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Efficient synthesis of 3-oxygenated benzothiophene derivatives

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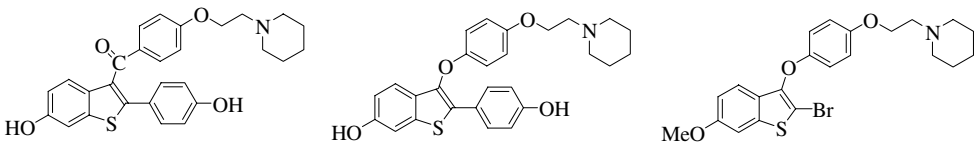
Abstract—An efficient synthesis of 2-bromo-3-aryloxybenzothiophene derivatives by a conjugate addition–elimination sequence of 2,3-dibromo benzothiophene dioxides with phenolic nucleophiles has been developed. These benzothiophene derivatives serve as important intermediates for the synthesis of SERM analogues.

Benzothiophenes are emerging as an important class of pharmacophores for medicinal chemistry, as exemplified by the successful launch of raloxifene (Evista®, **1**), a representative of a class of compounds known as selective estrogen receptor modulators (SERMs) that exhibit estrogen agonist-like actions on bone tissues and serum lipids while displaying potent estrogen antagonist properties in the breast and uterus. Recently, 3-oxygenated benzothiophene (**2**) has been reported to display a substantial (10-fold) increase in estrogen antagonist potency relative to raloxifene.[1–5] To further expand the structure activity relationship (SAR) studies for this class of molecules, compound **3** was identified as a pivotal intermediate to explore the chemical space around the 2-position of this particular platform (Fig. 1). However, there is paucity for the existence, let alone method of preparation for this type of compound in the chemical literature. Herein we wish to report our efforts on the preparation of 2-bromo-3-aryloxybenzothiophenes as versatile intermediates for SAR.

The nucleophilic displacement of a bromide in the 3-position of a benzothiophene sulfoxide has been reported.[2–5] We envisioned applying the same synthesis strategy of activation to prepare compound **3** and analogues via sulfoxide **4**. However, bromination of 6-methoxybenzothiophene (**5**) gave 2,3-dibromo-6-methoxybenzothiophene (**6**) in only 5% yield (Scheme 1). Furthermore, sulfoxide **4** (prepared from **6** by selective oxidation) proved to be an unstable intermediate for the nucleophilic displacement.

We then investigated the use of a 2,3-dibromo benzothiophene dioxide (sulfone) for the nucleophilic displacement. It has long been known that the halide atom in the 3-position of benzothiophene dioxide could be displaced by amines, alcohols, and phenols in the presence of a base; however, this transformation has attained almost no practical synthesis utility.[6–8] Toward this end, compound **9**, 2,3-dibromo-6-methoxybenzothiophene dioxide, was prepared from 6-methoxybenzothiophene (**5**) by oxidation with *m*-CPBA, followed by bromination in 72% overall yield (Scheme 2). Attempts to selectively brominate at the 3-position proved to be futile due to superior activity at the 2-position and complications from other sites.



1, Raloxifene **2** **3**

Figure 1.

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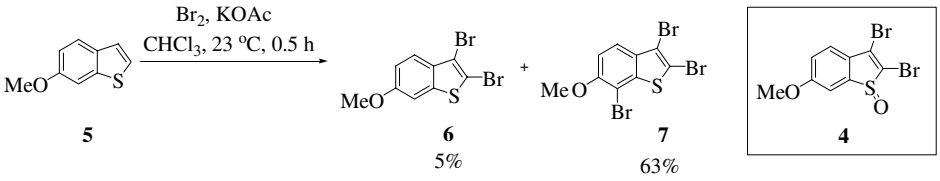
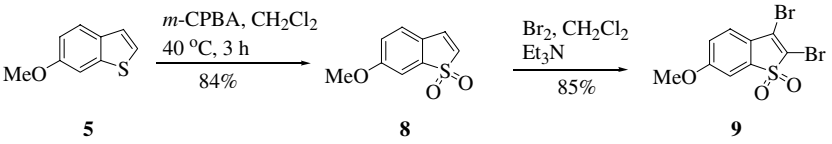


Scheme 1.

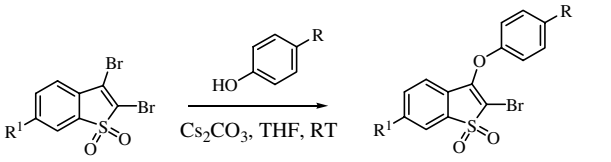


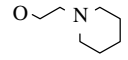
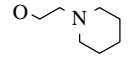
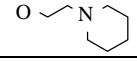
Scheme 2.

To our delight, reaction of benzothiophene dioxide **9** with 4-(2-piperidin-1-yl-ethoxy)-phenol (**10**) in the presence of cesium carbonate at ambient temperature provided the desired 2-bromo-3-aryloxy-6-methoxybenzothiophene dioxide **11** in 86% yield. Excellent regioselectivity was achieved as manifested by the single mono-addition product **11** being the only product isolated (Scheme 3). As in the case of the sulfoxide adduct, the sulfone adduct may proceed via a conjugate addition–elimination pathway. Since the C2–C3 bond in benzothiophene dioxide is likely olefinic and has limited aromatic character,[6] 2,3-dibromo-6-methoxybenzothiophene dioxide (**9**) can be considered as an unsaturated sulfone, which serves as a conjugate acceptor.[9,10]

In order to investigate the scope of conjugate addition–elimination reaction, several 2,3-dibromo-6-substitued benzothiophene dioxides were prepared to serve as conjugate acceptors. The results of conjugate addition–elimination reaction between benzothiophene dioxides and phenols are summarized in Table 1.

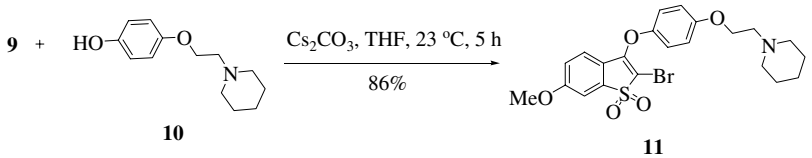
Table 1. Conjugate addition–elimination reaction of benzothiophene dioxides and phenols



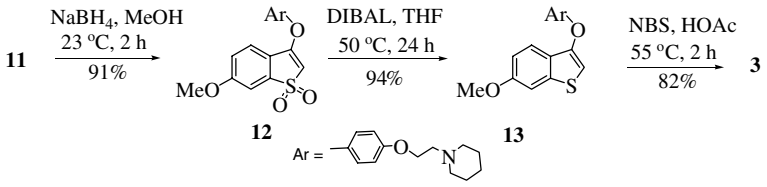
Entry	R^1	R	Time (h)	Yield (%)
1	H	H	2	95
2	H	F	2	95
3	H		3	86
4	OMe	H	3	85
5	OMe		5	86
6	CH_3CO		24	52

As indicated in Table 1, a series of phenols were found to add to 2,3-dibromo-benzothiophene dioxides with or without an electron-donating group in good to excellent yield. However, the yield was low when an electron-withdrawing group was present on the phenyl ring of the benzothiophene (entry 6) as a result of attenuated nucleophilicity.

With benzothiophene dioxide **11** on hand, we investigated the reduction of benzothiophene dioxide **11** to benzothiophene **3**. A number of methods have been reported for the reduction of sulfones to sulfides using LAH,[11] DIBAL,[12] Zn[13], and SmI_2[14] as reducing reagents. Unfortunately, none of these methods proved satisfactory for the reduction of sulfone **11** to benzothiophene **3**, providing a complicated mixture from reduction, debromination, and decomposition. We found that reaction of **11** with sodium borohydride gave only debromination product **12**, with the sulfone moiety intact. Eventually sulfone **12** was successfully reduced to 3-aryloxy-6-methoxybenzothiophene **13** with DIBAL in 94% yield. Bromination of **13** with *N*-bromo succinimide provided **3** in 82% yield (Scheme 4). The net outcome is a six-step process for the synthesis of benzothiophene **3** in 43% overall yield starting from 6-methoxybenzothiophene (**5**).[15]



Scheme 3.



Scheme 4.

In conclusion, the conjugate addition–elimination reaction of benzothiophene dioxides and phenols has been investigated and has been applied to a six-step process for the synthesis of the target compound **3**. This key intermediate was used for the preparation of hundreds of 2-substituted 3-oxygenated benzothiophene derivatives for drug discovery. The developed process for preparing **3** is also amenable to multi-kilogram preparative scale.

Acknowledgments

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15. Typical procedures are as follows:
Preparation of **8**: To a solution of 6-methoxythianaphthene **5** (30.0 g, 183 mmol) in 300 mL of methylene chloride was added slowly *m*-CPBA (99.0 g, 70%, 400 mmol) over a 60-minute period. The mixture was heated at 40 °C for 3 h, and then cooled to room temperature. Ethyl acetate (600 mL) was added to dissolve the white precipitates. Saturated sodium thiosulfate solution (200 mL) was added and stirred at ambient temperature for 1 h to quench the excess of *m*-CPBA. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic solutions was washed with saturated sodium bicarbonate and brine. After concentrated and recrystallized from ethanol and MTBE (1:20), 30.1 g of the desired product **8** was obtained as white crystals. Yield 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 2H, $J = 8.1$ Hz), 7.16 (d, 1H, $J = 6.9$ Hz), 7.10 (dd, 1H, $J = 8.1$ and 2.4 Hz), 6.59 (d, 1H, $J = 7.2$ Hz), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 138.7, 132.7, 129.1, 126.6, 123.5, 118.9, 107.8, 56.3.
Preparation of **9**: To a mixture of sulfone **8** (19.6 g, 100 mmol) in 200 mL of methylene chloride was added dropwise a solution of bromine (6.1 mL, 120 mmol) in 50 mL of methylene chloride at ambient temperature. The resulting solution was stirred at ambient temperature for 15 min and then 10 mL of triethylamine was added. After stirring at ambient temperature for 20 min, the reaction was quenched by the addition of water. The organic layer was separated and dried over sodium sulfate. After filtration, a pale yellow solution was obtained. To this pale yellow solution was added a solution of bromine (6.1 mL, 120 mmol) in 50 mL of methylene chloride. The resulting red solution was stirred at ambient temperature for 4 h. Triethylamine (10 mL) was added and stirred at ambient temperature for 30 min. The reaction was quenched by the addition of 200 mL of water and extracted with methylene chloride (2×100 mL). The combined organic solutions were dried over sodium sulfate. After filtering and concentrating, 30.0 g of desired product **9** was obtained without further purification. Yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, 1H, $J = 8.0$ Hz), 7.30 (d, 1H, $J = 2.5$ Hz), 7.10 (dd, 1H, $J = 8.0$ and 2.5 Hz), 3.91

(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 137.1, 128.8, 125.6, 123.6, 120.2, 119.0, 108.0, 56.2.

Preparation of **11**: To a solution of 2, 3-dibromo-6-methoxybenzothiophene dioxide **9** (27.0 g, 76.5 mmol) and 4-(2-piperidin-1-yl-ethoxy)-phenol **10** (18.9 g, 85.4 mmol) in 300 mL of THF was added cesium carbonate (74.7 g,229.0 mmol) to form a green mixture. After stirring at ambient temperature for 5 h, the reaction was quenched by the addition of water and extracted with ethyl acetate (2×200 mL), and dried over sodium sulfate. After purification by recrystallization from ethanol, 32.4 g of the desired product **11** was obtained as a white solid. Yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, 1H, $J = 8.7$ Hz), 7.30 (d, 1H, $J = 2.1$ Hz), 7.03 (m, 2H), 6.99 (d, 1H, $J = 2.4$ Hz), 6.86 (m, 2H), 4.08 (m, 2H), 3.86 (s, 3H), 2.75 (t, 2H, $J = 6.0$ Hz), 2.75 (t, 4H, $J = 4.8$ Hz), 1.59 (m, 4H), 1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 156.9, 152.8, 147.1, 138.9, 122.9, 122.2, 120.9, 118.8, 115.5, 107.8, 95.5, 66.8, 58.2, 56.4, 55.4, 26.3, 24.5.

Preparation of **12**: A solution of sulfone **11** (15.0 g, 30.4 mmol) in 150 mL of methanol was treated with sodium borohydride (2.3 g, 60.0 mmol) at ambient temperature for 2 h. Acetone (5 mL) was added to quench the reaction. Solvents were evaporated. The residue was dissolved in 200 mL of ethyl acetate and 100 mL of water. The organic layer was separated and dried over sodium sulfate. After evaporating and recrystallizing from methylene chloride and pentane (1:9), 11.5 g of the desired product **12** was obtained as white crystals. Yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 1H, $J = 8.0$ Hz), 7.27 (d, 1H, $J = 2.5$ Hz), 7.10 (m, 3H), 6.95 (m, 2H), 4.11 (t, 2H, $J = 6.0$ Hz), 3.90 (s, 3H), 2.79 (t, 2H, $J = 6.0$ Hz), 2.52 (m, 4H), 1.62 (m, 4H), 1.46 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 161.9, 157.5, 147.5, 141.8, 122.8, 121.7, 121.3, 118.7, 115.9, 106.7, 101.4, 66.7, 58.1, 56.3, 55.3, 26.1, 24.4.

Preparation of **13**: To a solution of sulfone **12** (10.5 g, 25.3 mmol) in 100 mL of THF was added a solution of DIBAL (100 mL, 1.0 M, 100 mmol) in methylene chloride at ambient temperature. The resulting solution was heated at 50 °C for 18 h. Additional 50 mL of DIBAL was added and continued to stir at 50 °C for additional 6 h. The reaction was quenched by the addition of saturated sodium sulfate. White solids were removed by filtration. The filtrate was washed with water and brine, and dried over sodium sulfate. After concentrating, 9.1 g of the desired product **13** was obtained as a pale yellow solid without further purification. Yield 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 1H, $J = 8.7$ Hz), 7.23 (d, 1H, $J = 2.5$ Hz), 7.07 (m, 2H), 6.99 (dd, 1H, $J = 8.7$ and 2.5 Hz). 6.88 (m, 3H), 4.08 (t, 2H, $J = 6.0$ Hz), 3.87 (s, 3H), 2.77 (t, 2H, $J = 6.0$ Hz), 2.51 (m, 4H), 1.61 (m,4H), 1.46 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 155.5, 151.1, 149.5, 139.7, 126.4, 122.0, 120.2, 115.8, 114.5, 105.6, 101.8, 66.7, 58.2, 55.8, 55.3, 26.2, 24.4.

Preparation of **3**: A solution of benzothiophene **13** (7.6 g, 19.8 mmol) in 80 mL of acetic acid was treated with NBS (3.9 g, 21.8 mmol) at ambient temperature for 10 min. The resulting solution was heated at 55 °C for 2 h. The reaction was quenched by the addition of 200 mL of water and 200 mL of ethyl acetate. The organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic solutions were washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate. After concentrating and recrystallizing from ethanol, 7.5 g of the desired product **3** was obtained as a white solid. Yield 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–6.79 (m, 7H), 4.05 (t, 2H, $J = 6.0$ Hz), 3.84 (s, 3H), 2.75 (t, 2H, $J = 6.0$ Hz), 2.50 (m, 4H), 1.60 (m, 4H), 1.42 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 154.0, 151.8, 144.1, 138.7, 125.8, 121.6, 116.7, 115.5, 114.6, 105.3, 99.8, 64.5, 56.9, 55.6, 54.3, 23.8, 22.7.