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The use of anhydrous $CeCl_3$ as a catalyst for the synthesis of 3-sulfenyl indoles

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ABSTRACT

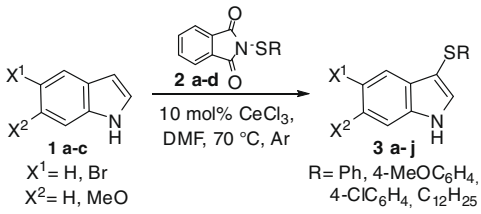
Anhydrous $CeCl_3$ was successfully used as a catalyst for the synthesis of several 3-sulfenyl indoles in good to excellent yields through the reaction of indole with *N*-(alkylthio) and *N*-(arylthio)phthalimides in DMF.

1. Introduction

Indole and its derivatives are widely present in bioactive metabolites of numerous compounds isolated from natural sources.[1] Sulfenyl indoles are an important class of compounds due to their activity towards the treatment of several diseases, such as bacterial infection, HIV, obesity, heart diseases, and allergies.[2] They are also very useful as COX-2 inhibitors in medicinal chemistry[3] and potent inhibitors of tubulin polymerization.[4]

Several approaches for the preparation of 3-sulfenyl indoles were described in the recent years. Most of methods are based on electrophilic aromatic sulfenylation reaction.[5] Nucleophilic substitution on the indole system[6] and electrophilic sulfur cyclization[7] are also known. However, major drawbacks are still present such as accessibility, substrate compatibility, and stability of these reagents. Hence, a mild general approach for the 3-arylthiolation of indoles is still necessary.

Cerium chloride has emerged as a very useful Lewis acid imparting high regio- and chemoselectivity in various chemical transformations over the past few years, as a cheap, nontoxic, and water-tolerant catalyst. It has been used in several different forms, such as heptahydrate, anhydrous, and in combination with NaI.[8] In view of our interest in the development of new, cleaner methods for classical reactions promoted by cerium(III) species and in the organosulfur chemistry,[9] we decide to study the electrophilic substitution reaction of indoles **1** with *N*-(alkylthio) and *N*-(arylthio)phthalimides **2** to obtain 3-sulfenyl indoles **3** (Scheme 1, Tables 1 and 2).



Scheme 1.

Table 1
Optimization of conversion of **1a**–**3a**[a]

Entry	Solvent	$CeCl_3$ (equiv)	Temp (°C)	Time (h)	Yield (%)
1	MeCN	0.1	Reflux	4	43
2	CH_2Cl_2	0.1	Reflux	4	–[b]
3	DMA	0.1	70	3	68
4	DMF	0.1	70	3	88
5	NMP	0.1	70	3	73
6	DMF	0.05	70	3	79
7	DMF	0.2	70	3	88
8	DMF	0.1	rt	10	21
9	DMF	0.1	90	3	88
10	DMF	0.1[c]	70	3	61

[a] Reaction conditions: indole (**1a**, 1.0 mmol); *N*-(phenylthio)phthalimide (**2a**, 1.1 mmol).
[b] No reaction.
[c] Reaction performed with $CeCl_3 \cdot 7H_2O$.

2. Results and discussion

Initially, we chose indole (**1a**) and the commercially available *N*-(phenylthio)phthalimide (**2a**) as starting materials to establish

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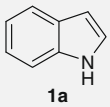
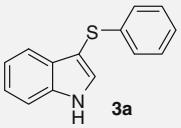
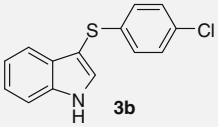
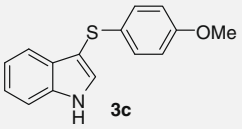
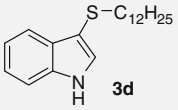
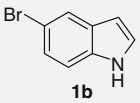
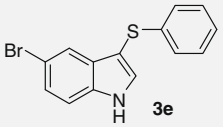
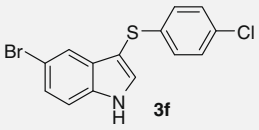
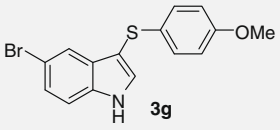
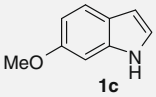
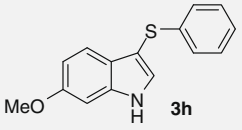
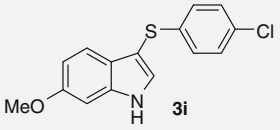
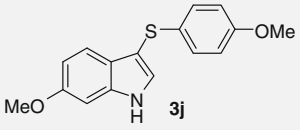
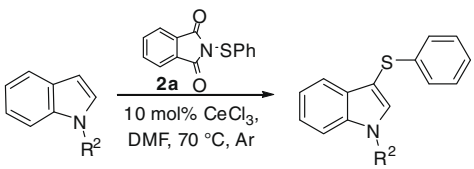
Table 2
Synthesis of 3-sulfenyl indoles **3**

Entry	Indoles **1**	R	Product **3**	Time (h)	Yield[a] (%)
1	 **1a**	Ph	 **3a**	3.0	88
2	**1a**	4-ClC_6H_4	 **3b**	4.0	93
3	**1a**	4-$MeOC_6H_4$	 **3c**	2.0	90
4	**1a**	$C_{12}H_{25}$	 **3d**	3.5	80
5	 **1b**	Ph	 **3e**	3.0	95
6	**1b**	4-ClC_6H_4	 **3f**	4.0	95[b]
7	**1b**	4-$MeOC_6H_4$	 **3g**	3.5	90[b]
8	 **1c**	Ph	 **3h**	2.0	87
9	**1c**	4-ClC_6H_4	 **3i**	1.5	88
10	**1c**	4-$MeOC_6H_4$	 **3j**	4.0	81

[a] Yields of pure products isolated by column chromatography (hexanes/AcOEt) and identified by mp, GC–MS, ^1H and ^{13}C NMR.
[b] Reaction performed in DMA as the solvent.

the best conditions for the reaction. We examined the solvent, amount of $CeCl_3$, and the reaction temperature (Table 1). At first, we found that by using 0.1 equiv of $CeCl_3$, in MeCN, the 3-sulfenyl indole (**3a**) was obtained in 43% yield after stirring under reflux for 4 h (Table 1, entry 1). We also used other solvents, such as dichloromethane, DMF, DMA, and NMP (Table 1, entries 2–5). The best yield was obtained when DMF was used as a solvent (88% isolated yield; Table 1, entry 4). In a search for even higher yield, we replaced anhydrous $CeCl_3$ by $CeCl_3{\cdot}7H_2O$; however, it was observed a reduction in the yield to 61% (Table 1, entry 10). The effect of the amount of the catalyst was also evaluated. When 0.05 equiv of dry $CeCl_3$ was used, **3a** was obtained in 79% yield (Table 1, entry 6). The use of larger amounts of $CeCl_3$ had no effect on the yield of reaction and the time to completion of reaction was the same (Ta-



3k R^2 = Me (60%), **3l** R^2 = Ts (no reaction)

Scheme 2.

ble 1, entry 7). Finally, the reaction was performed at both 90 °C and room temperature. The reaction carried out at 90 °C led to the formation of the desired product in very similar yield to 70 °C. By contrast, a significant decrease in the yield of 3-sulfenyl indole was observed when the reaction was performed at room temperature, even after long reaction time (Table 1, entry 8).

Since the best conditions were established (Table 1, entry 4), the protocol was extended to other *N*-(alkylthio) and *N*-(arylthio)phthalimides,[11] reacting with indole, 5-bromoindole and 6-methoxyindole (Table 2, Scheme 1).[12] For all the studied examples, the 3-sulfenyl indoles **3** were obtained in good to excellent yields after stirring at 70 °C for 1.5–4.0 h (Table 2). When 5-bromo-1*H*-indole (**1b**) was used, the respective brominated products were obtained in slightly higher yields, compared to **1a** (Table 2, entries 5–7). However, when 5-methoxy-1*H*-indole (**1c**) was used, the indole derivatives were obtained in slightly lower yields, compared to **1a** and **1b** (Table 2, entries 8–10). The *N*-(dodecylthio)phthalimide (**2d**) reacted with indole **1a** under the established standard condition to afford, after 3.5 h, 3-(dodecylthio)-1*H*-indole (**3d**) in 80% yield (Table 2, entry 4).

It is worth mentioning that the indole nitrogen need not be protected. In fact, when the reaction was performed with 1-methyl-1*H*-indole and *N*-(phenylthio)phthalimide (**2a**) the corresponding product **3k** was obtained in 60% yield after 5 h, and no reaction was observed when 1-tosyl-1*H*-indole was used even after several hours of reaction (Scheme 2).

In conclusion, we have been able to show that $CeCl_3$ is an effective catalyst for the synthesis of 3-sulfenyl indoles. The method is simple and general for the reaction of *N*-(arylthio)phthalimides with indoles.

Acknowledgments

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11. The *N*-(thio)phthalimides **2b–d** were prepared according to: Gillis, H. M.; Greene, L.; Thompson, A. *Synlett* **2009**, 112.
12. *General procedure for the synthesis of 3-sulfenyl indoles*: To a mixture of DMF (5 mL), indole (**1**, 1.0 mmol), and *N*-thioalkyl or *N*-thioarylphthalimides (**2**, 1.1 mmol), under Ar, was added dry $CeCl_3$ (0.0246 g, 0.1 mmol) at room temperature. The reaction mixture was followed by TLC and stirred at 70 °C for the time indicated on Table 2 and cooled to rt. Water (20 mL) was added and the mixture extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with water, aqueous 2% NaOH solution, and then brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate–hexanes, 5:95) to afford pure products (**3a–j**). Spectral data of selected compounds: **3a** mp 152–154 °C (lit.[10] 151–153 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (br s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.27–7.23 (m, 1H), 7.17–7.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.17, 136.42, 130.67, 129.04, 128.66, 125.76, 124,73, 123.01, 120.87, 119.62, 111.56, 102.70. MS: *m/z* (%) = 225 (M^+, 100), 193 (25), 165 (13), 148 (15), 112 (10), 77 (13); **3b** mp 127–129 °C (lit.[3a] 127.5–128.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (br s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 2.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.28–7.24 (m, 1H), 7.18–7.14 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.81, 136.51, 130.65, 128.73 (2C), 127.12 (2C), 123.21, 121.05, 119.51, 111.63, 102.52. MS: *m/z* (%) = 259 (M^+, 100), 224 (55), 148 (22), 112 (39), 77 (16).