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EFFICIENT METHOD FOR SYNTHESIS OF 2-ACETYLBENZO(b)THIOPHENE AND ITS DERIVATIVES, THE KEY SYNTHONS FOR 5-LIPOXYGENASE INHIBITORS

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An efficient method was developed for synthesis of 2-acetylbenzo(b)thiophene (2a), the key intermediate for zileuton (1). Synthesis involves treatment of 2-chlorobenzaldehyde (5a) with tert-butylmercaptan (6) to form 2-(tert-butylthio)benzaldehyde (7a), which upon treatment with HBr in water gave the disulfide derivative 2,2′-disulfanediyldibenzaldehyde (8a) in 97% yield. Finally, the reaction of 8a with acetylacetone (9) and 1-chloroacetone (10) gave 2-acetylbenzo(b)thiophene (2a) in 94% yield. The methodology is general and suitable for the preparation of its derivatives, 2b–d.

Keywords: 2-Acetylbenzo(b)thiophene; 5-lipoxygenease inhibitors; synthesis

INTRODUCTION

Inflammation of airways typically causes the hallmark clinical symptoms of asthma, which affects about 10% of the population, and its prevalence and mortality continue to increase.[1] Several factors contribute to the regulation of airflow in patients suffering with asthma, which include mediators such as histamine, prostaglandins, thromboxane, and leukotrienes. All act as chemo-attractants for inflammatory cells.[2] Leukotrienes (LTs) are potent inflammatory mediators, and they are formed from arachidonic acid, which is catalyzed by a key enzyme, 5-lipoxygenease (5-LOX).[3] The 5-LOX pathway, in addition to asthma, is also associated with a variety of other diseases, such as atherosclerosis, rheumatoid arthritis, cancer, osteoporosis, and liver fibrosis.[4] Thus, inhibitors of 5-LOX may lead to the development of novel therapeutic treatments, and the potential of this approach has been extensively highlighted.[5] Zileuton [A-64077, (±)-*N*-benzo(b)then-2-ylethyl)-*N*-hydroxyurea, **1**] is a selective inhibitor of 5-LOX (Fig. 1), which is believed to form a complex with the iron molecule in the active site of the enzyme and exhibits good efficacy.[6] The core unit, *N*-aryethyl hydroxyurea, is identified as critical for its novel

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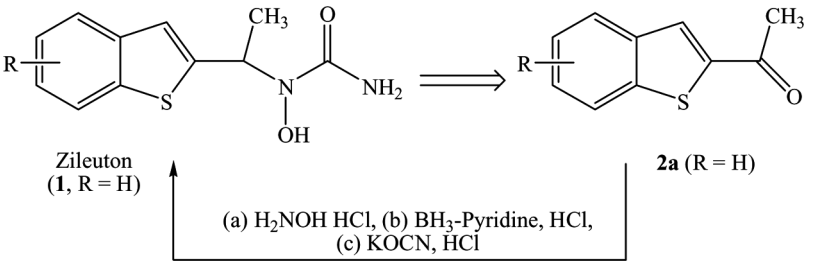


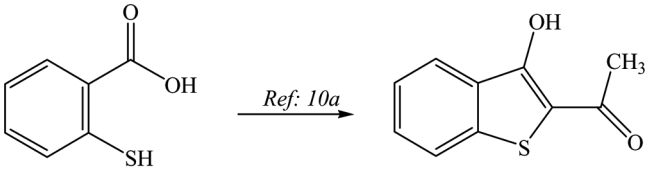
Figure 1. Zileuton (**1**) and its synthesis from 2-acetylbenzo(b)thiophene (**2a**).

activity, and research efforts continue to further understand and improve the activity.[7] Several approaches have been developed for the synthesis of zileuton (**1**).[8] Among these, the strategy based on conversion of 2-acetylbenzo(b)thiophene (**2a**) to zileuton (**1**) in a three-step sequence (Fig. 1) is efficient, cost-effective, and amenable for large-scale preparation.[8g,9] In this article, we describe an efficient method for the synthesis of 2-acetylbenzo(b)thiophene (**2a**), the key intermediates for preparation of zileuton (**1**) and its aryl substituted derivatives (**2b–d**).

RESULTS AND DISCUSSION

Several methods have been reported for the synthesis of 2-acetylbenzo(b)thiophene (**2a**) starting from 2-thiobenzoic acid,[10] 2-thiobenzaldehyde,[11] thiophenol,[8g] or thiophene.[12] Among these methods, the synthesis involving 2-thiobenzoic acid (**3**)[10c] produces 2-acetyl-3-hydroxy-benzo(b)thiophene (**5**) (Scheme 1) in good overall yield, which proceeds through a disulfide intermediate. However, the use of concentrated sulfuric acid as a solvent in this transformation and the need for removal of hydroxyl group at the 3-position of **4** make this method practically unsuitable for the preparation of 2-acetylbenzo(b)thiophene (**2a**) or its aryl substituted derivatives. We envisioned that a disulfide intermediate, such as (**8a**) with an aldehyde group at the 2-position, which can be prepared from 2-*tert*-butylthiobenzaldehyde (**7a**),[13] should yield the desired synthon, 2-acetylbenzo (b)thiophene (**2a**).

Accordingly, the key intermediate, 2,2′-disulfanediyldibenzaldehyde (**8a**), was prepared from 2-chlorobenzaldehyde (**5a**) via 2-*tert*-butylthiobenzaldehyde (**7a**) in two steps. Thus, reaction of 2-thiobenzaldehyde (**5a**) with 1.5 equiv. of

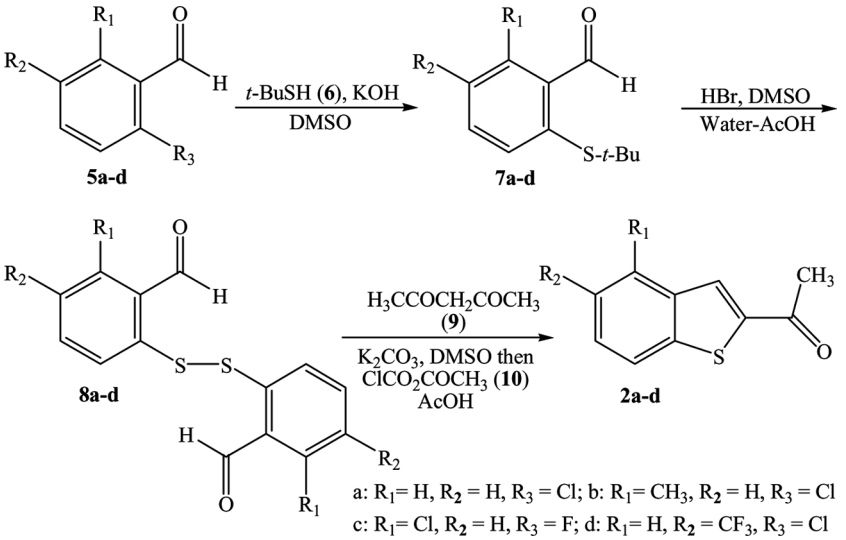


3 **4**

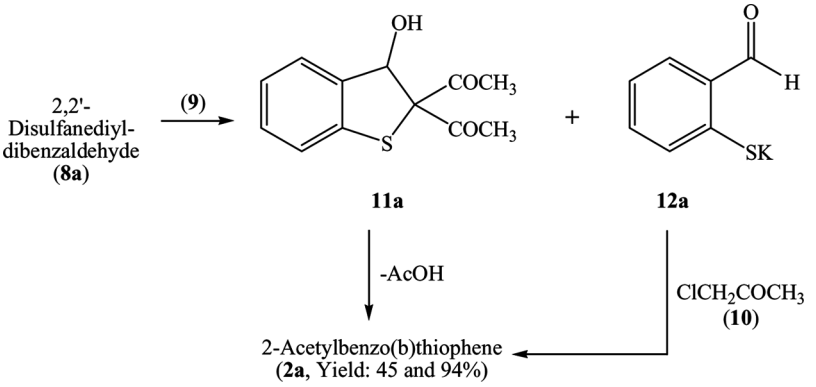
Scheme 1. Synthesis of 2-acetyl-3-hydroxybenzo(b)thiophene (**4**).

tert-butylmercaptan (**6**) and 1.1 equiv of potassium hydroxide in dimethylsulfoxide (DMSO) at 110 °C for 1 h gave 2-(*tert*-butylthio)benzaldehyde (**7a**) in almost quantitative yield. The next step in the synthesis was to convert 2-(*tert*-butylthio)benzaldehyde (**7a**) into the desired disulfide intermediate, 2,2′-disulfanediyldibenzaldehyde (**8a**), which was achieved in 97% yield by treatment of (**7**) with 3.0 equiv of 48% HBr in acetic acid[13] and DMSO. Our attempts to carry out this transformation of **7a** to **8a** using sulfuric acid[10a] produced the desired 2-acetylbenzo(b)thiophene (**2a**), but significant decomposition was also observed. In addition, the **2a** produced by using sulfuric acid[10a] required additional purification, including carbon treatment to remove unidentified colored impurities. Finally, we found that the reaction of disulfide derivative (**8a**) with acetylacetone (**9**) in the presence of anhydrous potassium carbonate in DMSO gave the desired key synthon, 2-acetylbenzo(b)thiophene (**2a**), in about 45% yield along with the by-product, sodium salt of mercaptobenzaldehyde (**12a**). Further, the by-product, mercaptobenzaldehyde (**12a**), was also productively converted to the desired 2-acetylbenzo(b)thiophene (**2a**), as described in the next section.

As expected, the reaction of bisulfide (**8a**) with acetylacetone (**9**) produces both 1,1′-(3-hydroxy-2,3-dihydrobenzo[b]thiophene-2,2-diyl)diethanone (**11a**) and the sodium salt of mercaptobenzaldehyde (**12a**), as shown in Scheme 3. However, only the intermediate **11a** yields 2-acetylbenzo(b)thiophene (**2a**) with the loss of acetic acid under reaction conditions, thus leaving theoretically 50% of mercaptobenzaldehyde (**12a**) as its sodium salt. We found that the addition of 1.1 equiv. of 1-chloroacetone (**10**) to the reaction mixture to convert **12a** to the desired **2a** effectively improved the yield of 2-acetylbenzo(b)thiophene (**2a**) to 94%. Thus, the overall yield of 2-acetylbenzo(b)thiophene (**2a**), in a three-step sequence starting from 2-chlorobenzaldehyde (**5a**), is 93%. The method is general and quite useful for the preparation of aryl substituted 2-acetylbenzo(b)thiophene derivatives (Schemes 2



Scheme 2. Synthesis of 2-acetylbenzo(b)thiophene (**2a–d**).



Scheme 3. Efficient conversion of 2,2′-disulfanediyldibenzaldehyde (**8a**) to 2-acetylbenzo(b)thiophene (**2a**).

and 3), such as 2-acetyl-4-methylbenzo(b)thiophene (**2b**), 2-acetyl-4-chlorobenzo(b)thiophene (**2c**), and 2-acetyl-5-(trifluoromethyl) benzo(b)thiophene (**2d**) in three steps starting from the corresponding aryl aldehydes (**5b–c**), respectively.

In summary, a novel and highly efficient method was developed for the synthesis of 2-acetylbenzo(b)thiophene (**2a**), the key intermediate for preparation of zileuton (**1**). The three-step sequence produces 2-acetylbenzo(b)thiophene (**2a**) in more than 93% overall yield. The methodology is suitable for preparation of substituted 2-acetylbenzo(b)thiophene derivatives (**2b–c**), which may be useful in the synthesis of improved 5-lipoxigenase inhibitors.

EXPERIMENTAL

General Methods and Materials

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (400 MHz), and the chemical shifts (δ) were reported. Mass spectrometry was performed on a ThermoFinnigan LCQ DECA XP quadrupole ion trap mass spectrometer utilizing positive-ion atmospheric pressure chemical ionization [APCI(+)]. Sample introduction was accomplished by flow injection with a flow solvent consisting of 1:1 acetonitrile/0.1M NH_4OH at a flow rate of 0.3 mL/min. High-resolution mass determinations were carried out on an Agilent LC/MSDTOF instrument using negative-ion electrospray [ESI(–)] using internal mass references. Helium is used as the collision gas for acquisition of data on LCQ DECA mass spectrometer. Sample introduction was accomplished by flow injection with a flow solvent consisting of 1:1 acetonitrile/0.1% HCOOH at a flow rate of 0.3 mL/min. Thin-layer chromatography (TLC) was performed on precoated TLC silica-gel $60\,F_{254}$ 5- × 10-cm plates and visualized with shortwave ultraviolet (UV) light (254 nm); solvent ratios are reported. Column chromatography was performed on silica gel, Merck grade 60 (70–230 mesh). All solvents were HPLC grade, and the reagents were purchased from Sigma-Aldrich (St. Louis, Missouri) and used without purification. Analytical reversed phase (RP) HPLC was performed using Agilent 1200 series HPLC instrument equipped with an Agilent Eclipse XD8-C18 column (4.6 × 150 mm, 5 mm).

Preparation of 2-Acetylbenzo(b)thiophene and Its Derivatives (2a–d) Using Example of 2-Acetylbenzo(b)thiophene (2a)

In a 250-mL round-bottom flask equipped with a stir bar, DMSO (20.0 mL, 0.28 mol, 4 equiv.) and powdered postassium hydroxide (KOH; 4.7 g, 0.084 mol, 1.1 equiv.) were mixed under nitrogen stirred at room temperature. After 5 min, 2-methyl-2-propanethiol (**6**, 12.0 mL, 0.106 mol, 1.5 eq) was added, and the mixture was stirred for 20 min. 2-Chlorobenzaldehyde (**5a**, 8.1 mL, 0.072 mol, 1.0 equiv.) was added, and the reaction was heated to 110 °C for 90 min. Reaction was monitored by TLC, and after completion of the reaction, it was diluted with water (200 mL) and extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with water (100 mL) and 3.5M aqueous NaCl solution (100 mL), dried (anhydrous Na_2SO_4), and concentrated on a rotary evaporator to afford 2-(*tert*-butylthio)benzaldehyde (**7a**), which was used in the next step with our purification. TLC: R_f 0.79 (20% ethyl acetate in hexanes; R_f 0.21 (20% dichloromethane in hexanes); analytical HPLC [gradient solvent, organic blend (19:1 acetonitrile/methanol): 20 mM; pH 4.01; KH_2PO_4 buffer 55:45 for 25 min to 80:20 in 5 min and hold for 5 min; 0.8 mL/min at 265 nm]; and R_t: 15.31 min. Yield 83.4%.

In a 250-mL round-bottomed flask, the crude 2-(*tert*-butylthio)benzaldehyde (**7a**, 13.6 g, 0.070 mol) was placed in an ice bath. Acetic acid (24.0 mL, 0.419 mol, 6.0 equiv.), 48% aqueous HBr (24.0 mL, 0.211 mol, 3.0 equiv.), and DMSO (5.0 mL, 0.070 mol, 1.0 equiv.) were added to the resulting cooled mixture. The reaction was then allowed to warm to room temperature and was stirred overnight. The reaction mixture, containing a solid precipitate, was diluted with cold water (50 mL), filtered, rinsed with hexanes, and dried to afford 2,2′-disulfanediyldibenzaldehyde (**8a**), which was used in the next step without further purification. TLC (R*f*): 0.23 in 20% ethyl acetate in hexanes.

DMSO (36.0 mL, 0.507 mol, 28 eqiv.), acetylacetone (**9**, 1.9 mL, 0.018 mol, 1.1 equiv.), and anhydrous K_2CO_3 (3.77 g, 0.027 mol, 1.5 equiv.) were added sequentially under nitrogen to a single-necked, 250-mL, round-bottomed flask equipped with a stir bar. The resulting slurry was stirred at room temperature for 20 min, and then the crude 2,2′-disulfanediyldibenzaldehyde (**8a**, 5.25 g, 0.019 mol, 1.0 equiv.) was added. The reaction continued to be stirred for an additional 90 min at room temperature. Chloroacetone (1.65 mL, 0.021, 1.1 equiv.) was then added, and the mixture was heated to 50 °C for 90 min. Progress of the reaction was monitored by TLC. Upon completion of reaction, the mixture was cooled to room temperature, poured into ice, and filtered to afford 2-acetylbenzo(b)thiophene (**2a**) 6.62 g in 94% yield. TLC (R_f): 0.31 in 3:1 hexanes/diethylether; analytical RP HPLC: gradient solvent, organic blend (19:1 acetonitrile/methanol): 20 mM; pH 4.01; KH_2PO_4 buffer 55:45 for 25 min to 80:20 in 5 min and hold for 5 min; 0.8 mL/min at 265 nm]; and R_t: 5.97 min. Yield 98.5%. ^{1}H NMR (DMSO-d6): δ 8.32 (s, 1H), 8.00 (m, 2H), 7.48 (m, 2H), 2.64 (s, 3H); ^{13}C NMR (DMSO-d6): δ, 191.9, 143.0, 141.1, 138.7, 130.9, 127.3, 125.9, 124.9, 122.8, 26.8; ESI-LCMS (m/z): 177.0 $(M + H)^+$. HRMS: calcd. m/z for $C_{10}H_8OS$, 177.0369 $(M + H)^+$; observed m/z, 177.0363.

2-Acetyl-4-methylbenzo(b)thiophene (2b)[14]

Compound **2b** was prepared from 6-methyl-2-chlorobenzaldehyde (**5b**) in three steps by following the general procedure described for **2a**. The crude compound was

purified by silica-gel column chromatography (10–30% ethyl acetate in hexanes) to afford 0.458 g in 39.1% yield. TLC (R_f): 0.44 in 20% ethyl acetate in hexanes; analytical RP HPLC: gradient solvent, organic blend (19:1 acetonitrile/methanol): 20 mM, pH 4.01, KH_2PO_4 buffer 55:45 for 25 min to 80:20 in 5 min and hold for 5 min; 0.8 mL/min at 265 nm, R_t: 8.42 min, 99.4%. ^{1}H NMR ($CDCl_3$): δ, 8.00 (d, 1H, $J = 0.96$ Hz), 7.69 (dd, 1H, $J_1 = 8.16$ Hz, $J_2 = 0.62$ Hz), 7.35 (m, 1H), 7.18 (dt, 1H, $J_1 = 7.17$ Hz, $J_2 = 0.94$ Hz), 2.68 (s, 3H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 191.6, 142.8, 142.4, 138.5, 135.1, 127.5, 127.3, 125.1,120.3, 27.1, 19.8; ESI-LCMS (m/z): 191.1 $(M + H)^+$. HRMS: calcd. m/z for $C_{11}H_{10}OS$, 191.0525 $(M + H)^+$; observed m/z, 191.0531.

2-Acetyl-4-chlorobenzo(b)thiophene (2c)[15]

Compound **2c** was prepared from 6-chloro-2-fluorobenzaldehyde (**5c**) in three steps by following the general procedure described for **2a**. The crude compound was purified by column chromatography (10–20% tetrahydrofuran in hexanes) to afford 3.01 g in 43.4% yield. TLC (R_f): 0.62 in 20% tetrahydrofuran in hexanes; analytical RP HPLC: gradient solvent, organic blend (19:1 acetonitrile/methanol): 20 mM, pH 4.01, KH_2PO_4 buffer 55:45 for 25 min to 80:20 in 5 min and hold for 5 min; 0.8 mL/min at 265 nm; R_t: 10.24 min. Yield 86.5%. ^{1}H NMR ($CDCl_3$): δ 8.06 (d, 1H, $J = 0.82$ Hz), 7.75 (ddd, 1H, $J_1 = 7.00$ Hz, $J_2 = 2.06$ Hz, $J_3 = 0.82$ Hz), 7.39 (d, 1H, $J = 0.96$ Hz), 7.38 (d, 1H, $J = 6.04$ Hz), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 191.4, 143.2, 137.5, 137.3, 130.4,127.7, 127.2, 124.6, 121.3, 27.0; ESI-LCMS (m/z): 211.1 $(M + H)^+$. HRMS: calcd. m/z for $C_{10}H_7ClOS$, 210.9979 $(M + H)^+$; observed m/z, 210.9981.

2-Acetyl-5-(trifluoromethyl)benzo(b)thiophene (2d)

Compound **2d** was prepared from 5-trifluoro-2-chlorobenzaldehyde (**5d**) in three steps by following the general procedure described for **2a**. The crude compound was purified by column chromatography (5–20% ethyl acetate in hexanes) to afford 0.550 g in 10.7% yield. TLC (R_f): 0.43 in 20% ethyl acetate in hexanes; analytical RP HPLC: gradient solvent, organic blend (19:1 acetonitrile/methanol): 20 mM; pH 4.01; KH_2PO_4 buffer 55:45 for 25 min to 80:20 in 5 min and hold for 5 min; 0.8 mL/min at 265 nm; R_t: 11.10 min. Yield 95.1%. ^{1}H NMR ($CDCl_3$): δ 8.16 (d, 1H, $J = 0.96$ Hz), 7.99 (s, 1H), 7.98 (dd, 1H, $J = 0.69$ Hz), 7.67 (dd, 1H, $J_1 = 8.58$ Hz, $J_2 = 1.3$ Hz), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 191.2, 145.7, 138.3, 128.9, 123.5, 123.21, 123.17, 122.79, 122.75, 122.70, 27.1. ESI-LCMS (m/z): 245.2 $(M + H)^+$. HRMS: calcd. m/z for $C_{11}H_7F_3OS$, 245.0243 $(M + H)^+$; observed m/z, 245.0243.

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