

[1]Benzothieno[3,2-*b*]furan Derivatives

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In a recent paper (1), the author described a one-step synthesis of methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate (**1a**) (2) from methyl *o*-nitrobenzoate. Since **1a** appeared to be an excellent precursor for the preparation of [1]benzothieno[3,2-*b*]furans, the synthesis of a variety of derivatives was undertaken.

Alkylation of **1a** has been reported to give either *C*-alkylated or *O*-alkylated products according to the reaction conditions (3). When **1a** was allowed to react with methyl chloroacetate in the presence of potassium *t*-butoxide in DMSO, *O*-alkylation occurred exclusively, and the carbomethoxymethyl ether **1b** was obtained in 92% yield. Similar treatment of **1a** with chloroacetonitrile and chloroacetone gave the ethers **1c** (85%) and **1d** (67%), respectively. Dieckmann ring closure of **1b** was accomplished using potassium *t*-butoxide in refluxing benzene (4), and the [1]benzothieno[3,2-*b*]furan derivative **2a** was formed in 84% yield. Similar treatment of **1c** yielded the nitrile **2b** (84%). Although this procedure failed for the preparation of the ketone **2c** from **1d**, cyclization did occur when sodium methoxide in methanol was used, and **2c** was obtained in 65% yield. Alkylation of the hydroxyl derivatives **2a**, **2b**, and **2c** with dimethyl sulfate in the presence of potassium *t*-butoxide in DMSO yielded the corresponding methyl ethers **2d** (74%), **2e** (83%), and **2f** (60%). These derivatives are the first reported examples of the [1]benzothieno[3,2-*b*]furan ring system. Finally, treatment of **1a** with

methyl isocyanate in refluxing methylene chloride containing triethylamine yielded the [1]benzothieno[2,3-*e*]-1,3-oxazine derivative **3** (65%).

## EXPERIMENTAL (5)

3-(Carboxymethoxy)benzo[*b*]thiophene-2-carboxylic Acid, Dimethyl Ester (**1b**).

To a solution containing 12.6 g. of methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate (60.5 mmoles) and 8.1 g. of potassium *t*-butoxide (72 mmoles) in 100 ml. of DMSO was added dropwise 14 ml. of methyl chloroacetate. The mixture was heated at steam bath temperature for 1 hour, poured into ice water, and collected. The crude product was crystallized from alcohol to yield 15.7 g. (92%) of product, m.p. 98-99°; nmr (deuteriochloroform):  $\delta$  3.78 (s, 3), 3.88 (s, 3), 5.03 (s, 2).

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>O<sub>5</sub>S: C, 55.71; H, 4.32; S, 11.44. Found: C, 55.59; H, 4.58; S, 11.40.

3-(Cyanomethoxy)benzo[*b*]thiophene-2-carboxylic Acid, Methyl Ester (**1c**).

The procedure was identical to the preparation of **1b**, except that 12 ml. of chloroacetonitrile was used as the alkylating agent. The crude product was crystallized from alcohol to yield 12.6 g. (85%) of product, m.p. 123-124°; nmr (deuteriochloroform):  $\delta$  3.90 (s, 3), 5.16 (s, 2).

*Anal.* Calcd. for C<sub>12</sub>H<sub>9</sub>NO<sub>3</sub>S: C, 58.29; H, 3.67; N, 5.66; S, 12.97. Found: C, 58.37; H, 3.86; N, 5.85; S, 12.88.

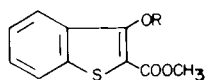
3-(Acetylmethoxy)benzo[*b*]thiophene-2-carboxylic Acid, Methyl Ester (**1d**).

The procedure was identical to the preparation of **1b**, except that 15 ml. of chloroacetone was used as the alkylating agent. The crude product was crystallized from alcohol-water to yield 10.7 g. (67%) of product, m.p. 57-58°; nmr (deuteriochloroform):  $\delta$  2.32 (s, 3), 3.89 (s, 3), 4.93 (s, 2).

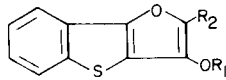
*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>O<sub>4</sub>S: C, 59.08; H, 4.58; S, 12.13. Found: C, 58.91; H, 4.86; S, 12.42.

3-Hydroxy[1]benzothieno[3,2-*b*]furan-2-carboxylic Acid, Methyl Ester (**2a**).

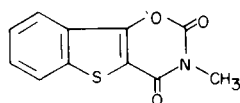
A solution containing 5.1 g. of **1b** (18.2 mmoles) and 2.7 g. of potassium *t*-butoxide (24.1 mmoles) in 100 ml. of benzene was refluxed for 2.5 hours. The mixture was cooled and extracted with 100 ml. of water. The aqueous layer was washed with benzene and then acidified. The crude solid was collected and crystallized from methanol-water. The yield was 3.8 g. (84%), m.p. 124-125°; nmr (DMSO-*d*<sub>6</sub>):  $\delta$  3.86 (s, 3); ir (Nujol): 1660 cm<sup>-1</sup>; uv  $\lambda$  max (alcohol): 214 nm ( $\epsilon$ , 12,550), 248 nm ( $\epsilon$ , 11,990), 305 nm ( $\epsilon$ ,



- 1a** R H  
**b** R CH<sub>2</sub>COOCH<sub>3</sub>  
**c** R CH<sub>2</sub>CN  
**d** R - CH<sub>2</sub>COCH<sub>3</sub>



- 2a** R<sub>1</sub> H R<sub>2</sub> COOCH<sub>3</sub>  
**b** R<sub>1</sub> H R<sub>2</sub> CN  
**c** R<sub>1</sub> H R<sub>2</sub> COCH<sub>3</sub>  
**d** R<sub>1</sub> CH<sub>3</sub> R<sub>2</sub> COOCH<sub>3</sub>  
**e** R<sub>1</sub> CH<sub>3</sub> R<sub>2</sub> CN  
**f** R<sub>1</sub> CH<sub>3</sub> R<sub>2</sub> COCH<sub>3</sub>



3

24,260).

*Anal.* Calcd. for  $C_{12}H_8O_4S$ : C, 58.05; H, 3.25; S, 12.92. Found: C, 57.87; H, 3.29; S, 12.76.

3-Hydroxy[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**2b**).

A solution containing 7.4 g. of **1c** (30 mmoles) and 4.0 g. of potassium *t*-butoxide (36 mmoles) in 100 ml. of benzene was refluxed for 2 hours. The product was isolated as in the case of **2a** and crystallized from alcohol-water to yield 5.45 g. (84%) of product, m.p. 174-175°; ir (Nujol): 2220  $cm^{-1}$ ; uv  $\lambda$  max (alcohol): 210 nm ( $\epsilon$ , 14,550), 244 nm ( $\epsilon$ , 16,860), 300 nm ( $\epsilon$ , 20,420).

*Anal.* Calcd. for  $C_{11}H_5NO_2S$ : C, 61.39; H, 2.34; N, 6.51; S, 14.90. Found: C, 61.21; H, 2.60; N, 6.29; S, 14.62.

3-Hydroxy[1]benzothieno[3,2-*b*]furan-2-yl Methyl Ketone (**2c**).

A solution of 2.6 g. of **1d** (9.9 mmoles) and 0.65 g. of sodium methoxide (12 mmoles) in 50 ml. of methanol was stirred at room temperature for 4 hours. The mixture was poured into ice water and acidified. The crude solid was collected and crystallized from alcohol to yield 1.5 g. (65%) of product, m.p. 196-197°; nmr (DMSO- $d_6$ ):  $\delta$  2.49 (s, 3); uv  $\lambda$  max (alcohol): 220 nm ( $\epsilon$ , 17,820), 229 nm ( $\epsilon$ , 12,140), 258 nm ( $\epsilon$ , 10,740), 328 nm ( $\epsilon$ , 28,580).

*Anal.* Calcd. for  $C_{12}H_8O_3S$ : C, 62.06; H, 3.47; S, 13.81. Found: C, 61.78; H, 3.37; S, 13.53.

3-Methoxy[1]benzothieno[3,2-*b*]furan-2-carboxylic Acid, Methyl Ester (**2d**).

Dimethyl sulfate (10 ml.) was added dropwise to a solution containing 5.0 g. of **2a** (20 mmoles) and 2.7 g. of potassium *t*-butoxide (24 mmoles) in 60 ml. of DMSO, and the mixture was stirred at room temperature for an additional hour. The mixture was poured into ice water, and the solid was collected and crystallized from alcohol to yield 3.9 g. (74%) of product, m.p. 145-146°; nmr (deuteriochloroform):  $\delta$  3.95 (s, 3), 4.18 (s, 3); ir (Nujol): 1715  $cm^{-1}$ ; uv  $\lambda$  max (alcohol): 216 nm ( $\epsilon$ , 17,870), 245 nm ( $\epsilon$ , 12,290), 263 nm ( $\epsilon$ , 8,690), 305 nm ( $\epsilon$ , 29,990).

*Anal.* Calcd. for  $C_{13}H_{10}O_4S$ : C, 59.53; H, 3.84; S, 12.22. Found: C, 59.41; H, 3.88; S, 12.34.

3-Methoxy[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**2e**).

To a mixture of 2.15 g. of **2b** (10 mmoles) and 1.35 g. of potassium *t*-butoxide (12 mmoles) in 40 ml. of DMSO was added dropwise 5 ml. of dimethyl sulfate. The solution was stirred for 1 hour, and the product was isolated as in the case of **2d**. The yield was 1.9 g. (83%) of product, m.p. 155.5-157°; nmr (deuteriochloroform):  $\delta$  4.17 (s, 3); ir (Nujol): 2220  $cm^{-1}$ ; uv  $\lambda$  max (alcohol): 212 nm ( $\epsilon$ , 19,060), 242 nm ( $\epsilon$ , 15,150), 296 nm ( $\epsilon$ , 24,810).

*Anal.* Calcd. for  $C_{12}H_7NO_2S$ : C, 62.87; H, 3.08; N, 6.11; S, 13.99. Found: C, 63.13; H, 3.13; N, 5.87; S, 14.01.

3-Methoxy[1]benzothieno[3,2-*b*]furan-2-yl Methyl Ketone (**2f**).

Dimethyl sulfate (3 ml.) was added dropwise to a solution containing 1.25 g. of **2c** (5.4 mmoles) and 0.75 g. of potassium *t*-butoxide (6.7 mmoles) in 25 ml. of DMSO. The mixture was stirred for 1.5 hours, and the product was isolated as in the case of **2d**, except that the product was crystallized from alcohol-water. The yield was 0.8 g. (60%), m.p. 176-179°. An analytical sample, m.p. 180-181°, was recrystallized from alcohol-water; nmr (DMSO- $d_6$ ):  $\delta$  2.42 (s, 3), 4.21 (s, 3); uv  $\lambda$  max (alcohol): 220 nm ( $\epsilon$ , 20,730), 323 nm ( $\epsilon$ , 31,560).

*Anal.* Calcd. for  $C_{13}H_{10}O_3S$ : C, 63.40; H, 4.09; S, 13.02. Found: C, 63.15; H, 4.08; S, 13.02.

3-Methyl-2*H*-[1]benzothieno[2,3-*e*]-1,3-oxazine-2,4(3*H*)dione (**3**).

A solution containing 3.0 g. of methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate (14.4 mmoles), 2 ml. of methyl isocyanate, and 3 ml. of triethylamine in 30 ml. of methylene chloride was refluxed for 48 hours. Ethyl acetate (50 ml.) was added and the product crystallized to yield 2.2 g. (65%), m.p. 200-201°; nmr (DMSO- $d_6$ ):  $\delta$  3.35 (s, 3); ir (Nujol): 1765 and 1690  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{11}H_7NO_3S$ : C, 56.64; H, 3.03; N, 6.01; S, 13.75. Found: C, 56.36; H, 3.07; N, 5.79; S, 13.89.

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- (5) Melting points were determined on a Mel-Temp apparatus and are uncorrected.