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A Facile Synthesis of 3-Aryl-Substituted-Benzothiophenes *via* a Lewis Acid Mediated Cyclization of 2-Arylthio-Acetophenones

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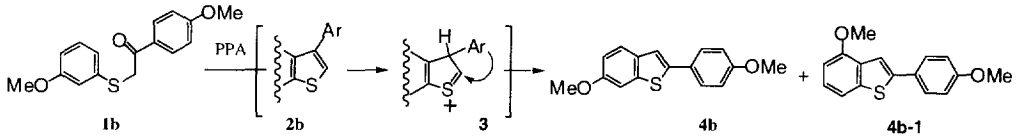
Abstract: *The boron trifluoride-etherate mediated cyclization of 2-arylthio-ketones* ***1a-h*** *at ambient temperature gave 3-aryl-substituted benzothiophenes* ***2a-h*** *in excellent yield. None of the rearranged 2-aryl-substituted benzothiophenes were observed.*

Benzothiophenes are of interest in many pharmaceutical areas, since they exhibit a variety of biological properties, such as antiallergic[1] and ocular hypotensive activities,[2] in addition to serving as bioisosteres of indoles,[3] and recently, raloxifene (LY139481 HCl),[4] a poly-substituted 2-aryl-benzothiophene, that was approved for the prevention of osteoporosis in postmenopausal women. In conjunction with a medicinal chemistry program, a method to synthesize 3-aryl substituted benzothiophenes was needed. Although there is a general method[5] by which 2-arylbenzothiophenes can be prepared, there are relatively few general syntheses[6] of 3-arylbenzothiophenes available, due to the easy migration of the aromatic group from the 3- to the 2-position under acidic conditions. In addition, some of the known methods required multistep sequences with low overall yields.[7] In this communication, we report an expedient, convenient procedure for the preparation of 6-methoxy-3-aryl-substituted benzothiophenes by condensation of 2-arylthio-acetophenones with Lewis acid boron trifluoride-etherate, at ambient temperature.

Equation 1



1b **2b** **3** **4b** **4b-1**

Initially, we attempted the cyclization of **1b** with polyphosphoric acid at 70 °C, a known method by Kost,[5b] which afforded only the rearranged benzothiophenes **4b** (68% yield) and **4b-1** (23%), the reported products[5a] from both possible cyclization modes [equation 1]. A thermal and proton-mediated rearrangement *via* **3** was postulated as the reaction mechanism.[5b] It seemed prudent that modification of the reaction conditions such as the use of lower temperatures and/or the use of other acids might avoid the facile migration of the aryl group, but the results of such attempts were unsatisfactory. We next attempted to utilize the Stille[8] and Suzuki[9] cross coupling methods, hoping that the undesired rearrangement would not occur under the neutral and/or basic conditions. While the cross coupling reaction of bromo-benzothiophene **5** with the boronic acid **7** gave no reaction, the corresponding iodide **6** gave rise to a coupled product which proved to be **4b** instead of the anticipated **2b** (equation 2). A similar result was observed in the analogous Stille[10]

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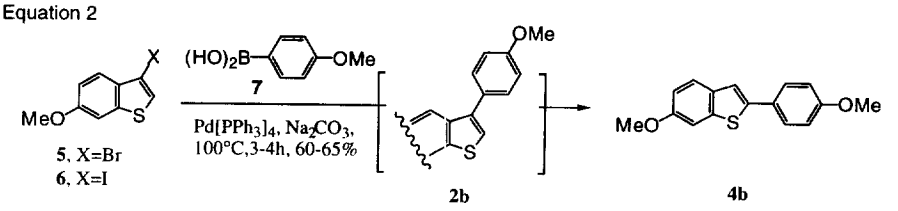
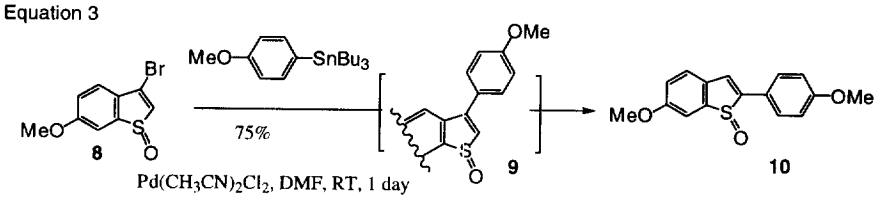
reaction of bromo-sulfoxide **8** (equation 3). To our knowledge, this rearrangement is without precedent and the reaction mechanism, which warrants further study, is uncertain.

Equation 2

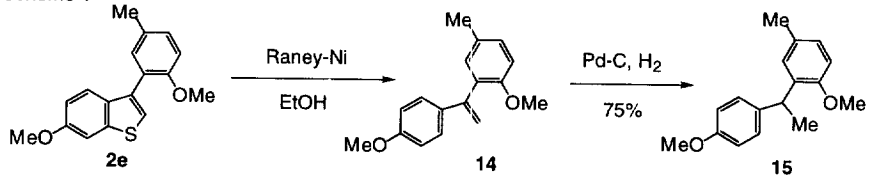


Equation 3



Finally, after some experimentation, we were pleased to find that **1b** underwent cyclization in the desired fashion in the presence of boron trifluoride-etherate to provide the long-sought **2b**, albeit in low yield, 10-15%, even after 1 day. The reaction efficiency could be improved by simply employing the BF_3OEt_2 as solvent, and in this way an inseparable mixture of **2b** and **13b** was produced in 85% yield (**2b:13b**=6:1) after 15 h at room temperature. Encouraged by this success, we extended the scope of the reaction to include both electron rich and electron deficient aromatics, and Table 1 illustrates these results. Regardless of the electronic nature of the substituent at the *para*-position of the phenyl ring, the thio-ketone **1**[11] underwent smooth cyclization to afford a mixture of the desired, major product **2** and **13** in excellent yields. Condensation of highly electron rich phenyl groups (entry 4, 5) occurred in equally high yield without any evidence of migration. The structural assignment of the products was unequivocally confirmed by Raney nickel desulfurization of **2e**, followed by hydrogenation with Pd-C to produce **15** in 75% yield (scheme 1), as had been previously demonstrated for the structure proof[5a] of **4b**.

Scheme 1



A typical procedure is exemplied for the synthesis of **2d/13d**: A flask was charged with thio-ketone **1d** (0.13 g, 0.4 mmol) and BF_3OEt_2 (5 mL) under an N_2 atmosphere at room temperature. The reaction mixture was stirred until starting material was consumed (approximately 13-15h) as monitored by TLC. The reaction mixture was poured into saturated $NaHCO_3$/ice water, stirred 10 min, and extracted with dichloromethane.

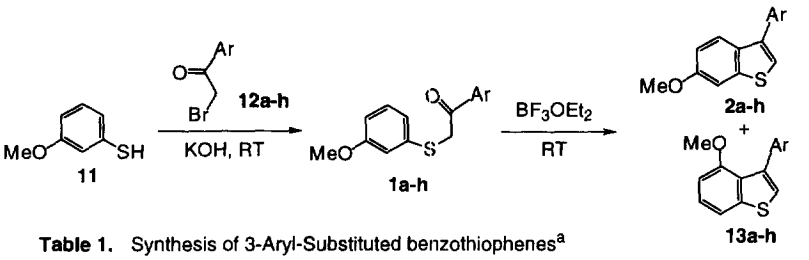


Table 1. Synthesis of 3-Aryl-Substituted benzothiophenes[a]

Entry	-Ar	Yield[b]	
	12	1a-h	2a-h+13a-h[12] (ratio)[c]
1	12a	87%	81% (7:1)
2	12b	80%	85% (6:1)
3	12c	85%	90% (9:1)
4	12d	85%	95% (9:1)
5	12e	85%	90% (9:1)
6	12f	79%	92% (7:1)
7	12g	96%	89% (6:1)
8	12h	83%	85% (10:1)

(a) A mixture of **1a-h** and xs BF_3OEt_2 was stirred at room temperature for 10-15h;
(b) Isolated yield after column chromatography, and all new compounds were characterized spectroscopically; (c) The isomer ratio was determined using ^{1}H-NMR.

The organic extract was washed with brine (2 X 50 mL), dried with Na_2SO_4, and concentrated *in vacuo* to afford a light yellow oil. Purification *via* flash chromatography (EtOAc/Hex=1:5) provided 0.14 g (95%) of the desired compound **2d** and **13d** (9:1) as an oil; **2d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47 (d, J=9Hz, 1H), 7.34 (d, J=2.4Hz, 1H), 7.30 (d, 1H), 7.19 (s, 1H), 6.95 (dd, 1H), 6.55 (d & dd, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H); MS m/z 301(M^++1).

In summary, the method described herein provides a simple, high yielding alternative for the preparation of 6-methoxy-3-arylbenzothiophenes utilizing the same starting material **1** which normally provides the corresponding 2-arylbenzothiophenes under different reaction conditions. The application of the present method for the synthesis of more complex, biologically active benzothiophene analogs is currently underway.[12]

References and Notes:

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11. General procedure:[5a] To a freshly prepared solution of 70% EtOH in H_2O and 0.77 g of KOH (ca 1.1 eq) at room temperature was added 3-methoxybenzenethiol (1.43 g, 10 mmol) **11**, and the solution was cooled to 0°C. A solution of the **12c** (2.3 g, 10 mmol) in EtOAc was added slowly. The reaction mixture was allowed to stir for 3h at ambient temperature and was then partitioned between water and EtOAc, the layers were separated, and the aqueous layer was extracted again with EtOAc. The combined organic layers were dried (Na_2SO4), filtered, and evaporated *in vacuo*.The resulting oil was purified by flash chromatography (EtOAc/Hex=6:1) to provide 2.46 g(85%) of **1c** as a solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.74 (dd, J=1.5 & 7.7 Hz, 1H), 7.48 (dt, 1H), 7.16 (dd, 7.8 & 8.1 Hz, 1H), 6.9 (m, 1H), 6.91 (d, 1H), 6.87 (m, 2H), 6.73 (m, 1H), 4.34 (s, 2H), 3.89 (s, 3H), 3.75 (s, 3H); MS m/z: 288 (M^+).
12. Although the desired product **2a-h** was contaminated by ca. 10% of **13a-h**, no serious attempt was made to effect separation. Instead, it was found that the mixture could be used in a synthetic sequence which provided more readily purified materials.