The Preparation of 5-Substituted Thieno[2,3-*b*]furan-2-sulfonamides

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An efficient synthetic route is reported for the preparation of thieno[2,3-*b*]furan-2-sulfonamides bearing oxygenated functionality at C-5. The method employs conversion of furan-3-carboxaldehyde to an intermediate that, in the key step, undergoes facile cyclodehydration to the fused [5,5] heterocycle under mild Knoevenagel conditions.

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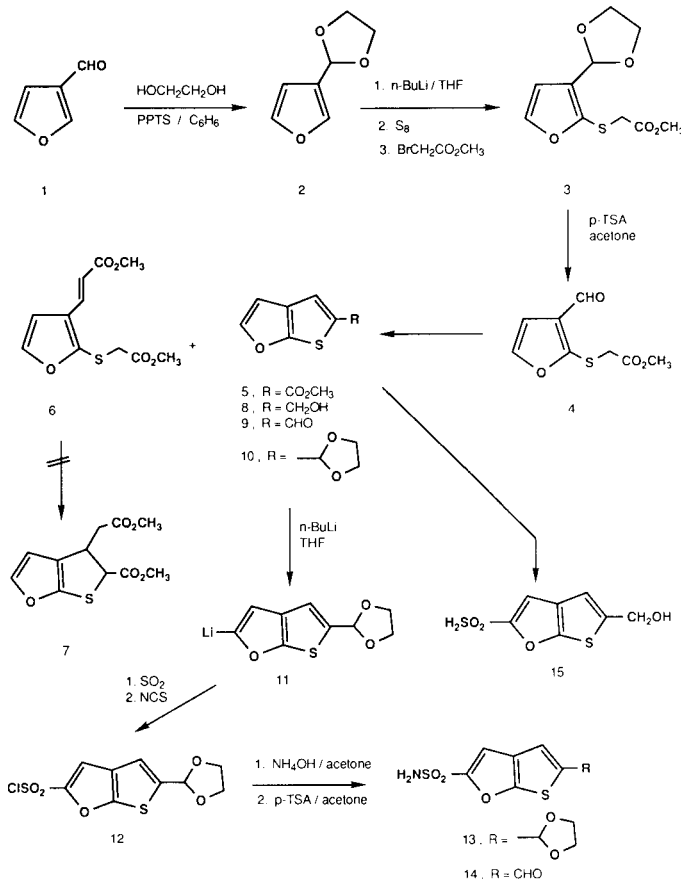
As part of our ongoing effort to prepare novel aryl sulfonamides for use as topically effective ocular antihypertensive agents, [1] we became interested in the preparation of thieno[2,3-*b*]furan-2-sulfonamides. These compounds were of interest because of their structural analogy to known inhibitors of carbonic anhydrase II, [2,3] as well as for their expected physical and enzyme antagonist properties. We anticipated that the extended planar topology of the thieno[2,3-*b*]furan system would be readily accommodated in a steric sense at the zinc binding site of the enzymic cavity, [4,5] and that the ring heteroatoms would offer the opportunity for favorable electrostatic interactions. We now wish to report an efficient synthesis of this class of sulfonamides, along with methodology that allows the preparation of intermediates that are useful in the preparation of a variety of analogues.

There is a paucity of information in the literature relating to the preparation and chemical reactivity of the thieno[2,3-*b*]furan system. Initial synthetic attempts [6-8] toward this ring system provided complex product mixtures from which the desired products were obtained only in low yield. Although the stabilized benzo-annulated systems have been studied, [9] and, despite the expanded theoretical interests in the electrophilic reactivity of fused [5.5] systems [10], there appears to be little recent work either on the parent thieno[2,3-*b*]furan or simple derivatives.

Our synthetic route to thieno[2,3-*b*]furans is modeled after previous work [11,12] directed toward the thieno[2,3-*b*]thiophene system and is shown in the Scheme. Treatment of commercially available furan-3-carboxaldehyde (**1**) with ethylene glycol in the presence of pyridinium *p*-toluenesulfonate as catalyst provided acetal **2** in 86% yield. Utilization of *p*-toluenesulfonic acid as catalyst resulted in significantly reduced yields of **2** due to decomposition. Metallation of **2** at −78° with *n*-butyllithium provided the **2**-lithio species, [13] which was trapped by sulfur, and this intermediate was alkylated with methyl bromoacetate to give **3** in 76% overall yield. No evidence of products derived from competitive deprotonation at other furan positions was seen. The key cyclization intermediate **4** was generated from **3** *via* *p*-toluenesulfonic acid-catalyzed transacetalization in the presence of excess acetone. Successful conversion to **4** required neutralization of the reaction mixture before workup, in order to inhibit decomposition and reversion to the starting acetal during solvent removal.

Initial attempts at cyclodehydration of **4** to the thieno[2,3-*b*]furan-5-carboxylate **5** proved problematic. Treatment of **4** with various bases such as sodium ethoxide, which led to efficient cyclization in the thieno[2,3-*b*]thiophene series, [11,12] sodium hydride, potassium carbonate, and sodium bicarbonate under phase transfer conditions gave complex reaction mixtures. Cyclization of **4** in

Scheme



the presence of DBN or DBU provided **5** in *ca.* 10% yield contaminated with excessive amounts of tar. Interestingly, a component of these product mixtures was the diester **6** derived from self-condensation of **4**. Attempted conversion of **6** to **7** *via* base-catalyzed Michael cyclization was not successful. In contrast to these failures, treatment of **4** under Knoevenagel conditions [14] with piperidinium acetate in benzene, afforded the desired ester **5** in 61% yield.

Reduction of **5** with lithium aluminum hydride provided carbinol **8**, which was oxidized to aldehyde **9** with pyridinium chlorochromate and then protected as its ethylene glycol acetal **10**. Metallation of **10** with *n*-butyllithium regioselectively afforded the 2-lithio species **11**, which was converted to the desired sulfonyl halide **12** by sequential treatment with sulfur dioxide and *N*-chlorosuccinimide. Addition of aqueous ammonium hydroxide to an acetone solution of the sulfonyl chloride **12** kept at 0° provided the sulfonamide **13**. Deprotection of the aldehyde function under standard conditions generated 5-formylthieno[2,3-*c*]-furan-2-sulfonamide (**14**). The efficient conversion of **10** to **13** as described is in contrast with the low yield of **15** obtained when **8** is subjected to the same sequence of reactions.

In summary, this report describes an efficient synthetic route to 5-substituted thieno[2,3-*b*]furan-2-sulfonamides. The key cyclodehydration step to generate the fused [5,5] ring system employs mild Knoevenagel conditions that should have broad application in the synthesis of other chemically sensitive fused heterocycles.

EXPERIMENTAL

Melting points were determined in air employing a Thomas Hoover apparatus and are uncorrected. Proton nmr spectra were obtained using a Nicolet NT360 spectrometer with TMS as internal standard. The elemental analyses were performed by Dr. W. C. Randall and his staff. Ethylene glycol, 3-furancarboxaldehyde, methyl bromoacetate, sulfur, and pyridinium *p*-toluenesulfonate were purchased from Aldrich and were used without purification. *N*-Butyllithium in hexane was purchased from Alfa.

3-[2-(1,3-Dioxolanyl)]furan (**2**).

To a solution of 100 g (1.04 moles) 3-furancarboxaldehyde (**1**) in 400 mℓ of benzene was added 225 g (3.63 moles) of ethylene glycol and 100 mg of pyridinium *p*-toluenesulfonate (PPTS) and the resulting mixture was stirred and heated at reflux utilizing a Dean-Stark trap. After the theoretical amount of water was collected (usually 3 hours), the cooled reaction mixture was diluted with 100 mℓ of ether and 200 mℓ of water. The organic phase was separated and the aqueous phase was reextracted with 100 mℓ of ether. The organic phases were combined, washed with 2 × 100 mℓ portions of water and brine, and then dried over anhydrous sodium sulfate. The drying agent was removed by filtration and after solvent removal on the rotary evaporator, the residue was distilled to provide 125 g (86%) of pure **2**, bp 78-82°/20 mm; ^{1}H nmr (300 MHz, deuteriochloroform): δ 4.03 (2H, m), 4.11 (2H, m), 5.88 (1H, s), 6.50 (1H, d, J = 2 Hz), 7.44 (1H, dd, J = 2.2 Hz), 7.58 (1H, d, J = 4 Hz).

Methyl 3-[2-(1,3-Dioxolanyl)]furan-2-yl mercaptoacetate (**3**).

To a mechanically-stirred solution of 69.0 g (0.49 mole) **2** in 250 mℓ of THF under nitrogen and cooled to −78° was added 0.49 mole of *n*-butyllithium (in hexane) dropwise at < −70°. The resulting reaction mixture was stirred at −78° for 45 minutes to provide a white suspension. Then, 16.64 g (0.52 mole) of sulfur was added portionwise *via* Gooch tubing portionwise over 5 minutes (the internal temperature rose to −65°) to provide an orange suspension. This suspension was stirred at −78° for 30 minutes and then at −50° for 30 minutes to afford a deep purple reaction mixture. Then, 91.8 g (0.60 mole) of methyl bromoacetate in 50 mℓ of THF was added dropwise over 15 minutes. After stirring at −78° for 30 minutes, the reaction mixture was allowed to gradually warm to −10° over 1.5 hours.

The reaction mixture was quenched with 250 mℓ of brine/250 mℓ of ether and the aqueous phase was separated and reextracted with ether. The organic phases were combined, washed with brine, dried over sodium sulfate and the solvent was removed *in vacuo*. The resulting oil was taken up in ether and passed through a silica gel pad to provide a clear filtrate. The solvent was removed *in vacuo* to give crude **3** as a clear oil, R_f 0.4 on silica gel eluting with 20% ethyl acetate/hexane. This oil was purified by flash chromatography on silica gel eluting with 25% ethyl acetate/hexane to give 90.8 g (76%) of **3** as a clear oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 3.50 (2H, s), 3.69 (3H, s), 4.0 (2H, m), 4.12 (2H, m), 5.87 (1H, s), 6.51 (1H, d, J = 2 Hz), 7.49 (1M, d, J = 2 Hz). Exact mass: Calcd. 244.26814. Found: 244.26810.

(3-Formylfuran-2-yl)mercaptoacetate (**4**).

To a solution of 6.8 g (0.028 mole) of **3** dissolved in 50 mℓ of acetone was added 100 mg of *p*-toluenesulfonic acid monohydrate and the resulting solution was kept at room temperature for 3 hours. To this was added 15 mℓ of saturated sodium bicarbonate solution and the resulting suspension was stripped on the rotary evaporator to remove acetone. The resulting slurry was extracted with 2 × 40 mℓ portions of ether and the combined organic extracts were washed with brine and dried. The solvent was removed *in vacuo* to give 4.65 g (83%) of **4** as an oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 3.71 (5H, s), 6.79 (1H, d, J = 2 Hz), 7.51 (1H, d, J = 2 Hz), 10.0 (1H, s). Exact mass: Calcd. 200.21456. Found: 200.21450.

Methyl Thieno[2,3-*b*]furan-5-carboxylate (**5**).

Piperidine (6.97 mℓ, 0.0704 mole) was added to a solution of acetic acid (4.40 mℓ, 0.0705 mole) in benzene (200 mℓ). The slightly warm solution was stirred for 15 minutes and then 11.4 g (0.057 mole) of **4** in benzene (150 mℓ) was added. An additional amount of benzene (150 mℓ) was used to rinse out the flask. The vessel was purged with nitrogen, and the contents were heated to reflux with water removal *via* a Dean-Stark trap. The originally bright yellow solution became dark red upon heating. After 2.5 hours, 85% of the theoretical amount of water was collected.

The reaction mixture was cooled to 20°, poured into a 2 ℓ separatory funnel and diluted with 1.2 ℓ of ether. This solution was extracted with 2 × 200 mℓ of 5% hydrochloric acid, 1 × 200 mℓ of 50% saturated sodium bicarbonate, 1 × 200 mℓ of water, and 1 × 50 mℓ of saturated sodium chloride. The washed organic phase was dried over magnesium sulfate, filtered, and the solvents removed *in vacuo* to give 19 g of a black-brown solid. This

was taken up in a minimum of ethyl acetate and passed through a silica gel column (150 g silica gel) using 20% ethyl acetate/hexane as eluent, to give 6.57 g (61%) of **5** as a yellowish solid. Recrystallization reduced the bad smell, and was effected by dissolving the product in ether (100 mℓ) and cooling to −35°. The white crystals were collected and dried at 20° (house vacuum) for 72 hours to yield 4.40 g of product **5**, mp 95-96°, 99.4% pure by hplc (at 210 nm); ^{1}H nmr (300 MHz, deuteriochloroform): δ 3.90 (3H, s), 6.74 (1H, d, J = 2.2 Hz), 7.66 (1H, d, J = 2.2 Hz), 7.72 (1H, s).

Anal. Calcd. for $C_8H_6O_3S$: C, 52.53; H, 3.31. Found: C, 52.83; H, 3.37.

Thieno[2,3-*b*]furan-5-carbinol (**8**).

To a suspension of 3.80 g (0.1 mole) of lithium aluminum hydride in 650 mℓ of ether cooled to 0-10° under nitrogen was added a solution of 9.19 g (0.05 mole) of **5** in ether (150 mℓ) dropwise over 20 minutes. This suspension was stirred at room temperature for 4 hours at which time all starting material was consumed. The reaction mixture was cooled and quenched with 30 mℓ of saturated sodium/potassium tartrate solution added dropwise. The resulting mixture was then stirred at room temperature for 30 minutes. The ether phase was decanted away from the gummy solid and this solid was thoroughly triturated with ether. The organic extracts were combined, washed with brine, dried over sodium sulfate and the solvent removed *in vacuo*. The resulting amber oil was purified by flash chromatography on silica gel eluting with 20% ethyl acetate/hexane to give 7.3 g (94%) of **8** as a clear oil; ^{1}H nmr (300 MHz, deuteriochloroform): δ 4.80 (2H, s), 6.65 (1H, d, J = 2 Hz), 6.87 (1H, s), 7.59 (1H, d, J = 2 Hz). Exact mass: Calcd. 154.18867. Found: 154.18863.

Anal. Calcd. for $C_7H_6O_2S$: C, 54.53; H, 3.92. Found: C, 54.29; H, 3.88.

Thieno[2,3-*b*]furan-5-carboxaldehyde (**9**).

To a mechanically-stirred suspension of 15.22 g (0.071 mole) of pyridinium chlorochromate in 150 mℓ of methylene chloride at room temperature was added a solution of 7.26 g (0.0476 moles) of **8** in 150 mℓ of methylene chloride in one portion. After stirring for 2 hours at room temperature, all starting material was consumed. The reaction mixture was diluted with 200 mℓ of ether and was filtered through a silica gel pad. The residue in the flask and on the pad was washed thoroughly with methylene chloride. The organic extracts were combined and the solvent was removed *in vacuo* to provide 5.42 g (76%) of **9** as an oil that partially crystallized on standing. It was anticipated that this material would have only moderate stability, so it was generally used directly in the next step; ^{1}H nmr (300 MHz, deuteriochlorofrom): δ 6.80 (1H, d, J = 2 Hz), 7.69 (1H, s), 7.71 (1H, d, J = 2 Hz), 9.90 (1H, s). Exact mass: Calcd. 152.17273. Found: 152.17274.

Anal. Calcd. for $C_7H_4O_2S$: C, 55.25; H, 2.65. Found: C, 55.46; H, 2.30.

5-[2-(1,3-Dioxolanyl)]thieno[2,3-*b*]furan (**10**).

To a solution of 5.91 g (0.039 mole) of **9** and 4.96 (0.08 mole) of ethylene glycol in 75 mℓ of benzene was added 100 mg of pyridinium *p*-toluenesulfonate and the resulting mixture was heated at reflux utilizing a Dean-Stark trap. After approximately 8 hours the theoretical amount of water was evolved and tlc showed that all starting material was consumed. The cooled reaction mixture was diluted with 75 mℓ of water/100 mℓ of ether and the organic phase was separated, washed with water, brine and dried. This was passed through a silica gel pad and the solvent was removed *in vacuo* to give crude **10**. Crude **10** was purified by flash chromatography on silica gel eluting with 12% ethyl acetate/hexane to give 6.2 g (81%) pure of **10** (R_f 0.6 on silica gel eluting with 20% ethyl acetate/hexane), which crystallized on standing, mp 60-63°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 4.03 (2H, m), 4.13 (2H, m), 6.09 (1H, s), 6.67 (1H, d, J = 2 Hz), 7.02 (1H, s), 7.58 (1H, d, J = 2 Hz). Exact mass: Calcd. 196.22631. Found: 196.22638.

Anal. Calcd. for $C_9H_8O_2S$: C, 59.98; H, 4.47. Found: C, 60.16; H, 4.55.

5-[2-(1,3-Dioxolanyl)]thieno[2,3-*b*]furan-2-sulfonamide (**13**).

To a solution of 1.96 g (0.01 mole) of **10** in 20 mℓ of THF cooled at −78° under nitrogen was added 0.01 mole of *n*-butyllithium dropwise at < −70° and the resulting solution was stirred for 45 minutes at −78°. Then, sulfur dioxide gas was bubbled close to the surface of the reaction mixture as the temperature rose to *ca.* −60°. This suspension was stirred at −65° for 3 minutes while sulfur dioxide gas was continuously admitted and the mixture was allowed to gradually warm to 0° over 1 hour. The solvent was removed at < 35° under reduced pressure (water aspirator) to afford a tan solid. This solid was taken up in 20 mℓ of saturated sodium bicarbonate solution and, with cooling to 0-10°, 2.0 g (0.015 mole) of *N*-chlorosuccinimide was added portionwise over 5 minutes with vigorous stirring. The resulting suspension was stirred vigorously at 0-10° for 1.5 hours. This mixture was extracted with 3 × 50 mℓ portions of chloroform and the combined organic extracts were washed with brine and dried. The solvent was removed *in vacuo* to give the intermediate sulfonyl chloride **12** as a tan solid. This solid was dissolved in 15 mℓ of acetone and, with cooling to 5°, 15 mℓ of concentrated ammonium hydroxide solution was added in one portion. This was stirred at 5° for 1.5 hours and then extracted with 5 × 50 mℓ, portions of ethyl acetate. The combined organic extracts were washed with brine, dried and the solvent removed *in vacuo* to give 1.66 g (60%) **13** as a tan solid; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 3.97 (2H, m), 4.03 (2H, m), 6.09 (1H, s), 7.29 (1H, s), 7.36 (1H, s), 7.90 (2H, bs). Exact mass: Calcd. 275.27678. Found: 275.27674.

Anal. Calcd. for $C_7H_9NO_5S_2$: C, 39.27; H, 3.30; N, 5.09. Found: C, 39.16; H, 3.60; N, 5.28.

5-Formylthieno[2,3-*b*]furan-2-sulfonamide (**14**).

To a solution of 1.66 g (0.006 mole) **13** in 35 mℓ of acetone was added 25 mg of *p*-toluenesulfonic acid monohydrate and the resulting solution was kept at room temperature for 2 hours. Then, 25 mℓ of saturated sodium bicarbonate solution was added and the acetone was removed *in vacuo*. The residue was extracted with 3 × 50 mℓ portions of ethyl acetate and the combined organic extracts were washed with brine, dried and passed through a silica gel pad. The solvent was removed from the filtrate to give 1.34 g (95%) of **14** as a tan solid, mp 165-167°; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 7.56 (1H, d, J = 2 Hz), 8.09 (2H, bs), 8.17 (1H, d, J = 2 Hz), 10.0 (1H, s). Exact mass: Calcd. 231.25020. Found: C, 231.25027.

Anal. Calcd. for $C_7H_5NO_4S_2$: C, 36.36; H, 2.18; N, 6.06. Found: C, 36.64; H, 2.22; N, 6.30.

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