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SYNTHESIS OF A 5-SUBSTITUTED BENZO[*b*]THIOPHENE

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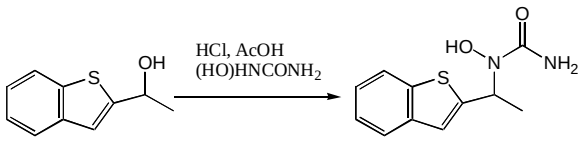
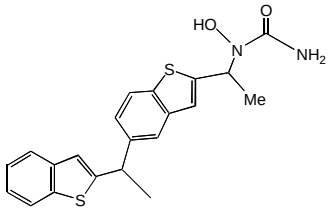
Abstract- The synthesis of a 5-substituted dimeric benzo[b]thiophene (**3**), utilizing a Friedel-Crafts alkylation and subsequent Newman-Kwart rearrangement, is described.

Inhibition of leukotriene synthesis has been an area of intense pharmaceutical interest as a means of targeting inflammatory and vascular diseases.[1] The 5-lipoxygenase enzyme catalyzes the formation of leukotriene-A_4 ultimately from arachidonic acid.[2] Zileuton (Zyflo®), (**2**) a 5-lipoxygenase inhibitor discovered at Abbott Laboratories,[3] is the first selective 5-lipoxygenase inhibitor to receive approval by the FDA. The compound is marketed as the racemate, with several racemic syntheses having been reported to date.[2,4]



1 **2**, zileuton (1)

A synthetic route has been developed for the large scale manufacture of zileuton based on nucleophilic substitution by hydroxyurea under acidic conditions (equation 1).[5] Not surprisingly, impurities from di- and/or *O*-alkylation of hydroxyurea were observed in the final crystallized product. However, an unknown impurity that was present in amounts up to 0.6% was also observed with regularity. In order to do extensive toxicological testing, larger amounts of this impurity were required. An effort was undertaken to characterize and synthesize the unknown impurity.



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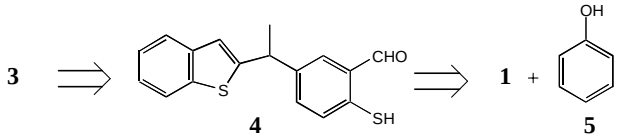
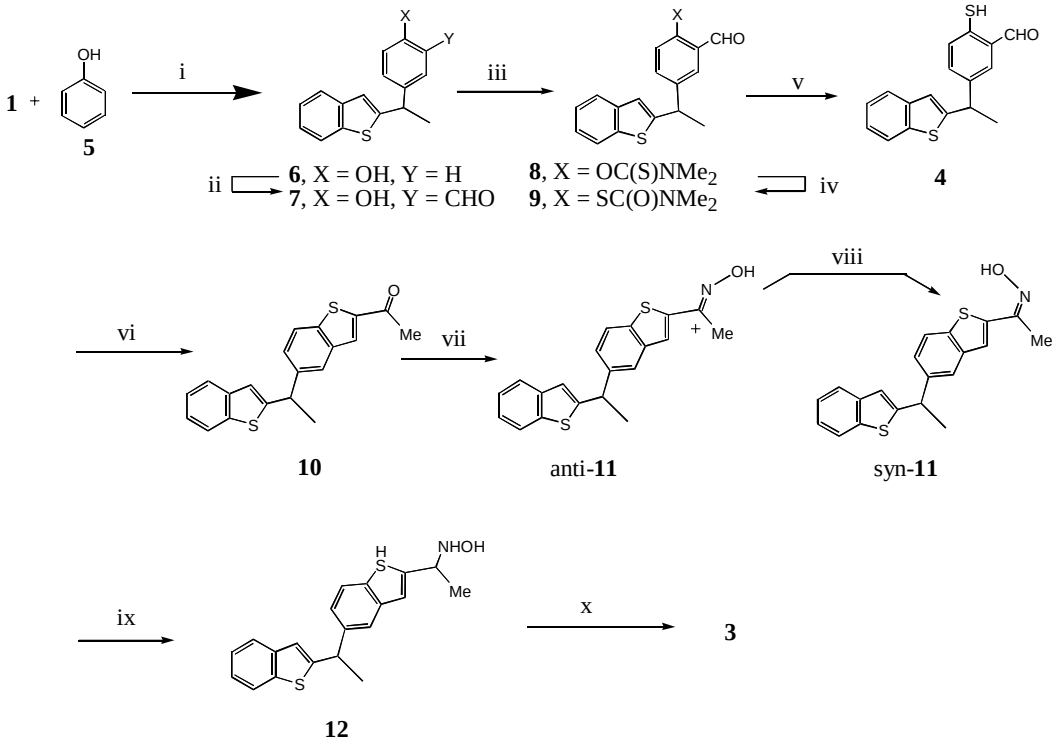
While attempting to characterize this impurity, the 5-substituted dimeric benzo[*b*]thiophene (**3**) was initially identified as a potential target, from a Friedel-Crafts reaction between **1** and **2**.[6] This note describes our efforts to synthesize this molecule.

Scheme 1



An approach based on mimicking, and optimizing, the reaction conditions that led to **3** was not considered feasible since electrophilic substitution in the 5-position is not favored.[7] However, a retrosynthetic analysis suggested that the 2-mercaptobenzaldehyde derivative (**4**) might be a key intermediate for obtaining the 5-substituted benzo[*b*]thiophene (Scheme 1).[8] This in turn was seen as coming from a *para*-selective Friedel-Crafts coupling of the alcohol (**1**) with phenol (**5**).[9] The synthetic pathway to prepare the 5-substituted benzo[*b*]thiophene (**3**) is outlined in Scheme 2.

Scheme 2



Reagents : i, BF_3•OEt, CH_2Cl_2; ii, NaOH, $CHCl_3$; iii, dimethylthiocarbamoyl chloride, KOH; iv, triglyme, 200°C; v, NaOH, 60°C; vi, chloroacetone; vii, NH_2OH; viii, HCl, EtOH; ix, BH_3-pyridine; x, potassium cyanate.

Treatment of **1** with 2 equiv. of **5** in the presence of 1 equiv of BF_3Et_2O provided two products in a ratio of 89:11.[10] Chromatographic purification afforded the *p*-phenol (**6**) in 56% overall yield. Attempts at introducing the carboxaldehyde group *ortho* to the phenol employing Vilsmeier-Haack conditions ($POCl_3$/DMF)[11] or $SnCl_4$/lutidine/paraformaldehyde[12] were unsuccessful. However, Reimer-Tiemann[13] conditions ($CHCl_3$/NaOH) provided the desired 2-hydroxybenzaldehyde derivative

(**7**) in 23% yield (92% based on recovered starting material).

Once construction of the dimeric substrate (**7**) had been achieved, the second thiophene unit needed to be installed. Conversion of the hydroxyl in **7** to a thiol was achieved *via* a Newman-Kwart rearrangement.[14] The hydroxyl group in **7** was first converted to the *O*-thiocarbamate (**8**) in 66% yield, followed by thermal rearrangement to the *S*-thiocarbamate (79% yield). Hydrolysis of the *S*-thiocarbamate (**9**) to the thiol (**4**) was followed by *in-situ* cyclization, using chloroacetone, to provide the methyl ketone (**10**) in 49% yield. Subsequent oximation with aqueous hydroxylamine provided **11** as a mixture of *syn-anti* isomers.[15]

The oximes needed to be reduced to the hydroxyamine prior to reaction with potassium cyanate. It has previously been observed that the *syn*-oxime is consumed faster than the *anti*-oxime, suggesting that the reduction rate is dependent upon the stereochemistry of the oxime.[16] To take advantage of this rate difference, the oxime mixture was equilibrated with ethanolic HCl[17] to a 2.3/1 (*syn/anti*) mixture of oximes (**11**). Reduction of the *syn* rich oxime mixture with 4 equiv. of BH_3-pyridine gave 72% conversion in 1 hour.[18] Addition of 4 more equiv. of BH_3-pyridine provided the hydroxylamine (**12**) quantitatively. Immediate treatment of the unstable hydroxylamine (**12**) with potassium cyanate gave the desired target compound (**3**) in 81% yield from the ketone (**10**).

EXPERIMENTAL

General Methods. All commercial reagents were used as purchased without any further purification. 2-Acetylbenzothiophene was obtained from Sumitomo Seika. Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.5 MHz respectively. Analytical TLC was performed on Merck silica $60F_{254}$ or C18-silica 60 plates. Flash chromatography was performed using Silica Gel 60 (230-400 mesh) or C-18 Silica Gel 60. HPLC analyses were run on a Zorbax SB-C8 reverse-phase column using CH_3CN: $0.1\%H_3PO_4$ (60:40) as the mobile phase (λ=254nm).

1-(Benzo[*b*]thien-2-yl)ethanol (1). To a solution of 2-acetylbenzo[*b*]thiophene (25.0 g, 0.14 mol) in methanol (100 mL) cooled to 0^{o}C, was added $NaBH_4$ (6.4 g, 0.17 mol). After 20 min, the solution was quenched with water (200 mL), and extracted twice with ethyl acetate (200 mL). The organics were combined, washed with water (100 mL), and concentrated *in-vacuo* to provide a solid. The product was crystallized from heptane/ethyl acetate (200 mL/15 mL) to give 21.7g (87%) of **1**: mp 60-62^{o}C (lit.,[19] 62-63^{o}C); ^{1}H NMR ($CDCl_3$) δ 7.90-7.70 (m, 2H), 7.40-7.20 (m, 2H), 7.20 (s, 1H), 5.25 (qd, 1H, *J* = 6.3, 5.4 Hz, 2.15 (d, 1H, *J* = 5.4 Hz), 1.70 (d, 3H, *J* = 6.3 Hz).

4-[1-(Benzo[*b*]thien-2-yl)ethyl]phenol (6). To a solution of phenol (**5**) (53 g, 0.56 mol) and **1** (50 g,

0.28 mol) in CH_2Cl_2 (3 L), at -6°C, was slowly added BF_3-OEt_2 (34.4 mL, 0.28 mol). The solution was stirred for 15 min at 0-5°C before quenching with saturated sodium bicarbonate (1 L). The organics were separated and washed with water (500 mL). Concentration *in vacuo* gave 91 g of oil as a 89:11 ratio of isomers.[20] Column chromatography (C-18 functionalized silica gel; MeOH/H_2O, 50/50 to 70/30) gave after crystallization from methanol/water (v/v, 50/50), 40 g (56%) of phenol (**6**) as a white crystalline solid: mp 112-113°C; IR 3431 (br), 1599, 1509, 1449, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (d, 1H, *J* = 8.4 Hz), 7.54 (d, 1H, *J* = 8.4 Hz), 7.20-7.10 (m, 2H), 7.10-7.02 (m, 2H), 6.90 (s, 1H), 6.70-6.65 (m, 2H), 4.62 (br s, 1H), 4.22 (q, 1H, *J* = 7.3 Hz), 1.62 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) (DEPT) δ 154.2, 152.0, 139.9, 139.5, 137.6, 128.6(+), 124.0(+), 123.6(+), 123.0(+), 122.1(+), 119.9(+), 115.3(+), 40.6(+), 22.9(+). Anal. Calcd for $C_{16}H_{14}OS$: C, 75.56; H, 5.55; S, 12.61. Found: C, 75.50; H, 5.41; S, 12.58.

5-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-hydroxybenzaldehyde (7). A suspension of powdered NaOH (19.0g, 474 mmol) and **6** (14.7 g, 57.9 mmol) in ethanol (72 mL) and water (23 mL) was heated to 65°C. Chloroform (16.1 g, 135 mmol) was added portionwise, maintaining the temperature above 65°C. After the addition was complete, the reaction mixture was stirred at 70°C for 40 min. The reaction mixture was cooled to 5°C and ethyl acetate (150 mL) added. The pH was adjusted to 3-4 with 2M HCl. The organic layer was separated and the aqueous back-extracted with ethyl acetate (2 x 100 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to give crude product (14.3 g). This was purified by column chromatography (toluene) to provide **7** as an oil (3. 7 g, 23%). Unreacted starting material was also recovered (9.5 g). ^1H NMR ($CDCl_3$) δ 10.95 (s, 1H), 9.81 (s, 1H), 7.73-7.65 (m, 2H), 7.45 (m, 2H), 7.33-7.21 (m, 2H), 7.03 (s, 1H), 6.94 (d, 1H, *J* = 8Hz), 4.37 (q, 1H, *J* = 7 Hz), 1.75 (d, 3H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) (DEPT) δ 196.4(+), 160.4, 150.6, 139.7, 139.3, 136.8, 136.2(+), 131.8(+), 124.2(+), 123.8(+), 123.1(+), 122.1(+), 120.3, 120.2(+), 117.75(+), 40.2(+), 22.6(+). MS (DCI/NH_3) *m/z* (rel. intensity 300 ($[M+NH_4]^+$ 100). IR (film) 1655 cm^{-1}; Anal. Calcd for $C_{17}H_{14}O_2S$: C, 72.31; H, 5.00; S, 11.36. Found: C, 72.46; H, 5.00; S, 11.09.

5-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-(*O*-dimethylthiocarbamate)benzaldehyde (8). A solution of KOH (1.43 g, 25.5 mmol) in water (20 mL) was cooled to 0°C and slowly treated with a solution of **7** (6.0 g, 21.3 mmol) in THF (20 mL). This was warmed to 15°C and stirred for 20 min. After cooling to 5°C, a solution of dimethylthiocarbamoyl chloride (2.74 g, 22.2 mmol) in THF (33 mL) was added slowly. Reaction was warmed to rt and stirred for 2 h. The reaction was cooled to 10°C and ethyl acetate (150 mL) added. The layers were separated and the aqueous extracted with ethyl acetate (60 mL). The organics were combined, dried over $MgSO_4$ and concentrated to an oil. This was purified

by column chromatography (5% EtOAc in toluene) to provide 5.15 g (66%) of **8** as a solid: mp 126-137ºC; ^{1}H NMR ($CDCl_3$) δ 10.05 (s, 1H), 7.86 (d, 1H, *J* = 2.6 Hz), 7.74-7.66 (m, 2H), 7.55 (dd, 1H, *J* = 2.2, 8.1 Hz), 7.34-7.23 (m, 2H), 7.09 (d, 1H, *J* = 8.5 Hz), 7.06 (br s, 1H), 4.48 (q, 1H, *J* = 7.4 Hz), 3.47 (s, 3H), 3.40 (s, 3H), 1.80 (d, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 188.3 (+), 187.1, 154.1, 150.1, 143.5, 139.7, 139.4, 134.0(+), 129.0, 128.1(+), 124.6(+), 124.2(+), 123.8(+), 123.2(+), 122.1(+), 120.5(+), 43.4(+), 40.7(+), 38.9(+), 22.6(+); IR (KBr) 1700 cm^{-1}; MS (CI) *m/z* (rel. intensity 370 ($[M+H]^+$ 100). Anal. Calcd for $C_{20}H_{19}N_2O_2S_2$: C, 65.01; H, 5.18; N, 3.79; S, 17.36. Found: C, 65.07; H, 5.11;N, 3.77; S, 17.14.

5-[1-(Benzo[*b*]thien-2-yl)ethyl]-2-(*S*-dimethylthiocarbamate)benzaldehyde (9). A solution of **8** (1.9g, 5.1 mmol) in triglyme (100 mL) was heated to 200°C for 2 hours. After cooling to rt, the mixture was diluted with ethyl acetate (150 mL) and water (200 mL). The organic layer was separated and washed with water (3 X 50 mL) and brine (100 mL). This was then concentrated to an oil which was purified by column chromatography, eluting with methylene chloride to provide 1.5 g (79%) of an oil. ^{1}H NMR ($CDCl_3$) δ 10.32 (s, 1H), 7.99 (s, 1H,), 7.71-7.64 (m, 2H,), 7.49 (m, 2H), 7.31-7.20 (m, 2H), 7.03 (s, 1H), 4.45 (q, 1H, *J* = 7.0 Hz), 3.11 (br s, 3H), 2.98 (br s, 3H), 1.76 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 191.1(+), 165.2, 149.6, 147.5, 139.6, 139.3, 137.7, 137.6(+), 132.7(+), 130.5, 127.3(+), 124.1(+), 123.8(+), 123.1(+), 122.0(+), 120.5(+), 41.0(+), 37.0(+), 22.4(+); IR (KBr) 1670, 1690 cm^{-1}; MS (EI) m/z (rel intensity 370 $[M+H]^+$).

1-{5-[1-(Benzo[*b*]thien-2-yl)ethyl]benzo[*b*]thien-2-yl}ethanone (10). A mixture of **9** (1.8g, 4.9 mmol), isopropanol (40 mL) and 50% NaOH (0.6 g) was heated to 60°C and held at that temperature for 3 h. The reaction was then cooled to 0°C and chloroacetone (1.1 g, 11.9 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h. Water (200 mL) and ethyl acetate (200mL) were added. The organic layer was washed with 0.1% NaCl (3 x 100 mL) and dried over $MgSO_4$. After concentrating, the residue was purified by column chromatography (toluene) to provide 0.8 g of **10** (49%).

mp 139.5-140.7°C; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, 1H, *J*=0.7 Hz), 7.81-7.78 (m, 2H), 7.73-7.66 (m, 2H), 7.41 (dd, 1H, *J* = 7.0, 1.5 Hz), 7.33-7.22 (m, 2H), 7.07 (s, 1H), 4.52 (q, 1H, *J* = 7.0 Hz), 2.63 (s,3H), 1.82 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 192.2, 150.9, 144.4, 142.5, 141.1, 139.7, 139.4, 139.4, 129.6(+), 127.6(+), 124.2(+), 124.0(+), 123.8(+), 123.1(+), 122.1(+), 120.3(+), 41.2(+), 26.8(+), 22.9(+); IR (KBr) 1660 cm^{-1}; MS (CI) *m/z* (rel. intensity 337 ($[M+H]^+$ 100). Anal. Calcd for $C_{20}H_{16}OS_2$: C, 71.39; H, 4.79; O, 4.76 . Found: C, 71.15; H, 4.99; O, 4.47.

syn/anti*-1-{5-[1-(Benzo[*b*]thien-2-yl)ethyl]benzo[*b*]thien-2-yl}ethanone oximes (11).** To a homogeneous solution of **10** (750 mg, 2.2 mmol) in isopropyl alcohol (15 mL) and ethyl acetate (15 mL) was added 3 drops of conc. HCl and 50% solution of hydroxylamine (0.31 g, 4.5 mmol) in H_2O (1 mL). The mixture was heated to reflux for 90 min. The reaction was cooled to rt and concentrated *in vacuo* to give a solid. The solid was dissolved in ethyl acetate (50 mL), washed with water (25mL), dried over $MgSO_4$, and concentrated *in-vacuo* to give a yellow solid (700 mg, 89%). HPLC showed a 3.2:1 ratio of *anti:syn* isomers. This mixture was used without further purification. MS (CI) *m/z* (rel. intensity 352 ($[M+H]^+$, 100) ***Anti*-11**: ^{1}H NMR ($CDCl_3$) δ 7.83-7.65 (m, 4H), 7.42 (s, 1H), 7.38-7.21 (m, 3H), 7.07 (s,1H, 4.49 (q, 1H, *J* = 7.2 Hz), 2.35 (s, 3H), 1.82 (d, 3H, *J* = 7.2 Hz); ***Syn-11: ^{1}H NMR ($CDCl_3$) δ 7.83-7.65 (m, 4H), 7.43 (s, 1H), 7.38-7.21 (m, 3H), 7.07 (s, 1H), 4.50 (q, 1H, *J* = 7.2 Hz), 2.42 (s, 3H), 1.83 (d, 3H, *J* = 7.2 Hz).

N-(1-{5-[1-(Benzo[*b*]thien-2-yl)ethyl]benzo[*b*]thien-2-yl}ethyl)-*N*-hydroxyurea (3). To a solution of oximes (**11**) (580 mg, 1.65 mmol) in methylene chloride (15 mL) was added a solution of $HCl_{(g)}$ in ethanol (1.2 g in 15 mL). This was stirred at ambient temperature overnight. Analysis of the reaction mixture by HPLC showed 70% *syn* oxime. The mixture was concentrated *in vacuo* to an oil and redissolved in ethanol (10 mL) and methylene chloride (10mL). The solution was cooled to 15°C and BH_3-pyridine (613 mg, 6.6 mmol) was slowly added. A solution of $HCl_{(g)}$ in ethanol (450 mg in 5mL) was slowly added to the mixture over 10 min. The temperature was maintained below 19°C during the addition. After 1.5 h, additional BH_3-pyridine (613 mg, 6.6 mmol) was added. The reaction was shown by HPLC to be more than 90% complete after 3 h. The mixture was concentrated to a foam and dissolved into ethyl acetate (30 mL) and water (15 mL). While stirring rapidly and with the temperature below 10°C, the pH was raised to >10 by the addition of 50% NaOH solution. The organic layer was separated and the aqueous extracted with ethyl acetate. The ethyl acetate layers were combined and carried on without isolation.

To the ethyl acetate solution was added 15 mL of aqueous potassium cyanate (134 mg, 1.65 mmol) and the mixture was cooled to 10-15°C. While stirring rapidly, conc. HCl was added dropwise until the pH was <2. The reaction mixture was allowed to warm to rt and stirred for 10 min. HPLC showed that the reaction was complete. The ethyl acetate layer was separated and the aqueous extracted with ethyl acetate (15 mL). The combined ethyl acetate layers were dried over $MgSO_4$ and concentrated *in vacuo* to a tan-colored solid (560 mg, 86%). The crude product was recrystallized from toluene to provide a creme-colored powder (620 mg, 50%): mp 112-113°C; ^{1}H NMR (CD_3CN) δ 7.90-7.82 (s, 4H), 7.45-7.29 (m, 5H), 5.73 (q, 1H, *J* = 7.0 Hz), 4.66 (q, 1H, *J* = 7.0 Hz), 1.90 (d, 3H, *J* = 7.2 Hz), 1.68 (d, 3H, *J*

= 7.0 Hz); ^{13}C NMR (CD_3CN) δ 162.4, 153.5, 147.9, 143.4, 141.3, 141.2, 140.6, 139.2, 125.6(+), 125.3/125.3(+),125.1(+), 124.4(+), 123.6(+), 123.4(+), 123.0/123.0(+), 121.3(+), 54.0(+), 42.1(+), 23.1(+), 17.7(+), 17.6(+); IR (KBr) 1655 cm^{-1}; MS (ESI) *m/z* (rel. intensity 397 ($[M+H]^+$ 100) High Resolution MS (FAB) *m/z* calcd 397.1044, found 397.1040 Anal. Calcd for $C_{21}H_{20}N_2O_2S_2 \cdot 1/2H_2O$: C, 62.21; H, 5.22; N, 6.91; S, 15.79. Found: C, 62.61; H, 5.14; N, 7.17; S, 15.60.

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