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Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

# Indium chloride: a versatile Lewis acid catalyst for the synthesis of 3-sulfenylindoles

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Published online: 31 Jan 2014.

To cite this article: P. Praveen Kumar, Y. Dathu Reddy, Ch. Venkata Ramana Reddy, B. Rama Devi & P.K. Dubey (2014) Indium chloride: a versatile Lewis acid catalyst for the synthesis of 3-sulfenylindoles, Journal of Sulfur Chemistry, 35:4, 356-361, DOI: 10.1080/17415993.2013.879870

To link to this article: http://dx.doi.org/10.1080/17415993.2013.879870

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*Journal of Sulfur Chemistry*, 2014
Vol. 35, No. 4, 356–361, http://dx.doi.org/10.1080/17415993.2013.879870

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# Indium chloride: a versatile Lewis acid catalyst for the synthesis of 3-sulfenylindoles

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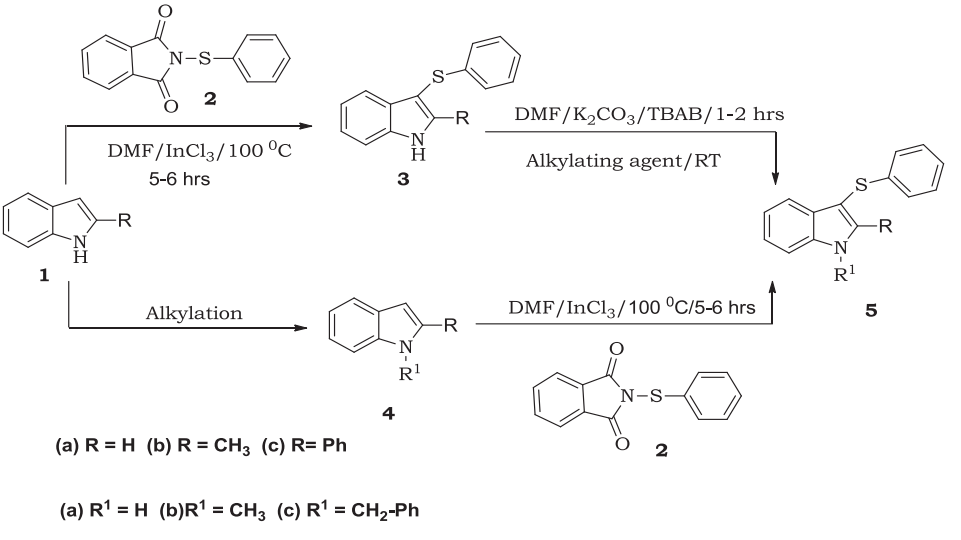
(*Received 20 September 2013; accepted 30 December 2013*)

Indium chloride has been used as a versatile Lewis acid catalyst for the synthesis of 3-sulfenylindoles in good yields by the independent reaction of indoles and N-alkylindoles with *N*-(phenylthio)phthalimide in dimethyl formamide (DMF) at 100°C for about 5–6 h.




**Keywords:** $InCl_3$; sulfenylation; alkylation; *N*-(phenylthio)phthalimide; 3-sulfenylindole

## 1. Introduction

The selective introduction of C–S bond into organic molecules, in particular in heterocycles, has played a significant role in medicinal chemistry.[1–4] 3-Sulfenylindoles are a popular class of compounds for their activity in the treatment of HIV,[5–7] obesity,[5–7] cancer,[5–7] heart diseases [5–7] and allergies.[5–7] Several methods for the preparation of 3-sulfenylindoles

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have been reported [8–26] in recent years. The synthesis of 3-sulfenylindoles included the direct sulfenylation of the indole ring by disulfides,[8–10] quinone mono-O,S-acetals,[11,12] sulfenyl halides,[13,14] N-(arylthio)succinimides,[15] N-(arylthio)phthalimides[16] and activated thiols.[17–23] 3-Sulfenylindoles have also been prepared by palladium-catalyzed annulation of 2-(1-alkynyl)benzenamines with disulfides [24] and by tetra-*n*-butylammonium iodide-induced electrophilic cyclization of the same starting materials with arylsulfenylchlorides.[25,26] On the other hand, 3-substituted indols derivatives are very important compounds as they display various biological and pharmaceuticals activities.[27–29]

At present, many synthetic methods are available for the 3-sulfenylation of indoles.[13,21] Still, it is necessary to develop new methods that avoid the use of toxic and foul-smelling substances, more particularly, the use of sulphenyl chlorides and activated thiols, respectively. Indium chloride is one of the important Lewis acids employed in various chemical transformations over the past few years.

In view of our interest in the synthesis of C–S containing organic compounds [30] and continuation of our earlier work,[31,32] we wish to report electrophilic substitution on indoles at the third position with *N*-(phenylthio)phthalimides using indium chloride as a catalyst.

## 2. Result and discussion

Treatment of indole **1a** with *N*-(phenylthio)phthalimide **2** in the presence of indium chloride as the Lewis acid catalyst in DMF at 100°C for 5 h resulted in the formation of 3-sulfenylindole **3a** in 80% yield. Previously, the product is known in the literature,[13,21] it has been fully characterized in the present work by spectral methods. **3a** was, independently, treated with each of the alkylating agents, DMS and benzyl chloride, in the presence of $K_2CO_3$ (as a base) and TBAB (as a phase transfer catalyst) in DMF for about 1–2 h to obtain the previously reported [6,23] *N*-methyl-3-sulfenylindole **5a** and *N*-benzyl-3-sulfenylindole **5b**, respectively as products.

To find out the optimum conditions for the reaction of **1a** with **2**, the reaction was carried out by treating **1a** with **2** in the presence of $InCl_3$ as catalyst in different solvents (DMF, DMA and Acetonitrile [MeCN]) at different temperatures (Table 1). However, reaction with $InCl_3$ as a catalyst at 100°C for 5 h in DMF gave the best yield (85%) of the product **3a** (Table 1, Entry 3). For finding out the optimum amount of $InCl_3$, the reaction was carried out by changing the concentration of $InCl_3$ as a catalyst (Table 2). Results indicated that 20 mol% (0.2 mmol) $InCl_3$ at 100°C for 5 h in DMF gave the best yield of the product **3a** (80%) (Table 2, Entry 3). Further increase in the amount of indium chloride did not have any significant effect on the product yield.

Table 1. Effect of solvent and temperature on reaction of **1a** and **2** in the presence of 20 mol% $InCl_3$ yielding **3a**.

| Entry | Solvent | Temperature | Time/h | 3a (%) |
|---|---|---|---|---|
| 1 | DMF | RT | 15 | – |
| 2 | DMF | 50 | 12 | 60 |
| **3** | **DMF** | **100** | **5** | **85** |
| 4 | DMF | 140 | 4.5 | 70 |
| 5 | DMA | RT | 15 | – |
| 6 | DMA | 50 | 13 | 60 |
| 7 | DMA | 100 | 7 | 65 |
| 8 | DMA | 140 | 6.5 | 60 |
| 9 | MeCN | RT | 15 | – |
| 10 | MeCN | 50 | 12 | 45 |
| 11 | MeCN | 80 | 8 | 40 |

Table 2. The effect of the amount of $InCl_3$ in the preparation of **3a** from **1a** and **2** in DMF at 100°C.

| Entry | Mol % of $InCl_3$ | Time (h) | 3a (%) |
|---|---|---|---|
| 1 | – | 15 | – |
| 2 | 10 | 10 | 65 |
| **3** | **20** | **5** | **85** |
| 4 | 30 | 4.5 | 80 |
| 6 | 50 | 4.25 | 70 |
| 7 | 100 | 4 | 65 |

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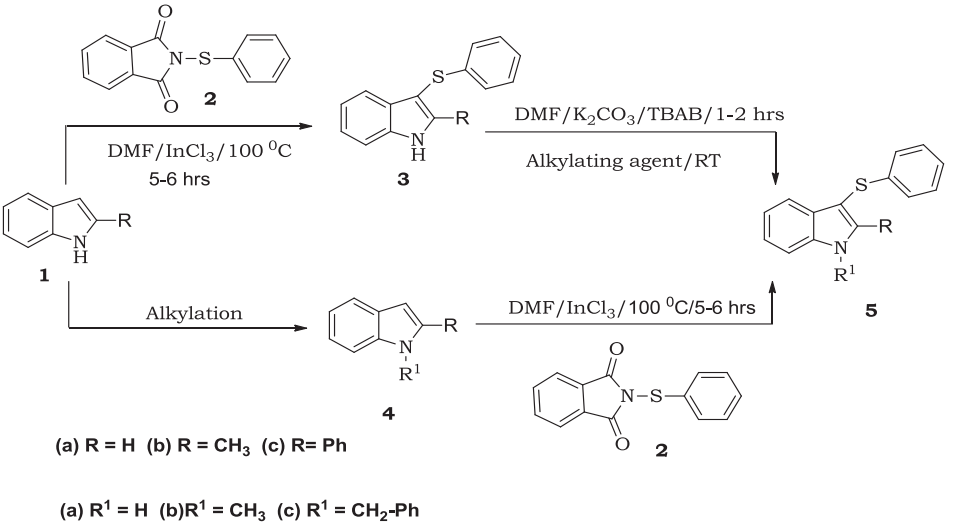
Having optimized the reaction conditions, the generality of the reaction **1a**–**3a** and **3a**–**5a** was established by using different 2-substituted indoles such as 2-methylindole (**1b**) and 2-phenylindole (**1c**) resulting in the formation of 2-substituted-3-sulfenylindoles (**3b–c**) and *N*-alkyl-2-substituted-3-sulfenylindoles (**5c–f**), respectively (for details see Section 4) (Scheme 1).




Scheme 1. Synthesis of 3-sulfenylindoles.

Alternatively, **5** could also be synthesized by the independent reaction of **1** with each of the alkylating agents methyl iodide and benzyl chloride to yield *N*-methyl (**4a**) and *N*-benzyl (**4b**) indoles **4**, respectively, and subsequent treatment of the latter, with *N*-(phenylthio)phthalimide **2** in the presence of 20 mol% (0.2 mmol) indium chloride in DMF at 100°C for about 5–6 h.

## 3. Conclusion

In conclusion, $InCl_3$ has proved to be a useful and efficient Lewis acid for the sulfenylation of indoles at the 3-position. In addition, this method produces 3-sufenylindoles in good yields in reasonable reaction times and provides easy access for the preparation of a range of 3-sulfenylindoles.

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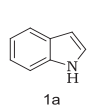
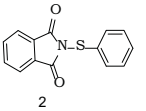
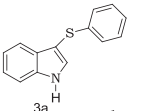
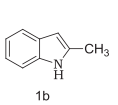
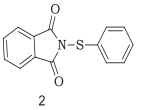
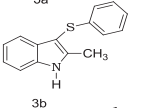
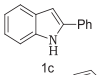
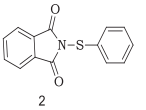
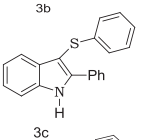
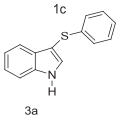
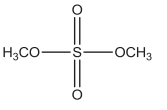
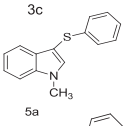
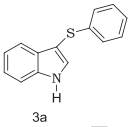
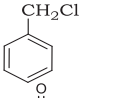
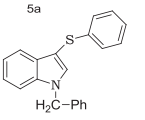
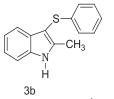
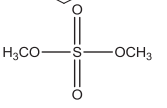
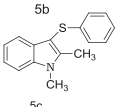
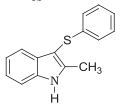
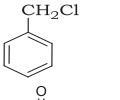
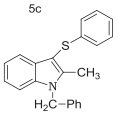
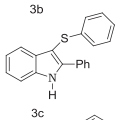
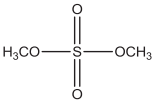
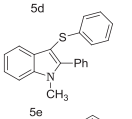
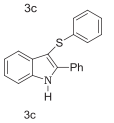
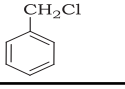
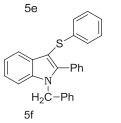
## 4. Experimental section

Melting points are uncorrected and were determined in open capillary tubes in sulfuric acid bath. TLC was run on silica gel-G and visualization was done using iodine or UV light. IR spectra were recorded using a Perkin–Elmer 1000 instrument in KBr pellets. $^1$H NMR spectra were recorded in DMSO-$d_6$ using TMS as internal standard using a 400 MHz spectrometer. Mass spectra were recorded on an Agilent-LCMS instrument. 2-Subtituted indoles and DMF were obtained from commercial sources and used as such.

### 4.1. *General procedure for the preparation of 3 from 1 and 2*

A mixture of **1** (10 mM), **2** (10 mM), $InCl_3$ (20 Mol%) and DMF (20 ml) was heated at 100°C for 5–6 h. The reaction mixture was monitored by TLC for the disappearance of **1**. On completion

Table 3. Characterization data, reaction time and yields of **3** and **5a–e**.

| Entry | Starting material used | | Product obtained | Time (h) | Yield% | M.P (°C) (Lit. M.P °C) |
|---|---|---|---|---|---|---|
| 1 |  1a |  2 |  3a | 5 | 85 | 150–152 (149–151) [13,21] |
| 2 |  1b |  2 |  3b | 5.5 | 85 | 112–114 (110–113) [6] |
| 3 |  1c |  2 |  3c | 6 | 80 | Liquid [6] |
| 4 |  3a |  |  5a | 1 | 82 | 89–91 (86–87) [6] |
| 5 |  3a |  |  5b | 1.5 | 85 | Liquid [2,3] |
| 6 |  3b |  |  5c | 1 | 80 | 116–118 (113–114) [11] |
| 7 |  3b |  |  5d | 1.5 | 83 | 93–95 (94–96) [27] |
| 8 |  3c |  |  5e | 1 | 84 | 108–110 (108) [11] |
| 9 |  3c |  |  5f | 2 | 82 | 90–92 |

of the reaction, the mixture was cooled to RT, diluted with water (50 ml) and extracted with ethyl acetate. The organic layer was separated, washed with a saturated solution of sodium hydrogen carbonate (10 ml) followed by brine and then dried with $Na_2SO_4$. The solvent ethylacetate (EtOAc) was evaporated to give a crude residue, which on purification by silica gel column chromatography (hexane–ethyl acetate, 90:10) gave **3** (Table 3).

### 4.2. *General procedure for the preparation of 5 from 3*

A mixture of **3** (10 mM), alkylating agent (DMS or benzyl chloride) (11 mM), $K_2CO_3$ (10 mM), catalytic amount of TBAB and DMF (20 ml) was stirred at RT for 1–2 h. At the end of this period, the mixture was poured into cold-water (50 ml) and extracted with ethyl acetate. The organic layer was separated, washed with a saturated solution of sodium hydrogen carbonate (10 ml) followed by brine (10 ml) and then dried with $Na_2SO_4$. The solvent EtOAc was evaporated to give a residue of crude **5**. The products were recrystallized from a suitable solvent to obtain pure **5** (Table 3).

### 4.3. *General procedure for the preparation of 5 from 4 and 2*

A mixture of **4** (10 mM), **2** (10 mM), $InCl_3$ (20 Mol%) and DMF (20 ml) was heated at 100°C for 5–6 h. The reaction mixture was monitored by TLC for the disappearance of **4**. On completion of the reaction, the mixture was cooled to RT, diluted with the water (50 ml) and extracted with ethyl acetate. The organic layer was separated, washed with a saturated solution of sodium hydrogen carbonate (10 ml) followed by brine (10 ml) and then dried with $Na_2SO_4$. The solvent was evaporated to obtain a residue which on purification by the silica gel column chromatography (hexane–ethyl acetate, 90:10) gave **5** (Table 3).

## Acknowledgements

Authors are thankful to the authorities of *Jawaharlal Nehru Technological University Hyderabad*, for providing laboratory facilities and for constant encouragement.

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