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Synthesis and antioxidant activity of new C-3 sulfenyl indoles

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ABSTRACT

A convenient and efficient methodology for the synthesis of new C-3 sulfur-substituted indoles under $CeCl_3{\cdot}7H_2O$ promotion is reported. Model bis(indol-3-yl)sulfide **4a** and bis(indol-3-yl)sulfone **5a** proved to display potent antioxidant activity at the low micromolar level, in DPPH, ABTS, and FRAP assays, as well as in the inhibition of the peroxidation of linoleic acid.

Introduction

Involvement of oxidative stress in the pathogenesis of various disorders and diseases is well documented.[1] Oxidative stress takes place when the production of reactive oxygen species (ROS), such as superoxide radical ($O_2^{\cdot -}$), H_2O_2, singlet oxygen ($^1O_2$) and peroxyl radical ($ROO^{\cdot}$), exceeds the capacity of the cellular antioxidant defenses to remove these toxic agents.[1c] ROS can attack membrane lipids, proteins, and nucleic acids, disrupting normal cell physiology.[1c]

Antioxidant pharmacotherapy has emerged as a tool to minimize the biomolecular damage caused by the attack of ROS to these vital constituents of living organisms,[1a] and therefore synthetic antioxidants have received much attention from the pharmaceutical viewpoint.[1] Interestingly, a significant number of research groups have focused on the role of sulfur- and selenium-containing compounds as antioxidants.[2]

The indole scaffold is widely found among natural products and synthetic compounds, which exhibit a range of important biological activities.[3] Many indole derivatives have been synthesized in search of new antioxidants.[4] Different functional groups and heterocyclic moieties attached to the indole nucleus have been shown to modulate the antioxidant ability of the resulting compounds,[5] and the nature of the C-3 functionalization is regarded as relevant for good potency.[6] Therefore, a facile access to these derivatives seems important. One of the most widely used protocols toward C-3 substituted indoles involves the Lewis or protic acid-promoted electrophilic substitution reaction.[7]

In view of our interest in the development of new and cleaner alternative methods for classical reactions, promoted by cerium(III) species,[8] and with the aim of preparing new and bioactive indoles, we decided to study the direct electrophilic substitution reaction of indoles at the C-3 position with aromatic sulfonothioates[9] and investigate the antioxidant activity of the resulting sulfur-containing compounds (Scheme 1).

Results and discussion

In preliminary experiments, the best reaction conditions were established by the use of indole (**1a**, $R_1 = R_2 = H$, 1.0 mmol) and *p*-toluene sulfonothioate (**2a**, $R_3 = Me$, 1.0 mmol) as starting materials. We examined the effect of the solvent [DMF, *N*,*N*′-dimethylacetamide (DMA), 2-propanol, MeCN, and $MeNO_2$], temperature (70–100 °C), and amount of $CeCl_3{\cdot}7H_2O$ [0.5–1.0 equiv] as the promoter.

The results revealed that all three variables affected the reaction, being the use 1.0 equiv of $CeCl_3{\cdot}7H_2O$ in DMF at 80 °C the conditions furnishing the best performance (98%; Table 1, entry 1). A decrease in the yield was observed when the transformation was carried out at 70 °C (81%), while at 110 °C the presence of bis(indol-3-yl)sulfide (**4a**) was detected by GC–MS in the crude reaction mixture and the yield of **3a** was significantly lower (49%).

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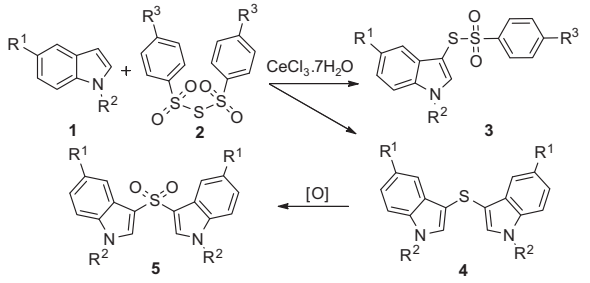


Scheme 1. Synthesis of 3-substituted indole derivatives (**3**–**5**).

In order to explore the scope and limitations of the method, the protocol was extended to other examples, under the optimized conditions.[10] The corresponding products were obtained in good to excellent yields from different indoles (Table 1). The reaction was also studied with the benzenesulfonothioate **2b** (R_3 = H), with comparable success, albeit in slightly lower yields.

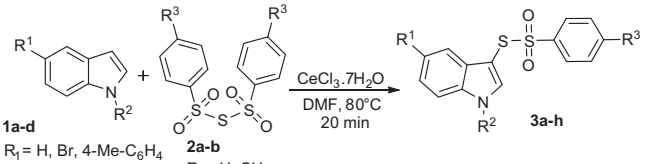
Taking into account our observation that higher temperatures led to the formation of bis(indol-3-yl)sulfides (**4**) and in view of the importance of these compounds in general organic synthesis as well as in materials science and in the pharmaceutical industry,[12] we decided to study further the above reaction.

When the reaction was carried out in DMA under microwave irradiation (160 °C), using Ce(III) as the promoter (1.0 mmol), indole (2.0 mmol) and **2a** (1.0 mmol), 53% of bis(indol-3-yl)sulfide (**4a**)[12e] was obtained after 20 min, along with minor amounts of the monosubstituted product **3a**. However, when 2.0 equiv of $CeCl_3{\cdot}7H_2O$ were employed, **4a** was accessed in 89% yield (Table 2, entry 1). Bis(indol-3-yl)sulfides **4b**–**d** were isolated in good yields under the same conditions (Table 2), demonstrating that the transformation is general.[13]

In view of the precedent of antioxidant activity among sulfone-linked bis heterocycles,[14] the bis(indol-3-yl)sulfides **4** were transformed into the corresponding sulfone derivatives **5**.[12e] The oxidation reaction was easily performed by treatment of **4a**–**d** with oxone in a 1:1 (v/v) H_2O/acetone medium, which smoothly provided good yields of **5a**–**d** (Table 3).[15]

In order to investigate the free radical scavenging ability of **3a** and **4a**, the DPPH [di(phenyl)-(2,4,6-trinitrophenyl)imino azanium] and ABTS (2,2′-azino-bis(3-ethyl benzothiazoline-6-sulfonic acid) assays were used. Both are synthetic free radicals; however, they sense different antioxidant mechanisms.

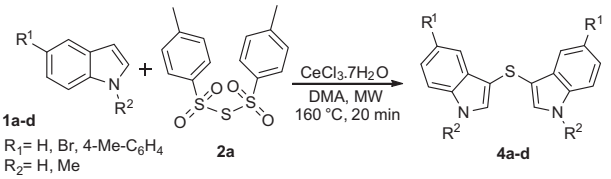
Table 1
Synthesis of C-3 monosubstituted indoles **3**



Entry	R_1	R_2	R_3	Product	Yield[a] (%)
1	H	H	Me	**3a**	98
2	H	Me	Me	**3b**	95
3	Br	H	Me	**3c**	87
4	4-Me–C_6H_4	H	Me	**3d**	90
5	H	H	H	**3e**	92
6	H	Me	H	**3f**	90
7	Br	H	H	**3g**	86
8	4-Me–C_6H_4	H	H	**3h**	86

[a] Isolated yield. All products were characterized by GC–MS, ^{1}H and ^{13}C NMR, and elemental analysis.[11]

Table 2
Ce(III)-mediated synthesis of bis(indol-3-yl)sulfides **4**[a]

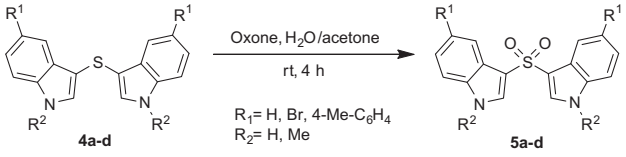


Entry	R_1	R_2	Product	Yield[b] (%)
1	H	H	**4a**	89
2	H	Me	**4b**	86
3	Br	H	**4c**	78
4	4-Me–C_6H_4	H	**4d**	70

[a] The reactions were carried out with the indoles (**1**, 2.0 mmol), *p*-toluene sulfonothioate (**2a**, 1.0 mmol) and $CeCl_3{\cdot}7H_2O$ (2.0 mmol) in DMA (4.0 mL), under microwave irradiation (160 °C, 100 W) for 20 min.

[b] Isolated yield. All products were characterized by GC–MS, ^{1}H and ^{13}C NMR, and elemental analysis.

Table 3
Synthesis of bis(indol-3-yl)sulfones **5**[a]



Entry	R^1	R^2	Product	Yield[b] (%)
1	H	H	**5a**	90
2	H	Me	**5b**	88
3	Br	H	**5c**	85
4	4-Me–C_6H_4	H	**5d**	86

[a] The reactions were carried out with bis(indol-3-yl)sulfides (**4**, 1.0 mmol) and oxone (1.0 mmol), in 1:1 (v/v) H_2O/acetone (5 mL), at room temperature for 4 h.

[b] Isolated yield. All products were characterized by GC–MS, ^{1}H and ^{13}C NMR, and elemental analysis.

DPPH has an unpaired electron which yields a strong absorption maximum at 517 nm. It is now widely accepted that its reaction with compounds like phenols proceeds through two different mechanisms, including the direct hydrogen atom transfer (HAT) and the sequential proton loss electron transfer.[16] Thus, the unpaired electron becomes paired in the presence of a free radical scavenging antioxidant or hydrogen donor, decreasing the absorption.[16b]

On the other hand, it was proposed that the reaction of indoles with ABTS involves a single electron transfer process.[16c]

In the DPPH test,[17] compounds **3a** and **4a** presented radical scavenging at concentrations as low as 50 and 10 μM, respectively (Table 4). The IC_{50} values (sample concentration required to inhibit 50% of the radicals) of 185.0 ± 39.7 (**3a**) and 22.5 ± 10.2 μM (**4a**) and the maximum inhibition (I_{max}) results (76.5 ± 2.8% for **3a** and 89.9 ± 2.5% for **4a**) revealed that **4a** is a more effective and more potent DPPH radical scavenger.

In the ABTS assay performed, as disclosed by Re et al.[18] the test compounds were active at 5 μM levels (Table 4). When the IC_{50} (**3a**: 27.0 ± 24.2 μM; **4a**: 3.6 ± 0.5 μM) and I_{max} results (**3a**: 99.7 ± 0.5%; **4a**: 99.9 ± 0.005%) were compared, it was also concluded that **4a** is a more effective and more potent ABTS radical scavenger.

On the other hand, lipid peroxidation involves a free radical chain reaction. Radical scavengers may directly react with peroxide radicals, quench their activity and terminate the peroxidation chain reactions. In the linoleic acid peroxidation inhibition induced

Table 4
Antioxidant activity of compounds **3a** and **4a** in the ABTS, DPPH, FRAP, and linoleic acid peroxidation assays

Conc.(μM)	Compound **3a**				Compound **4a**			
	Free radical scavenging ABTS (%)	Free radical scavenging DPPH (%)	Linoleic acid peroxidation inhibition (%)	FRAP (Abs_{593})	Free radical scavenging ABTS (%)	Free radical scavenging DPPH (%)	Linoleic acid peroxidation inhibition (%)	FRAP (Abs_{593})
Control	—	—	—	0.20 ± 0.06	—	—	—	0.20 ± 0.06
1	10.9 ± 2.9	NT	NT	0.25 ± 0.09	25.5 ± 13.5	NT	NT	0.23 ± 0.09
5	25.8 ± 8.6*	NT	NT	0.47 ± 0.22	68.4 ± 25.3 ***	15.5 ± 23.3	6.8 ± 2.6	0.49 ± 0.24
10	38.1 ± 13.5**	15.3 ± 16.3	10.8 ± 5.6	0.75 ± 0.40	92.6 ± 5.2***	38.6 ± 10.0 ***	42.0 ± 9.1***	0.76 ± 0.33***
50	77.4 ± 21.9***	30.6 ± 15.7*	19.5 ± 8.4**	1.59 ± 0.56***	97.0 ± 3.4***	79.8 ± 8.8***	66.7 ± 3.7***	—
100	94.8 ± 5.8***	42.1 ± 13.3**	58.2 ± 8.7***	—	96.8 ± 3.5***	86.2 ± 6.7***	95.6 ± 8.8***	—
500	—	78.3 ± 4.1***	99.7 ± 0.6***	—	—	—	—	—

The asterisks denote $p < 0.05$ (*), $p < 0.01$ (**) and $p < 0.001$ (***) as compared to the respective control sample (one-way ANOVA/Newman–Keuls).
IC_{50}: concentration (μM) providing 50% inhibition in the assays; I_{max}: maximal inhibition (%); NT = no tested. Number of repetition = 5.

with Fe-ascorbic acid, carried out as reported by the group of Choi,[17] the symmetric sulfide **4a** (IC_{50}: 12.5 ± 0.3 μM) was also more effective than its parent **3a** (IC_{50}: 85.5 ± 10 μM), although both exhibited similar I_{max} values (**3a**: 99.7 ± 0.6%; **4a**: 95.6 ± 8.8%).

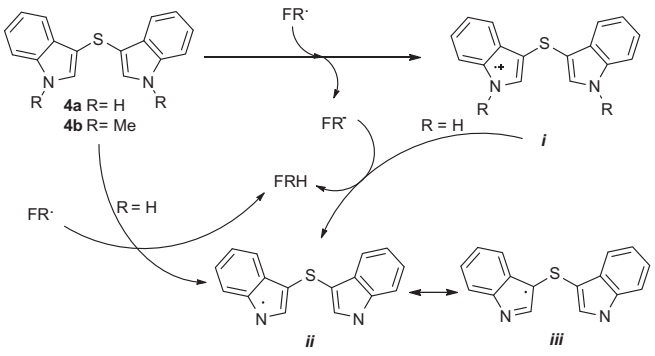
The FRAP (ferric reducing antioxidant power) assay relates the electron donation capability, which reflects the reducing power of the test compound, with its antioxidant activity. When the test was performed according to Stratil et al.[19] indoles **3a** and **4a** showed potential reducing power at concentrations of 50 and 10 μM, respectively, and above.

The structural requirements and mode of action of the in vivo and in vitro antioxidant activity of polysubstituted indoles have been the subject of several investigations.[20] Although the exact mechanism of action of these indole derivatives is still unknown, a mechanistic picture can be drawn taking into account that many naturally-occurring and synthetic indoles display antioxidant activity, and the reactions of the antioxidant agent melatonin[21] and related indoles with free radicals have been recently examined through computational models,[22] and that it has been shown that melatonin exerts its biological activity as radical scavenger via a nitrogen centered radical, the indolyl (or melatonyl) cation radical.[23]

Accordingly, it can be proposed (Scheme 2) that compounds **3** and **4** interact with a free radical source (FR·), through one of two pathways, involving either single electron transfer (SET) or hydrogen abstraction.[24] In the first case, electron transfer from the antioxidant to the active radical would yield an anion (FR^-) and a cation radical species like ***i***. A structure resembling ***i*** has also been proposed as an intermediate for the hypervalent iodine-mediated SET oxidation of indole derivatives.[25] In the case if *N*-unsubstituted compounds, the electron transfer may be followed by proton transfer from the cation radical to the anion, generating species ***ii***.

When the indolic nitrogen is unsubstituted, a direct transfer of hydrogen between the antioxidant and the active radical may take place, furnishing the corresponding nitrogen-centered indolyl radical (***ii***), which is the resonant form of ***iii***.

The contribution of the C-3 substituent to the electronic density of the indole nucleus may explain the differences in potency observed between **3a** and **4a**. Increased activity due to a better stabilization of the indole ring and delocalization of the electrons as a consequence of the C-3 substitution has been also noticed recently within the indole family.[6]



Scheme 2. Proposed mechanism for the antioxidant activity of the bis(indol-3-yl)sulfides (**4**).

Conclusion

In summary, we have shown that $CeCl_3 \cdot 7H_2O$ is a very convenient promoter for the reaction of indoles with aromatic sulfonothioates, furnishing monosubstituted indoles **3** and bis(indol-3-yl)sulfides **4** under conventional heating or microwave irradiation, respectively, both in excellent yields. The bis(indol-3-yl)sulfides were also converted into the very useful sulfones derivatives **5** under very mild conditions. On the other hand, **3a** and **4a** displayed antioxidant activity, bis(indol-3-yl)sulfide **4a** being a more potent antioxidant.

Acknowledgments

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10. *Typical procedure for the synthesis of monosubstituted indoles* **3**. To a mixture of the indole (1.0 mmol) and $CeCl_3{\cdot}7H_2O$ (1.0 mmol) in DMF (5 mL) was added the appropriate sulfonothioate (1.0 mmol). The reaction mixture was stirred at 80 °C for 20 min. The reaction progress was monitored by TLC. After complete consumption of the starting materials, the reaction mixture was cooled to rt, water (15 mL) was added and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were successively washed with water and brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel (hexanes–EtOAc, 70:30). Spectral data of selected compounds:[11] **3a**: mp 140–142 °C; ^{1}H NMR δ 11.84 (s, 1H), 7.52 (d, J = 2.9, 1H), 7.46–7.41 (m, 3H), 7.27 (d, J = 8.3, 2H), 7.18–7.14 (m, 2H), 7.01 (t, J = 7.8, 1H), 2.36 (s, 3H); ^{13}C NMR δ 144.2, 139.8, 136.0, 134.9, 129.3 (2C), 128.0, 126.8 (2C), 122.2, 120.4, 117.8, 112.1, 96.5, 20.7; EI-MS (m/z, rel. int., %): 303 (M^+, 100); 289 (7); 211 (19); 197 (30); 149 (45); Anal. Calcd for $C_{15}H_{13}NO_2S_2$ C, 59.38; H, 4.32; N, 4.62; found C, 59.76; H, 4.28; N, 4.72; **3b**: mp 119–120 °C; ^{1}H NMR δ 7.63 (s, 1H), 7.51 (d, J = 8.0, 1H), 7.43 (d, J = 8.2, 2H), 7.29 (d, J = 8.2, 2H), 7.24–7.20 (m, 1H), 7.11 (d, J = 7.0, 1H), 7.04 (t, J = 7.0, 1H), 3.88 (s, 3H), 2.37 (s, 3H); ^{13}C NMR δ 144.2, 139.8, 136.0, 134.9, 129.3 (2C), 129.0, 126.8 (2C), 122.2, 121.2, 118.8, 112.1, 96.5, 33.5, 20.7; EI-MS (m/z, rel. int., %): 317 (M^+, 100); 303 (9); 227 (16); 211 (25); 163 (35); Anal. Calcd for $C_{16}H_{15}NO_2S_2$ C, 60.54; H, 4.76; N, 4.41; found C, 60.64; H, 4.77; N, 4.42; **3f**: mp 110–113 °C; ^{1}H NMR δ 7.69–7.65 (m, 2H), 7.57 (d, J = 7.2, 2H), 7.53–7.47 (m, 3H), 7.24 (t, J = 7.2, 1H), 7.09 (d, J = 7.2, 1H), 7.03 (t, J = 7.2, 1H), 3.82 (s, 3H); ^{13}C NMR δ 142.7, 138.4, 136.7, 133.6, 129.0 (2C), 128.4, 126.7 (2C), 122.2, 120.7, 117.8, 110.5, 95.1, 32.8; EI-MS (m/z, rel. int., %): 303 (M^+, 100); 289 (17); 212 (99); 197 (30); 149 (45); Anal. Calcd for $C_{15}H_{13}NO_2S_2$ C, 59.38; H, 4.32; N, 4.62; found C, 59.68; H, 4.33; N, 4.62.
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13. *Typical procedure for the synthesis of bis(indol-3-yl)sulfides* **4**. $CeCl_3{\cdot}7H_2O$ (1.0 mmol) was added to a mixture of the indole (1.0 mmol) and the appropriate sulfonothioate (0.5 mmol) in DMA (5 mL). The reaction mixture was submitted to microwave irradiation at 160 °C for 20 min, in a closed vessel (maximum power 100 W). Water (15 mL) was added and the product was extracted with EtOAc (3 × 10 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel (hexanes–EtOAc, 80:20). Spectral data of selected compound: **4c**: mp 148–150 °C; ^{1}H NMR δ 11.41 (s, 2H), 7.80 (s, 2H), 7.72 (s, 2H), 7.34 (d, J = 8.3, 2H), 7.20 (d, J = 8.3, 2H); ^{13}C NMR δ 134.7 (2C), 130.9 (2C), 129.9 (2C), 123.9 (2C), 120.3 (2C), 113.7 (2C), 112.0 (2C), 104.4 (2C); EI-MS (m/z, rel. int., %): 421 [(M+2)$^+$, 98]; 420 [(M+1)$^+$, 18]; 419 (M^+, 100); 341 (15); 226 (9); 149 (45); Anal. Calcd for $C_{16}H_{10}Br_2N_2S$ C, 45.52; H, 2.39; N, 6.64; Found C, 45.54; H, 2.62; N, 6.42.
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15. *Typical procedure for the synthesis of bis(indol-3-yl)sulfones* **5**. Oxone (1.0 mmol) was added to a solution of bis(indol-3-yl)sulfides **4** (1.0 mmol) in a 1:1 (v/v) mixture of water/acetone (5 mL). The reaction mixture was stirred for 4 h at rt. Then, water (15 mL) was added and the product was extracted with EtOAc (3 × 10 mL), the organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel eluted with hexane/EtOAc (50:50). Spectral data of selected compound: **5c**: mp 270–271 °C; ^{1}H NMR δ 12.24 (s, 2H), 8.53 (s, 2H), 7.92 (s, 2H), 7.45 (d, J = 8.5, 2H), 7.25 (d, J = 8.5, 2H); ^{13}C NMR δ 135.5 (2C), 132.1 (2C), 126.1 (2C), 124.9 (2C), 121.1 (2C), 117.0 (2C), 115.3 (2C), 114.5 (2C); EI-MS (m/z, rel. int., %): 453 [(M+2)$^+$, 98]; 452 [(M+1)$^+$, 5]; 451 (M^+, 100); 435 (7); 419 (19); 341 (30); 264 (12); 149 (45); Anal. Calcd for $C_{16}H_{10}Br_2N_2O_2S$ C, 42.32; H, 2.22; N, 6.17; found C, 42.74; H, 2.44; N, 5.92.
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