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A rapid synthesis of 3-sulfenyl indoles using Selectfluor™

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Abstract—The direct 3-arylthiolation of indoles with aromatic thiols has been achieved in the presence of Selectfluor™ under mild conditions to produce 3-arylthioindoles in relatively good to excellent yields and with high selectivity. This method is effective even with 2-unsubstituted indoles.

3-Arylthioindoles are very useful as COX-2 inhibitors in medicinal chemistry.[1] These motifs are very common in various drugs for the treatment of HIV, obesity, cancer, heart diseases and allergies.[2,3] Such compounds are generally prepared by means of electrophilic aromatic sulfenylation. The direct 3-arylthiolation of indoles has been reported using various sulfenylating agents such as disulfides, sulfenyl halides, quinone mono-*O*,*S*-acetals and *N*-thioarylphthalimides.[4–6] However, most of these methods are often impractical due to the instability, scarcity and incompatibility of the reagents and the formation of bis-sulfides and chlorinated by-products. Sulfenylations of indoles with thiols activated in situ by *N*-chlorosuccinimide, phenyliodine(III)bistrifluoroacetate and transition metal catalysts have been reported under mild conditions.[1,7] Some of these methods are only useful for sulfenylation of 2-carboxyindoles. Therefore, the development of a simple, convenient and general methodology for the sulfenylation of indoles utilizing a stable and readily available reagent would extend the scope of this reaction for the possible discovery of new selective COX-2 inhibitors.

Recently, Selectfluor™ [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate)], has been introduced commercially as a user-friendly electrophilic fluorinating agent (Fig. 1).[8] It is a commercially available, stable, non-volatile, non-hygroscopic, and easy to handle solid and is widely used for site-selective fluorination of a variety of carbonyl compounds. Selectfluor™ is one of the most popular electrophilic fluorinating agents and is also recognized as a convenient mediator of several 'fluorine free' functionalizations of organic compounds.[9] These reactions are based on the fact that F–TEDA–BF_4 has considerable oxidative power, being one of the strongest in the family of N–F reagents. However, investigations taking advantage of this property are scarce[10] and there have been no examples of the use of Selectfluor™ for the electrophilic thiolation of indoles.

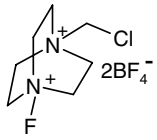

Figure 1.

In this Letter, we report a simple and efficient protocol for 3-sulfenylation of indoles using Selectfluor™. Initially, we attempted the sulfenylation of indole (**1**) with thiophenol (**2**) using a stoichiometric amount of Selectfluor™. The reaction went to completion within 20 min at room temperature and the product, 3-phenylthioindole **3a**, was obtained in 96% yield (Table 1, entry a, Scheme 1).

Encouraged by this result, we turned our attention to various indoles and thiols. Interestingly, substituted indoles such as 5-bromo-, 5-methoxy-, 7-ethyl-, and 2-methylindole, reacted rapidly with thiophenol to afford the corresponding 3-arylthioindole derivatives (Table 1, entries b–e). In addition, *N*-benzylindole also participated in this reaction (Table 1, entry f). This method

Keywords: Thiolation; Indoles; Thiols; 3-Arylthioindoles.
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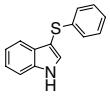
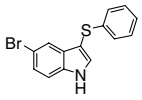
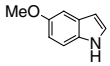
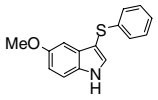
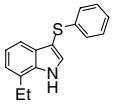
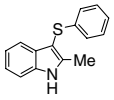
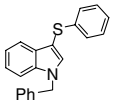
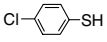
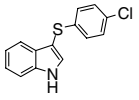
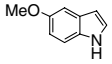
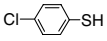
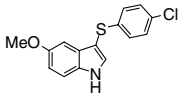
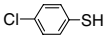
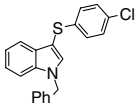
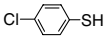
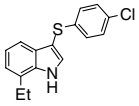
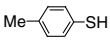
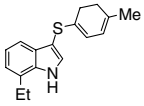
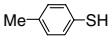
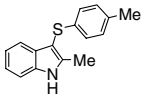
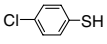
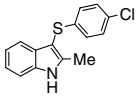
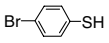
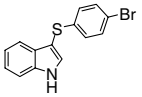
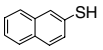
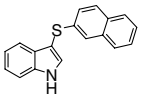
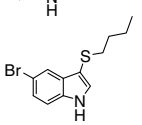
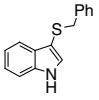
Table 1. Selectfluor™ promoted preparation of 3-sulfenylindoles

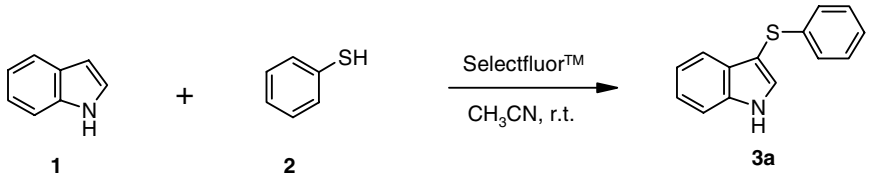
Entry	Indole	Thiophenol	Product[a]	Time (min)	Yield[b] (%)
a				20	96
b				30	85
c				20	96
d				25	89
e				25	89
f				25	87
g				20	92
h				20	97
i				25	93
j				20	90
k				25	89
l				20	94
m				20	94
n				25	90
o				30	78

(*continued on next page*)

Table 1 (*continued*)

Entry	Indole	Thiophenol	Product[a]	Time (min)	Yield[b] (%)
p				25	87
q				25	85
r				35	87
s				30	78
t				20	82

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 1.

worked equally well with electron deficient *p*-nitrothiophenol and sterically hindered thionaphthol (Table 1, entries o and q). Furthermore, alkyl thiols also participated well in this reaction (Table 1, entries r–t). The reactions proceeded rapidly at room temperature affording 3-sulfenylated indoles in good to excellent yields. The products were characterized by ^{1}H NMR, IR and mass spectroscopy and also by comparison with authentic samples.[1,6,7] The advantages of this procedure include milder conditions than when using corrosive chlorine or sulfuryl chloride, as well as fast reaction times, easy workup and improved yields. This method also avoids the formation of 1 equiv of thiol waste, which occurs when using a disulfide as the electrophilic sulfur source. There was no considerable difference in yields when comparing protected and unprotected indoles. Unlike reported methods, no bis-sulfenylation was observed in this reaction. In all cases, the products were 3-sulfenyl indoles as confirmed by ^{1}H NMR spectroscopy. Moreover, no sulfenylation was observed in the case of 3-methylindole under similar conditions. As solvent, acetonitrile gave the best results. No fluorination of indole was observed under the reaction conditions. The scope and generality of this process is illustrated with respect to various indoles and thiols and the results are presented in Table 1.[11]

In summary, Selectfluor™ has proved to be a useful and highly efficient reagent for the sulfenylation of indoles at the 3-position under mild conditions. In addition to its simplicity and efficiency, this method produces 3-arylthioindoles in excellent yields in short reaction times.

Acknowledgement

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11. *Typical procedure*: A mixture of 5-methoxyindole (0.04 g, 0.28 mmol), 4-chlorothiophenol (0.04 g, 0.28 mmol) and Selectfluor™ (0.1 g, 0.28 mmol) in acetonitrile (5 mL) was stirred at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with dichloromethane (2×15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford 3-(4-chlorophenylthio)-5-methoxyindole (0.078 g, 0.269 mmol, 97%). Spectral data for selected products: **3g**: 3-(4-chlorophenylthio)-1*H*-indole: Pale brownish solid, mp: 126–130 °C; IR (KBr): ν_{max} 3403, 2923, 1640, 1505, 1473, 1452, 1090, 1008, 811, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (br s, 1H), 7.32–7.58 (m, 4H), 6.89–7.20 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 100.6, 111.5, 119.5, 121.1, 123.4, 127.5, 128.7, 130.6. LC–MS: *m*/*z* (%): 260 (M+1, 45), 161 (100), 177 (30), 169 (20), 149 (15), 117 (10), 101 (5). HRMS calcd for $C_{14}H_{10}NSCl$: 259.0144. Found: 259.0141. Compound **3h**: 3-(4-chlorophenylthio)-5-methoxy-1*H*-indole: Pale brownish solid, mp: 97–105 °C; IR (KBr): ν_{max} 3406, 2922, 2852, 1632, 1581, 1475, 1285, 1206, 1090, 1030, 813 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.36 (br s, 1H), 7.41 (s, 1H), 7.20–7.33 (m, 2H), 7.02–7.18 (m, 1H), 6.77–7.03 (m, 4H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.2, 99.3, 101.5, 106.5, 109.5, 125.7, 125.9, 126.0, 126.8, 128.0, 128.1, 128.2, 155.2. LC–MS: *m*/*z* (%): 289 (M^+, 30), 279 (20), 257 (10), 197 (20), 169 (15), 147 (100), 117 (10). HRMS calcd for $C_{15}H_{12}NOSCl$: 289.0249. Found: 289.0250. Compound **3l**: 3-(*p*-tolylthio)-2-methyl–1*H*-indole: Liquid, IR (KBr): ν_{max} 3395, 2924, 2854, 1735, 1626, 1456, 1220, 1082, 1019, 803, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (br s, 1H), 7.44–7.55 (m, 1H), 7.20–7.29 (m, 1H), 6.99–7.17 (m, 2H), 6.83–6.96 (m, 4H), 2.50 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.1, 20.7, 100.0, 110.5, 119.0, 120.6, 122.1, 125.8, 129.4, 130.3, 135.4, 135.6, 140.8. LC–MS: *m*/*z* (%): 254 (M+1, 100), 175 (40), 140 (20). HRMS calcd for $C_{16}H_{16}NS$ ($M+H^+$): 254.1003. Found: 254.1011. Compound **3m**: 3-(4-chlorophenylthio)-2-methyl-1*H*-indole: Liquid, IR (KBr): ν_{max} 3393, 2920, 2851, 1576, 1542, 1473, 1455,1088, 1009, 814, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.20 (br s, 1H), 7.44–7.55 (m, 1H), 7.02–7.32 (m, 5H), 6.86–6.99 (m, 2H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.1, 99.1, 110.7, 118.8, 120.8, 122.3, 126.7, 128.7, 130.0, 130.3, 135.4, 137.9, 141.1. LC–MS: *m*/*z* (%): 274 (M+1, 100), 260 (50), 206 (35), 132 (20), 120 (10). HRMS calcd for $C_{15}H_{13}NSCl$ ($M+H^+$): 274.0457. Found: 274.0459.