Synthesis of the 5-Lipoxygenase Inhibitor Zileuton from Thiophenol

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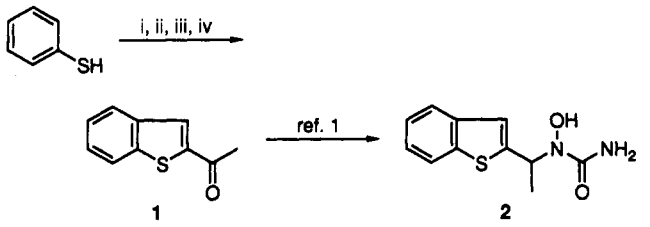
Zileuton (*N*-(1-benzo[*b*]thien-2-ylethyl)-*N*-hydroxyurea)[1-3] was the first orally administered selective 5-lipoxygenase inhibitor to demonstrate efficacy in ulcerative colitis[4,5] and in asthma.[6-8] The enzyme 5-lipoxygenase catalyses the first step in the biosynthetic pathway to the formation of the leukotrienes.[9] Preventing the formation of leukotrienes represents a promising new therapy for inflammatory and allergic disorders.[10] 2-Acetylbenzo[*b*]-thiophene (1) is a key intermediate for the synthesis of zileuton (2). Several methods have been reported to prepare 2-acetylbenzo[*b*]thiophene.[11,12] We were interested in exploring new efficient routes to this key intermediate which might be better suited to large-scale preparation of zileuton. In this paper we report the synthesis of 1 by a one-pot process from thiophenol as illustrated in Scheme I.

The published procedure for ortho lithiation of thiophenol was applied,[13-15] involving treatment of thiophenol with *n*-BuLi in a cyclohexane and trimethylethylenediamine mixture. After formation of the ortho-lithiated phenylthioate dianion successive addition of dimethylformamide and chloroacetone followed by a standard aqueous acidic workup provided the desired 2-acetylbenzo-[*b*]thiophene (1) in 75% yield. This intermediate was then converted to zileuton by oxime formation, reduction to the corresponding hydroxylamine and treatment with trimethylsilyl isocyanate as previously described.[1]

Thiophenol could also be used to prepare 2-2'-dithiobisbenzaldehyde (3), a useful stable precursor for generation of the relatively unstable 2-mercaptobenzaldehyde.[16] Mercaptobenzaldehyde has been utilized for the synthesis of various heterocycles such as benzo[*b*]thiophenes,[17] 1,2-benzoisothiazoles,[18] 2*H*- and 4*H*-1-benzopyrans,[19,20] and 1-benzoxepins.[21] Oxidation with iodine of the relatively unstable 2-mercaptobenzaldehyde formed in situ by the reaction of the ortho-lithiated phenylthioate dianion with dimethylformamide followed by aqueous acidic workup provided 3 in 90% yield (Scheme II).

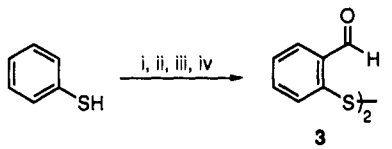
Scheme I[a]



1 2

[a] Reagents and conditions: (i) 2 equiv of *n*-BuLi/TMEDA/cyclohexane, 0 °C to rt; (ii) DMF; (iii) $ClCH_2COCH_3$; (iv) H_3O^+.

Scheme II[a]



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[a] Reagents and conditions: (i) 2 equiv of *n*-BuLi/TMEDA/cyclohexane, 0 °C to rt; (ii) DMF; (iii) 0.5 equiv of I_2; (iv) H_3O^+.

Practical, one-pot preparations of 2-acetylbenzo[*b*]-thiophene (1) and 2,2'-dithiobisbenzaldehyde (3) have been devised from readily available and inexpensive thiophenol which are applicable to the preparation of the 5-lipoxygenase inhibitor zileuton.

Experimental Section

General. All reagents were purchased from Aldrich. ^{1}NMR spectra were recorded at 300.15 MHz and mass spectra were obtained using a Hewlett-Packard HP 5985 (Cl, El) spectrometer. Tetrahydrofuran was distilled from benzophenone ketyl.

2-Acetylbenzo[*b*]thiophene (1). To a solution of *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 6.8 mL, 45.4 mmol) and *n*-BuLi (18 mL of 2.5 M in hexane, 45.4 mmol) in dry cyclohexane (50 mL) was added thiophenol (2.5 g, 22.7 mmol) at ice-bath temperature. The reaction mixture was stirred at room temperature for 20 h (the initial clear yellow mixture becomes an opaque white viscous slurry). Dimethylformamide (3 mL) in tetrahydrofuran (30 mL) was added at ice-bath temperature, and the mixture was stirred for 0.5 h. Then chloroacetone (2 mL, 24 mmol) was added, and the mixture was stirred for 4 h at room temperature. The mixture was diluted with ethyl acetate (50 mL), and 6 N HCl was added dropwise to make the solution acidic. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The product was crystallized with ethyl acetate/pentane or dichloromethane/pentane to give 3 g (75%) of desired 2-acetylbenzo[*b*]thiophene: ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3 H), 7.45 (m, 2 H), 7.89 (m, 2 H), and 7.95 (s, 1 H); MS *m/e* $(M + 1)^+ = 177$. Anal. Calcd for $C_{10}H_8SO$: C, 68.15; H, 4.58; S, 18.19. Found: C, 68.29; H, 4.57; S, 18.47.

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2,2'-Dithiobisbenzaldehyde (3). Under a nitrogen atmosphere, thiophenol (2.5 g, 22.7 mmol) and TMEDA (6.8 mL, 45.4 mmol) were dissolved in cyclohexane (20 mL) and the mixture was cooled in an ice–water bath (5 °C) while a solution of *n*-BuLi, (18 mL of 2.5 M in hexane, 45.4 mmol) was added slowly. The mixture was allowed to warm to room temperature, and after stirring for 20 h dimethylformamide (10 mL) was added. The mixture was stirred for 30 min and then cooled in an ice–water bath. A solution of I_2 (1.45 g, 11.4 mmol) in ethyl acetate (30 mL) was added dropwise, maintaining the temperature of the mixture near 5 °C with an ice–water bath. After the addition was complete the mixture was stirred for 1 h, and then it was acidified with 1 N HCl (30 mL) and stirred for 1 h further. The organic layer was separated and washed with aqueous $NaHSO_3$ to remove excess iodine, then washed with water. The organic extract was dried over $MgSO_4$ and filtered and the solvent removed under reduced pressure to provide a solid (3 g, 98%). Recrystallization from methylene chloride–pentane, gave crystals: mp 148–149 °C (lit. mp 145 °C); ^{1}H NMR ($CDCl_3$) δ 7.35–7.55 (4 H, m) 7.78 (2 H, d, J = 9 Hz), 7.88 (2 H, d, J = 9 Hz), 10.25 (2 H, s); CIMS, $M^+ + NH_4$ = 292.

Additions and Corrections

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Johann Mulzer,* Henrietta Dehmlow, Jürgen Buschmann, and Peter Luger. Stereocontrolled Total Synthesis of the Unnatural Enantiomers of Castanospermine and 1-*epi*-Castanospermine.

Page 3201, column 2, line 23. The data for (1*S*,6*R*,7*S*,8*S*,-8a*S*)-1,6,7,8-tetrahydroxyoctahydroindolizine hydrochloride were given instead of those for the free indolizidine **2**. The correct data for compound **2** are as follows.

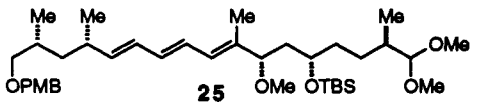
(1*S*,6*R*,7*S*,8*S*,8a*S*)-1,6,7,8-Tetrahydroxyoctahydroindolizine (2): ^{1}H NMR (500 MHz, D_2O + TSP) δ 4.23 (ddd, 1 H, J = 3, 6, 9 Hz), 3.6 (m, 1 H, J = 5, 9.5, 10 Hz), 3.37 (dd, 1 H, J = 9.5 Hz), 3.33 (dd, 1 H, J = 8.8, 17.5 Hz), 3.15 (dd, 1 H, J = 5, 11 Hz), 2.94 (dt, 1 H, J = 2.5, 8.8 Hz), 2.58 (dd, 1 H, J = 8.8, 17.5 Hz), 2.29 (m, 1 H), 2.24 (t, 1 H, J = 11 Hz), 2.13 (dd, 1 H, J = 9.5, 10 Hz), 1.69 (m, 1 H); ^{13}C NMR (D_2O + TSP; DEPT) δ 81.41 (CH), 76.45 (CH), 75.97 (CH), 75.57 (CH), 72.54 (CH), 57.47 (CH_2), 53.65 (CH_2), 35.18 (CH_2); HRMS calcd for $[C_8H_{15}NO_4]^+$, $[M]^+$ 189.100109, found 189.1022; MS *m/e* 189 (24.6, $[M]^+$), 172 (31), 154 (8.6), 145 (100, $[C_6H_{11}NO_3]^+$), 128 (11), 86 (35.9, $[C_4H_8NO]^+$).

Percy S. Manchand,* Peter S. Belica, Michael J. Holman, Tai-Nang Huang, Hubert Maehr, Steven Y.-K. Tam, and Roxana T. Yang. Syntheses of the Anti-AIDS Drug 2',3'-Dideoxycytidine from Cytidine.

Page 3474, column 2. Reference to compound **10** is 3b. The following reference should also be added: Belica, P. S.; Huang, T.-N.; Manchand, P. S.; Partridge, J. J.; Tam, S. U.S. Pat. 4900828, February 13, 1990.

Stephanie D. Meyer, Tetsuo Miwa, Masashi Nakatsuka, and Stuart L. Schreiber*. Synthetic Investigations of Rapamycin. 1. Synthesis of a C_{10}–C_{21} Fragment.

Page 5059, Structure **25** in Scheme III should be drawn as shown below:



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Edward C. Taylor* and Paul Gillespie. Further Acyclic Analogues of 5,10-Dideaza-5,6,7,8-tetrahydrofolic Acid.

Page 5757. The first two paragraphs should read as follows:

5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, Lometrexol, **1**) is an antitumor agent with a novel site of action as an inhibitor of glycinamide ribonucleotide formyltransferase (E.C. 2.1.2.1) in the purine de novo biosynthetic pathway.[1] In vitro studies have shown that DDATHF inhibits the growth of a large number of cancer cell lines, and in vivo studies have shown it to be effective against a range of solid tumors, including lung, mammary, and colon tumors.[2] Early syntheses of DDATHF[3] relied on catalytic hydrogenation to reduce the pyridine ring and led to the formation of a mixture of diastereomers epimeric at C-6, but a chiral synthesis of the drug has recently been developed.[4a] The separated diastereomers were found to be essentially equiactive as inhibitors of leukemia cell growth due to their effects on de novo purine synthesis.[4b]

We recently reported the preparation of 7-desmethylene-DDATHF (7-DM-DDATHF, **2**),[5] an acyclic analogue of the parent compound which lacks the C-6 chiral center. This compound showed high cytotoxicity against CCRF-CEM cells. We have now prepared several analogues of **2** to examine the effect of varying the pyrimidine ring substituents.

Page 5757. Reference 4 should now read as follows:

(4) (a) Barnett, C. J.; Wilson, T. M. *Tetrahedron Lett.* **1989**, *30*, 6291. (b) Moran, R. G.; Baldwin, S. W.; Taylor, E. C.; Shih, C. *J. Biol. Chem.* **1989**, *264*, 21047.

Page 5758, line 19. Reference 6 should be changed to ref 5.

Paul S. Engel,* Donald T. Robertson, John N. Scholz, and Henry J. Shine*. Reaction of Azoalkanes with Isolable Cation Radical Salts.

Page 6178. The name of the second author should read Donald T. Robertson.