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# An Improved and Regiospecific Synthesis of *trans*-3,4-Dihydrodiol Metabolite of Benzo[*b*]naphtho[2,1-*d*]thiophene

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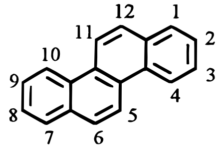
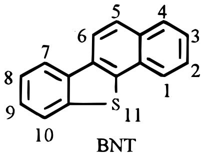
## Introduction

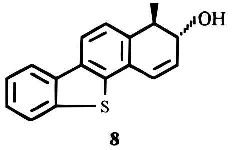
The thiachrysene, benzo[*b*]naphtho[2,1-d]thiophene (BNT), a thiaster of chrysene, is an ubiquitous environmental contaminant that has been detected in coal tar and derivatives,[2−4] crude oil,[5,6] shale oil,[7,8] fresh and used engine oils,[9,10] diesel exhaust,[11,12] and in smoke condensate of tobacco and related material.[13] In a recent study, BNT has been found in a concentration greater than benzo[*a*]pyrene in the air samples of an aluminum reduction plant.[14] BNT has been shown to be metabolically activated to products mutagenic to *Salmonella typhimurium*,[15−17] and more tumorigenic than its carbon analogue, chrysene.[18] Recent studies have shown that, like chrysene,[19] BNT is also metabolized to benzo-ring dihydrodiols[20,21] together with the sulfoxide and the sulfone.[20−22] Among these metabolites, the sulfone and *trans*-3,4-dihydroxy-3,4-dihydroBNT (**8**) are implicated in the bioactivation of BNT.[17,23] In an earlier study, Misra and Amin[17] reported the synthesis of **8** via 3-hydroxyBNT (**6**). However, the synthesis of **8** was nonregiospecific and required seven steps to produce it in <2.5% yield based on the starting material 3-methylbenzo[*b*]thiophene. The requirement of a fairly dilute solution during the photocyclization of the stilbene derivative further limits the efficiency of the synthesis of **6** and consequently of **8**. The present paper describes a short, regiospecific synthesis of **8** from easily accessible reactants.



Chrysene



BNT



**8**

## Results and Discussion

We have recently discovered the application of Suzuki cross-coupling reaction of arylboronic acids with 2-bromo-5-methoxybenzaldehyde (**2**) in the synthesis of the phenolic derivatives of a number of PAHs,[24−26] which are suitable intermediates for the synthesis of carcinogenic dihydrodiol and diol epoxide metabolites of PAHs. On the basis of these studies, we visualized an analogous reaction between benzo[*b*]thiophene-2-boronic acid (**1**) and 2-bromo-5-methoxybenzaldehyde (**2**) as a key step in for the regiospecific synthesis of **6** (Scheme 1). Thus the coupling reaction of **1** and **2** in refluxing dimethoxyethane (DME) containing saturated sodium bicarbonate and a catalytic amount of $Pd(PPh_3)_4$ produced **3** in 80−90% yield. The reaction of aldehyde **3** with trimethylsulfonium iodide and powdered potassium hydroxide in warm acetonitrile (65 °C) produced nearly quantitative yield of the relatively unstable ethylene oxide derivative **4**. The ethylene oxide formation under these conditions was more rapid compared to the phase transfer conditions reported for this kind of reaction.[24] The acid-catalyzed cyclization of the ethylene oxide **4** with boron trifluoride−ether complex in anhydrous ether gave 3-methoxyBNT (**5**) in 40−50% yield. 3-MethoxyBNT (**5**) has been prepared previously in 5.6% yield by Elbs reaction of 3-(4-methoxy-2-methylbenzoyl)benzo[*b*]thiophene.[27] Demethylation of **5** with boron tribromide in methylene chloride gave a nearly quantitative yield of **6**. Oxidation of **6** with Fremy's salt produced exclusively BNT-3,4-dione (**7**) which was finally reduced with sodium borohydride in ethanol while bubbling oxygen through the solution affording BNT *trans*-3,4-dihydrodiol (**8**). The $^1H$ NMR spectra of the dione **7** and the dihydrodiol **8** were

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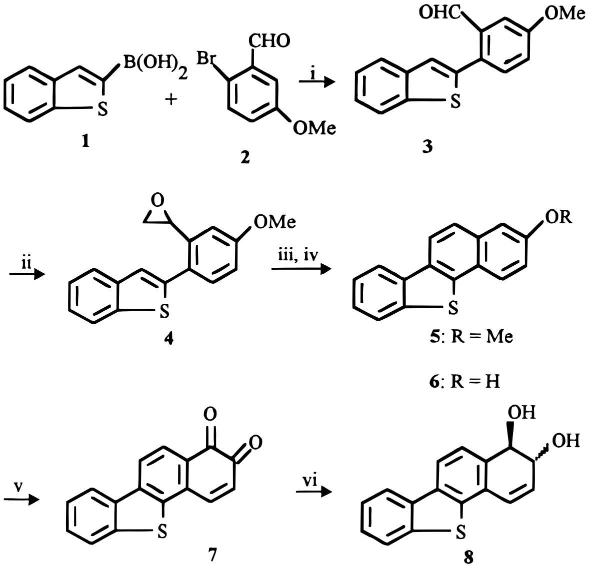
**Scheme 1**



Reagents: i, Pd(PPh$_3$)$_4$, NaHCO$_3$, DME, H$_2$O, reflux; ii, Me$_3$SI, KOH, MeCN, 60-65 °C; iii, BF$_3$-Et$_2$O/Et$_2$O; iv, BBr$_3$/CH$_2$Cl$_2$; v, ·ON(SO$_3$K)$_2$ ; vi, NaBH$_4$, O$_2$, EtOH

consistent with their structures and nearly identical to those reported earlier for these compounds.[17]

In summary, the present study describes an efficient application of the palladium-catalyzed cross-coupling reaction of readily available reactants to the concise and regiospecific synthesis of 3-methoxyBNT (**5**) and BNT *trans*-3,4-dihydrodiol (**8**). The overall yield of **8** from bromoaldehyde **2** was 27% which represent a significant improvement over the previous method.[17] In addition to providing a practical and concise synthesis of **5** and **8**, the present method holds promise as a general route to the synthesis of analogous phenolic and dihydrodiol metabolites of substituted BNTs and other thia-PAHs.

## Experimental Section

Benzo[*b*]thiophene-2-boronic acid (**1**) was obtained commercially (Lancaster synthesis). 2-Bromo-5-methoxybenzaldehyde (**2**) was synthesized according to the published procedure.[28] All reagents and solvents (anhydrous or otherwise) were used as received without further purification. Dry column grade silica gel was purchased from E. Merck. NMR spectra were recorded on 300, 400, or 500 MHZ NMR spectrometer in an appropriate solvent with tetramethylsilane (TMS) as internal standard at the NMR facility of the Chemistry Department, State University of New York, Buffalo, NY. Chemical shifts were recorded in ppm downfield from the internal standard. All the melting points were uncorrected.

**2-(Benzo[*b*]thienyl)-5-methoxybenzaldehyde (3).** A mixture of 2-bromo-5-methoxybenzaldehyde (**2**) (1.5 g, 7.0 mmol) and Pd(PPh$_3$)$_4$ (0.27 g, 0.73 mmol) in dimethoxyethane (40 mL) was stirred for 20 min in an argon atmosphere. To this mixture were added saturated NaHCO$_3$ (10 mL) and benzo[*b*]thiophene-2-boronic acid (**1**) (1.36 g, 7.7 mmol), and the resulting mixture was refluxed with stirring. The progress of the reaction was monitored by TLC (5% EtOAc−hexane) for 1 h at which point no more bromide **2** was detected. The reaction mixture was cooled to rt, diluted with water (50 mL), and then extracted with CH$_2$Cl$_2$. The organic solution was separated, washed with 5% NaOH and water, and dried (Na$_2$SO$_4$). The solvent was removed to afford a solid which was recrystallized from EtOAc−hexane to yield 1.55 g (83%) of **3** as nearly colorless crystals, mp 125−127 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.91 (s, 3 H), 7.19 (dd, 1 H, $J$ = 8.5, 3.5 Hz), 7.26 (s, 1 H), 7.35−7.44 (m, 2 H), 7.52 (d, 1 H, $J$ = 3 Hz), 7.55 (d, 1 H, $J$ = 8.5 Hz), 7.81 (d, 1 H, $J$ = 7.6 Hz), 7.86 (d, 1 H, $J$ = 7.9 Hz), 10.22 (s, 1 H). $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ 191.6 (CHO), 159.9, 140.5, 139.9, 138.8, 135.4, 132.7, 130.9, 125.9, 124.8, 124.7, 123.7, 122.1, 121.2, 110.3, 55.7 (OMe). Anal. Calcd For C$_{16}$H$_{12}$O$_2$S: C, 71.6; H, 4.5. Found: C, 71.2; H, 4.4.

**3-Methoxybenzo[*b*]naphtho[2,1-*d*]thiophene (5).** A mixture of **3** (1.04 g, 3.88 mmol), trimethylsulfonium iodide (0.85 g, 4.16 mmol), and powdered KOH (0.64 g, 16 mmol) in acetonitrile (50 mL) containing traces of water (0.1 mL) was stirred under argon at 65−70 °C for 16 h. The mixture was cooled, and extracted with EtOAc. The organic phase was washed with water, dried over Na$_2$SO$_4$, and concentrated in vacuo to yield 1.06 g (97%) sufficiently pure, relatively unstable 2-(2-(2-(epoxyethyl)-4-methoxyphenyl)benzo[*b*]thiophene (**4**) as a colorless syrupy oil. $^1$H NMR (400 MHZ, CDCl$_3$) of the major product: $\delta$ 2.82 (dd, 1 H, $J_{A,B}$ = 5.9 Hz, $J_{A,M}$ = 2.6 Hz), 3.18 (dd, 1 H, $J_{B,M}$ = 4.4 Hz), 3.86 (s, 3 H), 4.13 (pseudo-t, 1 H), 6.88−7.88 (m, 8 H). The product was used as such in the next step without further purification.

The cyclization of the epoxide **4** (1.06 g, 3.76 mmol) was performed in a solution of anhydrous ether (65 mL) by dropwise addition of BF$_3$·Et$_2$O (3.9 mL, 31.7 mmol) at 0 °C under argon. The solution was stirred for 15 h at room temperature. After completion of the reaction (monitored by TLC), the excess of BF$_3$·Et$_2$O was decomposed by addition of cold water. The product was extracted with CH$_2$Cl$_2$, and the combined organic extracts were successively washed with 10% NaHCO$_3$ and water and dried over Na$_2$SO$_4$. After removal of the solvent, the residue was chromatographed over dry column grade silica gel using hexane as eluant to produce 0.48 g (48.5%) of **5** as colorless crystals, mp 166 °C (lit.[27] mp 171 °C). $^1$H NMR (400 Mz, CDCl$_3$): $\delta$ 3.98 (s, 3 H), 7.29 (dd, 1 H, $J$ = 2.4 Hz, 8.8 Hz), 7.31 (d, 1 H, $J$ = 2.4 Hz), 7.42−7.54 (m, 2 H), 7.79 (d, 1 H, $J$ = 8.8 Hz), 7.95 (d, 1 H, $J$ = 7.3 Hz), 8.50 (d, 1 H, $J$ = 8.8 Hz), 8.15 (d, 1 H, $J$ = 8.4 Hz), 8.18 (d, 1 H, $J$ = 7.3 Hz).

**3-Hydroxybenzo[*b*]naphtho[2,1-*d*]thiophene (6).** To a stirred solution of **5** (0.96 g, 3.8 mmol) in anhydrous CH$_2$Cl$_2$ (25 mL) was added a 1 M solution of BBr$_3$ (7.4 mL, 7.4 mmol) in CH$_2$Cl$_2$ over a period of 2−3 min. After 12 h at room temperature, the mixture was hydrolyzed with ice-cold water, the organic layer was washed with water and dried (Na$_2$SO$_4$), and the solvent was removed to afford a solid. Trituration of the solid with hexane produced 0.76 g (84%) of pure **6**, mp 228−230 °C (lit.[17] mp 232−234 °C).

**Benzo[*b*]naphtho[2,1-*d*]thiophene-3,4-dione (7).** A solution of **6** (0.60 g, 2.49 mmol) in 200 mL of CH$_2$Cl$_2$/benzene (16:84) containing 9 drops of adogen-464 and 0.17 M KH$_2$PO$_4$ (70 mL) was stirred at room temperature while Fremy's salt (1.62 g, 6.06 mmol) was added in one portion with vigorous stirring. After stirring for 2 h at room temperature, the organic layer was separated, washed with water, and dried over Na$_2$SO$_4$. Evaporation of the solvent and the recrystallization of dark residue with CH$_2$Cl$_2$−hexane yielded 0.57 g (90.5%) of **7** as a bright red crystalline solid, mp 177−181 °C (lit.[17] mp 178−180 °C).

***Trans*-3,4-dihydroxy-3,4-dihydrobenzo[*b*]naphtho[2,1-*d*]thiophene (8).** To a well stirred suspension of quinone **7** (0.32 g, 1.2 mmol) in 250 mL of ethanol was added NaBH$_4$ (2.32 g, 81.2 mmol). The mixture was stirred at room temperature while a stream of oxygen was bubbled through the solution. After 16 h of stirring, the resulting light yellow solution was concentrated at room temperature under vacuum to one-third of its original volume. The residue was diluted with water, extracted with EtOAc, dried (Na$_2$SO$_4$), and concentrated. Trituration of the residue with 10% EtOAc−hexane afforded 0.28 g (86%) of **8** as light yellow solid, mp 205−207 °C. $^1$H NMR (400 MHz, acetone-$d_6$) spectrum of **8** was identical to that reported in the literature.[17]

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