The Synthesis of Substituted 2,3-Dihydrothieno[2,3-*b*]-thiophenes *via* Intramolecular Michael Addition

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The first regiospecific synthesis of the 2,3-dihydrothieno[2,3-*b*]thiophene ring system was achieved using an intramolecular Michael addition in the key cyclization step. This strategy represents a novel and potentially general method for dihydrothiophene and dihydrothiophene *S,S*-dioxide annellation.

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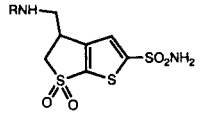
As part of a program to discover topically active antiglaucoma agents [1], we were interested in testing 4-alkylaminomethyl-6,6-dioxo-4,5-dihydrothieno[2,3-*b*]thiophene-2-sulfonamides **1** for ocular antihypertensive activity. The interest in these compounds stems from the topical effectiveness of the structurally related 4-alkylamino-7,7-dioxo-4*H*-5,6-dihydrothieno[2,3-*b*]thiopyran-2-sulfonamides **2** [2], which in the case of MK-927 (R = isobutyl) has been shown to lower intraocular pressure in normotensive healthy volunteers [3] and glaucoma patients [4]. These compounds exert their effect by inhibiting the enzyme carbonic anhydrase [5] and are currently undergoing clinical studies in patients with primary open angle glaucoma. The alkylamino substituent allows aqueous formulations at a concentration and *p*H suitable for ocular delivery and is a key element in our design of novel carbonic anhydrase inhibitors. We wish to report the first synthetically useful preparation of substituted 2,3-dihydrothieno[2,3-*b*]thiophenes, key intermediates in the preparation of the desired 4-alkyl-aminomethyl-6,6-dioxo-4,5-dihydrothieno-[2,3-*b*]thiophene-2-sulfonamides.

Although syntheses of the parent heterocycle thieno-[2,3-*b*]thiophene and the regioisomeric 2,3-dihydrothieno-[3,2-*b*]thiophene [6] are known, only a few examples of 2,3-dihydrothieno[2,3-*b*]thiophenes [7-9] are reported in the literature. In part this is because 2-(2-thienylmercapto)-acetic acid cyclizes under acidic conditions [7] to give a mixture of [2,3-*b*] and [3,2-*b*] ring fused products in 10% yield; moreover, the major component has the [3,2-*b*] ring fusion. Alternatively, thio-Claisen rearrangement of allyl thienyl sulfides [8] produces a mixture of 2-methyl-2,3-dihydrothieno[2,3-*b*]thiophene, 4*H*-5,6-dihydrothieno-[2,3-*b*]thiopyran and uncyclized products. We sought a synthesis which would lead unambiguously to dihydrothieno[2,3-*b*]thiophenes.



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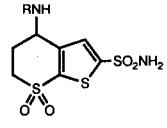

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Our novel approach to this ring system used thiophene with the appropriate functionality for annellation *via* intramolecular Michael addition. The readily available carboxaldehyde **3** [10] permits the introduction of a Michael acceptor by standard olefination procedures. Condensation of aldehyde **3** with excess nitromethane in acetic acid in the presence of one equivalent of *n*-butylamine [11] led to *trans* nitroolefin **4** (Scheme). Unexpectedly, attempted cyclization of **4** with a variety of bases led to complete decomposition. The reaction coordinate leading to **5** represents a 5-exo-trig ring forming reaction [12] and should be a favorable process; however in this case the reaction is reversible and it appears that the α-mercapto ester enolate is not particularly stable. It was found that sulfonyl ester **6** cyclized in high yield [13] when treated with sodium hydride and *t*-butyl alcohol in THF or DBU in methanol. The more highly stabilized anion of **6** undergoes a stereoselective internal Michael addition in quanti-

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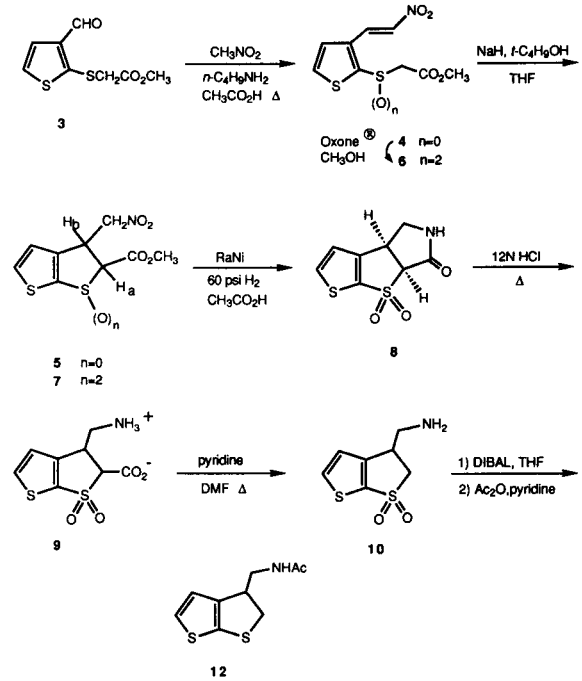

tative yield to produce mainly one (>95%) stereoisomer of **7**. Inspection of coupling constants ($J_{a,b}$ = 5.4 Hz) and nOe studies did not unambiguously establish the stereochemistry of the major product.

Hydrogenolysis of the nitro group in **7** with Raney nickel in acetic acid gave the tricyclic lactam **8** in modest yield. Single crystal X-ray diffraction [14] confirmed the structure of **8**. Hydrolysis of **8** to amino acid **9** required fairly vigorous conditions but proceeded in near quantitative yield. Thermal decarboxylation [15] of **9** took place at 110° in dimethylformamide in the presence of several equivalents of pyridine. Decarboxylation in neat pyridine reformed lactam **8** to the extent of 30%. Finally, sulfone **10** was reduced to the corresponding sulfide **11** (isolated as the acetamide **12**) with diisobutylaluminum hydride in preparation for regioselective sulfonylation of the thiophene ring. Although sulfones are usually only reduced with difficulty, it has been noted that sulfolanes are atypical in this respect [16] and undergo reduction with some facility. Sulfide **11** is the key intermediate in the preparation of sulfonamides **1**, the synthesis and biological activity of which will be reported separately.

In summary, we have developed a regiospecific synthesis of substituted 2,3-dihydrothieno[2,3-*b*]thiophenes using an intramolecular Michael addition as the key ring forming step. The cyclization proceeds in high yield for 2-sulfinyl- or sulfinylacetate Michael donors.

EXPERIMENTAL

Proton nmr spectra were obtained on a Varian XL300 spectrometer with TMS as internal standard. Melting points were determined with a Thomas Hoover apparatus and are uncorrected. Elemental analysis was obtained by the analytical staff at West Point. Nitromethane, *n*-butylamine, Oxone® , Raney nickel and diisobutyaluminum hydride (1*M* in THF) were purchased from Aldrich and were used without purification. Sodium hydride was purchased from Aldrich as a 60% dispersion in mineral oil and was washed three times with dry ether before use. THF was distilled under nitrogen from sodium benzophenone ketyl. Thin layer chromatography was conducted on Analtech Silica Gel GF plates. Low pressure column chromatography employed EM Reagents silica gel 230-400 mesh ASTM.

Methyl 2-(3-(*trans*-2-Nitrovinyl)thienyl)mercaptoacetate (**4**).

Nitromethane (32 ml, 0.59 mole) was added to a solution of aldehyde **3** (25.7 g, 0.119 mole) in glacial acetic acid (120 ml) under nitrogen at 20°. The reactants were heated with stirring to 80° and *n*-butylamine (17.6 ml, 0.178 mole) was added in a steady stream from an addition funnel. The temperature was raised and the reaction heated a total of 1 hour at 100° (R_f aldehyde = 0.43, R_f nitroolefin = 0.36, tlc plate developed thrice with 10% ethyl acetate in hexane). The resulting black solution was cooled for 10 minutes in an ice bath, and then poured over crushed ice (1 l). The solid was filtered and dissolved in chloroform. The chloroform solution was washed twice with water, once with saturated sodium chloride, then dried over magnesium sulfate. The drying agent was filtered and the filtrate treated with decolorizing carbon and allowed to stand overnight. The solution was filtered and solvents removed *in vacuo* to give **4** as a green solid (30.3 g, 98% crude yield) which was generally pure enough for use in subsequent transformations. A portion of the crude product was chromatographyed on silica gel eluting with 10% to 30% ethyl acetate in hexane. Nitroolefin **4** was obtained as a yellow solid. Recrystallization from methanol gave yellow plates, mp 83-85°; ^{1}H nmr (deuteriochloroform): 300 MHz δ 8.30 (1H, d, J = 13.7 Hz), 7.53 (1H, d, J = 13.7 Hz), 7.49 (1H, d, J = 5.6 Hz), 7.24 (1H, d, J = 5.6 Hz), 3.71 (3H, s), 3.53 (2H, s).

Anal. Calcd. for $C_9H_9NO_4S_2$: C, 41.68; H, 3.49; N, 5.40. Found: C, 41.89; H, 3.77; N, 5.38.

Methyl 2-(3-*trans*-2-Nitrovinyl)thienyl)sulfonylacetate (**6**).

Oxone® (12.09 g, 19.7 mmoles) was dissolved in water (60 ml) and added to a solution of sulfide **4** (1.70 g, 6.56 mmoles) in methanol (25 ml) with ice bath cooling. The reaction was stirred at 20° for 18 hours and then heated at 60° for 10 hours. The reaction was cooled, diluted with water and extracted with ethyl acetate. The ethyl acetate was washed with 10% sodium sulfite, saturated sodium chloride, and dried over magnesium sulfate. The solution was filtered and the solvent evaporated to give **6** as a yellow solid (1.87 g). Recrystallization from chloroform-methanol produced pale yellow needles (1.35 g, 71% yield), mp 147-148°; ^{1}H nmr (deuteriochloroform): 300 MHz δ 8.51 (1H, d, J = 13.7 Hz), 7.81 (1H, d, J = 5.4 Hz), 7.54 (1H, d, J = 13.7 Hz), 7.38 (1H, d, J = 5.3 Hz), 4.25 (2H, s), 3.76 (3H, s).

Anal. Calcd. for $C_9H_9NO_6S_2$: C, 37.10; H, 3.11; N, 4.80. Found: C, 37.02; H, 3.30; N, 4.77.

Methyl *trans*-1,1-Dioxo-3-nitromethyl-2,3-dihydrothieno[2,3-*b*]-thiophene-2-carboxylate (**7**).

A solution of sulfone **6** (1.13 g, 3.89 mmoles) and *t*-butyl alcohol (0.35 ml) in THF (60 ml) was added to a suspension of sodium hydride (0.66 g, 16 mmoles) in THF (50 ml) at 0°. After 0.5 hour 20% acetic acid in THF (50 ml) was slowly added. THF was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The ethyl acetate solution was washed thrice with water and once with saturated sodium chloride and dried over magnesium sulfate. The solution was filtered and the filtrate concentrated *in vacuo* to give **7** as a pale yellow oil (1.40 g) which was chromatographed on silica gel with 30-50% ethyl acetate in hexane. The product was obtained as a clear gum (1.13 g, 100%) which solidified upon standing mp = 89.5-90.5°; ^{1}H nmr (dimethylsulfoxide-d_6): 300 MHz δ 8.18 (1H, d, J = 4.9 Hz), 7.24 (1H, d, J = 4.9 Hz), 5.46 (1H, d, J = 5.4 Hz), 5.21 (1H, dd, J = 15.2, 4.1 Hz), 5.10 (1H, dd, J = 15.2, 8.1 Hz), 4.55 (1H, m), 3.83 (3H, s).

Anal. Calcd. for $C_9H_9NO_6S_2$: C, 37.10; H, 3.11; N, 4.80. Found: C, 37.20; H, 2.74; N, 4.81.

1*H*-3,4,4-Trioxo-2,3,3a,7b-tetrahydrothieno[2',3':5,4]thieno[2,3-*c*]-pyrrole (**8**).

Nitro ester **7** (13.5 g, 0046 mole) in glacial acetic acid (25 ml) was hydrogenated 3 hours at 60 psi hydrogen in the presence of Raney nickel (13 g). After flushing with nitrogen, the mixture was filtered through celite. The acetic acid was removed *in vacuo* and the residue diluted with water; adjusting the *p*H to 8.5 with aqueous sodium hydroxide precipitated lactam **8**, which was col-

lected and dried under vacuum (4.2 g, 36% yield). Slow recrystallization from methanol gave crystals suitable for single crystal X-ray analysis [14], mp 293-294°; ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz δ 8.25 (1H, br s, NH), 8.13 (1H, d, J = 4.8 Hz), 7.19 (1H, d, J = 4.8 Hz), 4.84 (1H, d, J = 8.5 Hz), 4.43 (1H, dt, J, 8.7 Hz, J_d = 3.9 Hz), 3.76 (1H, dd, J = 10.2, 9.2 Hz), 3.21 (1H, dd, J = 10.2, 3.9 Hz).

Anal. Calcd. for $C_8H_7NO_3S_2$: C, 41.91; H, 3.07; N, 6.10. Found: C, 42.03; H, 3.27; N, 6.00.

3-Aminomethyl-1,1-dioxo-2,3-dihydrothieno[2,3-*b*]thiophene-2-carboxylic Acid (**9**).

A suspension of lactam **8** (3.6 g, 0.015 mole) in concentrated hydrochloric acid (60 ml) was heated at 100° for 12 hours. The clear solution was cooled to room temperature and carefully poured into water (60 ml). The aqueous solution was filtered through a medium frit, and the solvent removed under reduced pressure to give **9** as a white powder. The solid was suspended in water which was evaporated under reduced pressure. This was repeated twice more. Subsequent trituration with diethyl ether gave **9** as a fine white powder, which was collected by filtration and dried under vacuum (4.5 g, 100% yield), mp 209-210° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz δ 8.2 (3H, br s, exch), 8.18 (1 H, d, J = 4.9 Hz), 7.37 (1H, d, J = 4.9 Hz), 5.18 (1H, d, J = 5.3 Hz), 4.10 (1H, m), 3.37 (1H, br s), 3.24 (1H, br s).

Anal. Calcd. for $C_8H_9NO_4S_2 \cdot H_2O$: C, 36.22; H, 4.17; N, 5.27. Found: C, 36.09; H, 3.98; N, 5.32.

3-Aminomethyl-1,1-dioxo-2,3-dihydrothieno[2,3-*b*]thiophene (**10**).

The amino acid **9** (4.1 g, 0.0157 mmole) was suspended in dimethylformamide (75 ml) with pyridine (0.63 ml, 0.023 mmole) and heated to 110-120° for 1 hour. The reaction was cooled and the dimethylformamide removed *in vacuo*. The residue was partitioned between 10% aqueous hydrogen chloride and ethyl acetate; the aqueous acid was rendered basic with sodium hydroxide and extracted thrice with ethyl acetate. The organic phase was washed twice with saturated brine and dried over magnesium sulfate. The free base **10** was obtained as a white solid, 1.9 g (64% yield); ^{1}H nmr deuteriochloroform): 300 MHz δ 7.70 (1H, d, J = 4.9 Hz), 6.99 (1H, d, J = 4.9 Hz), 3.99 (1H, dd, J = 13.4, 8.1 Hz), 3.80 (1H, dd, J = 13.4, 4.2 Hz), 3.59 (1H, m), 3.22 (2H, m), 1.27 (2H, br s, exch). Recrystallization of the hydrochloride salt of **10** from methanol-ether gave small cubes, mp 213-216° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): 300 MHz δ 8.25 (3H, br s), 8.13 (1H, d, J = 4.8 Hz), 7.29 (1H, d, J = 4.8 Hz), 4.16 (1H, dd, J = 13.5, 7.5 Hz), 4.04 (1H, dd, J = 13.5, 4.6 Hz), 3.93 (1H, m), 3.40 (1H, m, overlaps water peak), 3.09 (1H, m).

Anal. Calcd. for $C_7H_{10}NO_2S_2 \cdot HCl$: C, 35.06; H, 4.20; N, 5.84. Found: C, 35.40; H, 4.19; N, 5.75.

3-Acetamidomethyl-2,3-dihydrothieno[2,3-*b*]thiophene (**12**).

A solution of diisobutylaluminum hydride in THF (250 ml, 1*M*) was cooled to 0° under nitrogen and a solution of amino sulfone **10** (7.2 g, 0.035 mole) in THF (75 ml) was added. The reaction was stirred at 20° for 12 hours, after which an additional amount of diisobutylaluminum hydride was added (50 ml, 1*M* in THF) to effect complete reduction. After 27 hours at 20°, the reaction was quenched at 0° with 5% sodium hydroxide followed by saturated sodium potassium tartrate solution. The resulting mixture was stirred for 1 hour then extracted with ethyl acetate. The ethyl acetate was filtered through celite, dried over magnesium sulfate and concentrated to give the crude amino sulfide **11** as an oil (5.3 g, 88% yield); ^{1}H nmr (deuteriochloroform): 300 MHz δ 7.04 (1H, d, J = 5.0 Hz), 6.81 (1H, d, J = 5.0 Hz), 4.03 (1H, dd, J = 11.0, 8.1 Hz), 3.66 (1H, dd, J = 11.0, 5.4 Hz), 3.38 (1H, m), 3.00 (1H, dd, J = 12.7, 5.7 Hz), 2.90 (1H, dd, J = 12.7, 7.1 Hz), 1.85 (2H, br s, NH_2). The amine (2.67 g, 0.0156 mmole) was dissolved in chloroform (30 ml) and cooled to 0°. Pyridine (3.8 ml, 0.046 mmole) and acetic anhydride (2.20 ml, 0.023 mmole) were added and the reaction stirred at 20° for 12 hours. Saturated sodium bicarbonate was added and the reaction stirred for 1 hour. The layers were separated and the chloroform extracted with 10% aqueous hydrogen chloride, saturated sodium bicarbonate, saturated sodium chloride, and dried over magnesium sulfate. Chromatography on silica gel with 5% methanol in chloroform gave 3.30 g of **12** (91% yield); ^{1}H nmr (deuteriochloroform): 300 MHz δ 7.06 (1H, d, J = 5.1 Hz), 6.79 (1H, d, J = 5.1 Hz), 5.66 (1H, br s, NH), 4.03 (1H, m), 3.52 (5H, m), 1.99 (3H, s).

Anal. Calcd. for $C_9H_{11}NOS_2$: C, 50.67; H, 5.19; N, 6.56. Found: C, 50.59; H, 5.30; N, 6.44.

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