit. 312-313°C); IR cm$^{-1}$: 3382 (NH), 33217 ($NH_2$), 1724 (CO); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 1.90 (m, 2H, $CH_2$), 2.22 (m, 2H, $CH_2$), 2.65 (m, 2H, $CH_2$), 6.80 (d, *J* = 7.6 Hz, 1H, CH aromatic), 6.89 (t, *J* = 7.4 Hz, 1H, CH aromatic), 7.02 (d, *J* = 7.2 Hz, 1H, CH aromatic), 7.15 (td, *J* = 1.3, 7.5 Hz, 1H, CH aromatic), 7.23 (s, 2H, $NH_2$), 10.40 (s, 1H, CH aromatic); $^{13}$C NMR (62.9 MHz, DMSO-$d_6$-$CDCl_3$): δ 19.92, 26.86, 36.5, 47.01, 57.62, 109.3, 111.97, 117.5 (CN), 121.82, 123.33, 128.29, 134.66, 142.08, 158.77, 166.23 (C=O, ester), 178.30 (C=O amide), 195.20 (C=O).

**Ethyl-2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxylate (4e):**

White solid; yield: 72%; mp: 284-286°C (lit. 279-281°C), IR cm$^{-1}$: 3367 (NH), 3178 ($NH_2$), 1681(CO); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 0.81 (t, 3H, $CH_3$), 0.95 (s, 3H, $CH_3$), 1.10 (s, 3H, $CH_3$), 2.10 (d, *J* = 15.3, 1H, $CH_ACH_B$), 2.17 (d, *J* = 15.6 Hz, 1H, $CH_ACH_B$), 2.52 (m, 2H, C$H_2$), 3.7 (m, 2H, $CH_2$), 6.68 (d, *J* = 7.5 Hz, 1H, CH aromatic), 6.70-6.89 (m, 2H, CH aromatic), 7.05 (t, *J* = 6.9 Hz, 1H, CH aromatic), 7.88 (s, 2H, $NH_2$), 10.25 (s, H, NH); $^{13}$C NMR (62.9 MHz, DMSO-$d_6$-$CDCl_3$): *δ* 13.20 ($CH_3$), 26.81 ($CH_3$), 27.9. ($CH_3$), 31.71 (C-7), 46.72 (C-3'),

50.80 (C-6), 59.01 ($CH_2$), 76.41 (C-3), 108.30 (C-4), 113.18, 120.73, 122.38, 127.34, 144.10 (C-7'a), 159.20 (C-8a), 162.61 (C-2), 167.8. (C=O, ester), 180.00 (C=O, amide), 194.90 (C=O).

**Ethyl-2-amino-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxylate (4f):**
Brown solid; yield: 62%; mp: 268-270°C (lit. 262-264°C); IR $cm^{-1}$: 3359 (NH), 3155 ($NH_2$), 1720 (CO); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 0.9 (t, *J* = 7.1 Hz, 3H, $CH_3$), 1.90 (t, *J* = 5.5 Hz, 2H, $CH_2$), 2.20 (d, *J* = 5.7 Hz, 2H, $CH_2$), 2.52 (m, 2H, $CH_2$), 3.70 (m, 2H, $CH_2$), 6.67 (d, *J* = 7.6 Hz, 1H, CH aromatic), 6.75 (d, *J* = 7.3 Hz ,1H, CH aromatic), 6.81 (d, *J* = 6.6 Hz, 1H, CH aromatic), 7.00 (t, *J* = 7.4 Hz, 1H, CH aromatic), 7.65 (s, 2H, $NH_2$), 10.05 (s, 1H, NH).

**Ethyl-2-amino-5'-chloro-7,7-dimethyl-2',5-dioxo-5,6,7,8 tetrahydrospiro[chromene-4,3'-indoline]-3-carboxylate (4g):**
White solid; yield: 72%; mp: 295-29°C (lit. 292-293°C); IR $cm^{-1}$: 3359 (NH), 3182 ($NH_2$), 1701 (CO); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 0.90 (t, *J* = 7.0 Hz, 3H, $CH_3$), 1.00 (s, 3H, $CH_3$), 1.01 (s, 3H, $CH_3$), 2.10 (m, 2H, $CH_2$), 2.50 (m, 2H, $CH_2$), 3.80 (m, 2H, $CH_2$), 6.65 (d, *J* = 8.1 Hz, 1H, CH aromatic), 6.78 (s, 1H, CH aromatic), 7.00 (d, *J* = 7.9 Hz, 1H, CH aromatic), 7.66 (s, 2H, $NH_2$), 10.20 (s, 1H, NH); $^{13}$C NMR (62.9 MHz, DMSO-$d_6$-$CDCl_3$): δ 14.0 (**C**$H_3$), 27.9 ($CH_3$), 28.3 ($CH_3$), 32.4 ($CH_2$), 40.3, 51.4 ($CH_2$), 59.8 ($CH_2$), 110.2, 113.3, 123.2, 125.2, 127.8, 139.0, 144.0, 160.0, 163.7, 168.3 (C=O, ester), 180.4 (C=O, amide), 195.7 (C=O).

**Ethyl-2-amino-5-chloro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxlate (4h):**
White solid; yield: 70%; mp: 280-282°C (lit. 271-273°C); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 0.80 (t, *J* = 7.0 Hz, 3H, $CH_3$), 1.90 (m, 2H, $CH_2$), 2.20 (m, 2H, $CH_2$), 2.60 (m, 2H, $CH_2$), 3.70 (m, 2H, $CH_2$), 6.67 (t , *J* = 8.6 Hz, 1H, CH aromatic), 6.82 (d, *J* = 8.3 Hz, 1H, CH aromatic), 6.89 (d, *J* = 8.1 Hz, 1H, CH aromatic), 7.70 (s, 2H, $NH_2$), 10.20 (s, 1H, NH).

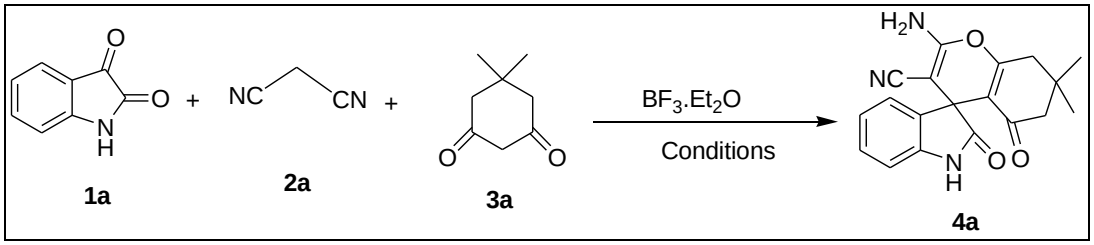
**2-amino-5-chloro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4i):**
White solid; yield: 89%; mp: ›300°C (lit. 293-294°C); $^1$H NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): δ 1.95 (d, *J* = 5.2 Hz, 2H, $CH_2$), 2.25 (d, *J* = 5.2 Hz, 2H, $CH_2$), 2.70 (m, 2H, $CH_2$), 6.82 (dd, *J* = 2.4, 8.2 Hz, 1H, CH aromatic), 7.02 (m, 1H, CH aromatic), 7.12 (d, *J* = 2.4 Hz, 1H, CH aromatic), 7.16 (s, 2H, $NH_2$), 10.55 (s, 1H, NH).

## RESULTS AND DISCUSSION

### Synthesis and Characterization

The catalytic behaviour of $BF_3.Et_2O$ was studied for the synthesis of 3-spirochromene-2-oxindole (4a). Thus, the model reaction of isatin (1a), malononitrile (2a) and 5,5-dimethyl-1,3-cyclohexanedione (3a) was carried out in the presence of different amounts of $BF_3.Et_2O$ under different conditions. The screening of the various optimized parameters for the model reaction (Table 1), showed that water/EtOH (10 ml, 1/1) was a solvent of choice and 10 mol% of the catalyst was sufficient to afford the desired product in excellent yield (Table 1, entry 6). Notably, the desired product could not be obtained under similar reaction conditions, even after longer time (4hours) in the absence of the catalyst (Table 1, entry 7).

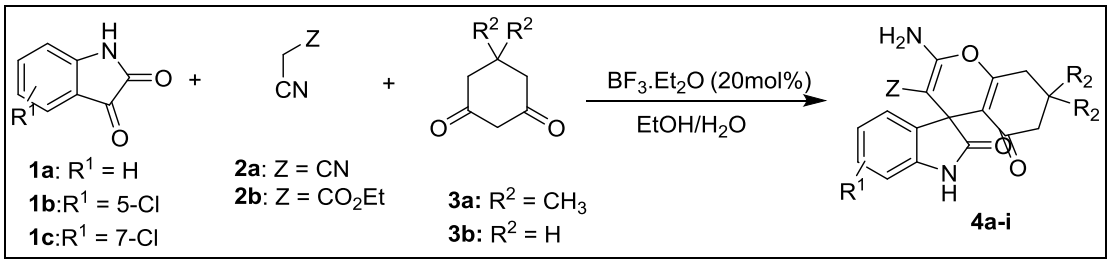
**Table 1: Optimisation of the reaction conditions**



| Entry | Solvent | Ctalyst (mol%) | Temperature (°C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 10 | Reflux | 24 | / |
| 2 | THF | 10 | Reflux | 24 | / |
| 3 | EtOH | 10 | Reflux | 12 | 32 |
| 4 | $H_2O$ | 10 | Reflux | 4 | 81 |
| 5 | $H_2O$/EtOH | 10 | r. t | 24 | 50 |
| 6 | EtOH/$H_2O$ | 10 | 80 | 2 | 95 |
| 7 | EtOH/$H_2O$ | none | 80 | 4 | traces |
| 8 | EtOH/$H_2O$ | 5 | 80 | 2.5 | 85 |
| 9 | EtOH/$H_2O$ | 15 | 80 | 3 | 87 |
| 10 | EtOH/$H_2O$ | 20 | 80 | 2 | 93 |
| 11 | EtOH/$H_2O$ | 30 | 80 | 2 | 89 |

[a]Isolated yields

Encouraged by this preliminary result and to examine the efficiency and applicability of the present protocol, the reaction was extended to other substituted isatin (1a-c), cyanoacetic acid derivatives (2a-b) and 1,3-dicarbonyl compounds (3a-b) (Scheme 1). All the reaction proceeded well to afford respective 3-spirochromene-2-oxindoles in good yields (Table 2, 4a-i), but better ones are obtained when using both of diethyl malonate and dimedone as stating materials. The results, summarized in Table 2, are significant in terms of yields and product purity in all cases when $BF_3.Et_2O$ was used as catalyst, whereas without $BF_3.Et_2O$, the reactions may need very long period of time to complete (Table 1, entry7).




**Scheme 1: Synthesis of spirooxindole derivatives**

**Table 2: Physical data of the prepared spirooxindole derivatives * (4a-i)**

| Entry | $R^1$ | Z | ketone | Product[a] | Time (h) | Yield[b] (%) | Mp (°C) found | Mp (°C) reported[ref] |
|---|---|---|---|---|---|---|---|---|
| 1 | H | CN | 3a | 4a | 2 | 95 | › 300 | 305–307 [12] |
| 2 | 7-Cl | CN | 3a | 4b | 0.5 | 82 | 296-298 | 291-293 [13] |
| 3 | 5-Cl | CN | 3a | 4c | 1 | 64 | 290-292 | 293-295 [13] |
| 4 | H | CN | 3b | 4d | 15 | 67 | › 300 | 312-313 [12] |
| 5 | H | $CO_2Et$ | 3a | 4e | 3 | 72 | 284-286 | 279-281 [13] |
| 6 | H | $CO_2Et$ | 3b | 4f | 6 | 62 | 268-270 | 262-264 [14] |
| 7 | 5-Cl | $CO_2Et$ | 3a | 4g | 2 | 72 | 295-298 | 292-293 [13] |
| 8 | 5-Cl | $CO_2Et$ | 3b | 4h | 12 | 70 | 280-282 | 271-273 [14] |
| 9 | 5-Cl | CN | 3b | 4i | 1 | 89 | ›300 | 293–294 [15] |

*Reaction conditions: isatin (1.0 mmol), cyanoacetic acid derivatives (1.0 mmol), 1,3-dicarbonyl compounds (1.0 mmo) l, catalyst (10 mol% with respect to isatin), refluxing water/ethanol (10 ml, 1/1); [a]All compounds are well characterized by spectroscopic analyses ; [b]Isolated yields

## CONCLUSION

In conclusion, we have described a highly efficient procedure for the preparation of spirooxindoles using an inexpensive and readily available $BF_3.Et_2O$ as catalyst. Moreover, the procedure offers several advantages including good yields, operational simplicity, cleaner reaction and low cost, which make it a useful and attractive process for the synthesis of such compounds with the minimum use and generation of hazardous substances which complies with the green chemistry philosophy. Development of other uses of $BF_3.Et_2O$ as catalyst in MCRS is ongoing in our laboratory.

## ACKNOWLEDGMENTS

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