A Simple Synthesis of Thieno[2,3-*b*]pyrazine and Thieno[2,3-*b*]pyridine (1)

S. W. Schneller, F. W. Clough, and L. E. Hardee*

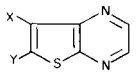
Department of Chemistry, University of South Florida, Tampa, Florida 33620

Received December 17, 1975

A facile synthesis of thieno[2,3-*b*]pyrazine (**1**) and thieno[2,3-*b*]pyridine (**9**) is reported. Furthermore, convenient preparations of a variety of synthetically useful compounds derived from these ring systems is also presented.

J. Heterocyclic Chem., 13, 273 (1976).

Thieno[2,3-*b*]pyrazine (**1**) is an unknown heterocycle which is isosteric and isoelectronic with quinoxaline and has been reported only as a constituent of several polycyclic ring systems (2,3). A simple synthesis of **1** from ethyl 7-aminothieno[2,3-*b*]pyrazine-6-carboxylate (**2**) (2a) has evolved from our program designed to study thieno analogs of quinoxalinic medicinal agents and this preparation is reported herein.



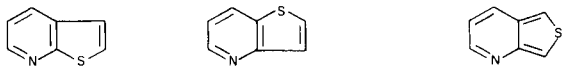
1: X = Y = H
2: X = NH_2, Y = $CO_2C_2H_5$
3: X = H, Y = $CO_2C_2H_5$
4: X = H, Y = CO_2H
5: X = Cl, Y = $CO_2C_2H_5$
6: X = Cl, Y = H
7: X = NH_2, Y = CO_2H
8: X = NH_2, Y = H

Diazotiaztion of **2** with sodium nitrite in sulfuric acid followed by hypophosphorus acid reduction led to ethyl thieno[2,3-*b*]pyrazine-6-carboxylate (**3**). Subsequent saponification of **3** formed the 6-carboxylic acid derivative **4** which was readily decarboxylated with copper powder to produce the desired **1** as a low melting solid.

Attempts to subject **2** to diazotization conditions which employed an acid possessing a suitably reactive nucleophilic conjugate base led to the appropriate ethyl 7-substituted thieno[2,3-*b*]pyrazine-6-carboxylate as illustrated for hydrochloric acid which formed compound **5**. This chloroester (**5**) could easily be saponified and decarboxylated to 7-chlorothieno[2,3-*b*]pyrazine (**6**). These results suggest a practical route to 7-substituted derivatives of **1**.

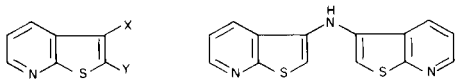
An alternative preparation of **1** from **2** was viewed as involving saponification of **2** to 7-aminothieno[2,3-*b*]-pyrazine-6-carboxylic acid (**7**) (2a) followed by its decarboxylation and subsequent diazotization/reduction. Thus, treatment of **7** with copper powder at high temperatures yielded 7-aminothieno[2,3-*b*]pyrazine (**8**) which, however, resulted in high melting, intractable solids when subjected to a variety of diazotization/reduction conditions.

A related research pursuit in this laboratory is the study of the importance of the benzene ring in quinolinic medicinal agents (*e.g.*, camptothecin). One approach to evaluating the biosignificance of this carbocyclic moiety is *via* molecular modification employing, for example, the bioisosteric relationship (4) between -CH=CH- and -S-. Such a structural variation in the case of quinoline produces the thienopyridines (**9-11**). Thus, to achieve one aspect of this program, it became necessary to avail a preparation of **9** which was more convenient than those presently known (5). The plan here paralleled that for **1** by commencing with the readily available ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate (**12**) (6).



9 **10** **11**

As with **2** diazotization of **12** followed by hypophosphorus acid mediated reduction of the intermediate diazonium salt produced ethyl thieno[2,3-*b*]pyridine-2-carboxylate (**13**). Saponification of **13** to the 2-carboxylic acid (**14**) followed by its decarboxylation in the presence of copper powder resulted in the desired **9**.



17

12: X = NH_2, Y = $CO_2C_2H_5$
13: X = H, Y = $CO_2C_2H_5$
14: X = H, Y = CO_2H
15: X = NH_2, Y = CO_2H
16: X = NH_2, Y = H

Another approach to **9** from **12** was also conceived to involve decarboxylation of the aminoacid **15** to **16** (7) and, subsequent diazotization/reduction of this amine. However, numerous decarboxylative approaches with **15** yielded nearly quantitative amounts of the secondary

amine **17** (7) and only trace amounts (8) of the desired **16**. Thus, this pathway to **9** was abandoned.

EXPERIMENTAL (9)

Ethyl Thieno[2,3-*b*]pyrazine-6-carboxylate (**3**).

To 50 ml. of 75% sulfuric acid was added 1.0 g. (4.48 mmoles) of **2** (2a) to give a blood red solution which was cooled to 0° in an ice-salt bath. Then 0.5 g. of sodium nitrite in 5 ml. of water was added at such a rate that the temperature did not rise above 5°. At this point stirring of the solution became difficult and the ice-salt bath was replaced by an ice water bath and stirring continued for 30 minutes. This homogeneous reaction solution was then added rapidly to 40 ml. of stirred and pre-chilled 50% hypophosphorus acid. Vigorous foaming ensued and the stirring was continued for 30 minutes in the ice bath and the resulting solution was placed in a refrigerator for 18 hours. The precipitated solid was filtered and air dried. Extraction of the filtrate with chloroform (3 x 50 ml.) followed by drying the combined extracts over anhydrous magnesium sulfate and subsequent evaporation of the chloroform yielded a second crop of the product. The combined product fractions were recrystallized from 95% ethanol to yield 0.6 g. (64%) of **3** as white crystals, m.p. 73-74.5°; ir (potassium bromide): 5.80 μ (C=O); ^{1}H nmr (deuteriochloroform): δ 1.45 (t, J = 7.0 Hz, CH_3), δ 4.43 (q, J = 7 Hz, CH_2), δ 8.08 (s, H-7), δ 8.50 (d, J = 2 Hz, H-2 or H-3), δ 8.65 (d, J = 2 Hz, H-2 or H-3).

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87. Found: C, 52.09; H, 3.97.

Thieno[2,3-*b*]pyrazine-6-carboxylic Acid (**4**).

A mixture of 0.22 g. (1.06 mmoles) of **3** and 0.2 g. of potassium hydroxide in 25 ml. of absolute ethanol was refluxed for 1 hour. After cooling to room temperature and evaporation of the solvent, the residue was dissolved in a minimum amount of water, filtered and the aqueous filtrate acidified with 5% hydrochloric acid. The resulting precipitate was filtered, air dried and recrystallized from 95% ethanol to yield 0.18 g. (95%) of **4** as white crystals, m.p. 261-262° dec.; ir (potassium bromide): 5.92 μ (C=O), 6.42 μ (C=N); ^{1}H nmr (hexadeuterodimethylsufoxide): δ 7.33 (broad, CO_2H), δ 7.98 (s, H-7), δ 8.59 (d, J = 2 Hz, H-2 or H-3), δ 8.71 (d, J = 2 Hz, H-2 or H-3).

Anal. Calcd. for $C_7H_4N_2O_2S \cdot H_2O$: C, 42.42; H, 3.03. Found: C, 42.48; H, 3.09.

Thieno[2,3-*b*]pyrazine (**1**).

A mixture of 0.23 g. (1.28 mmoles) of **4** and 0.32 g. of copper powder were heated very briefly over an open flame. The residue was extracted thoroughly with ether and the combined ether extracts were washed once with 10% sodium bicarbonate solution and then dried over anhydrous magnesium sulfate. Evaporation of the ether yielded an oil which solidified upon standing and was sublimed (35-40°/3.0 mm.) to produce 0.12 g. (68%) of **1** as white crystals, m.p. 43-44.5°; ir (potassium bromide): 6.51 μ (C=N); ^{1}H nmr (hexadeuterodimethylsulfoxide): δ 7.59 (d, J = 6 Hz, H-6), δ 8.30 (d, J = 6 Hz, H-7), δ 8.59 (d, J = 2 Hz, H-2 or H-3), δ 8.74 (d, J = 2 Hz, H-2 or H-3).

Anal. Calcd. for $C_6H_4N_2S$: C, 52.92; H, 2.96. Found: C, 52.90; H, 3.16.

Ethyl 7-Chlorothieno[2,3-*b*]pyrazine-6-carboxylate (**5**).

To a solution of 20 ml. of water and 60 ml. of concentrated hydrochloric acid was added 1.12 g. (5.0 mmoles) of **2** (2a). This homogeneous and blood red solution was then cooled in an ice-salt bath to -2 to -3° with stirring for 30 minutes. To this a solution of 0.5 g. (7.0 mmoles) of sodium nitrite dissolved in 4 ml. of water was added dropwise at such a rate that the temperature remained at -3° during which time the solution underwent a color change to light orange. After stirring at -3° for an additional 45 minutes, this solution was added in one portion to 20 ml. of pre-cooled 50% hypophosphorus acid and stirred at -3° for 30 minutes. The light yellow solution was refrigerated for 18 hours. After filtering off a small amount of white precipitate, the aqueous solution was extracted with chloroform (3 x 75 ml.), and the combined extracts dried over magnesium sulfate and the solvent removed to produce light yellow crystals which were recrystallized from 95% ethanol to give 0.8 g. (77%) of **5**; m.p. 104-105°; ir (potassium bromide): 5.90 μ (C=O); ^{1}H nmr (deuteriochloroform): δ 1.56 (t, J = 7 Hz, CH_3), δ 4.82 (q, J = 7 Hz, CH_2), δ 9.35 (d, J = 2 Hz, H-2 or H-3), δ 9.48 (d, J = 2 Hz, H-2 or H-3).

Anal. Calcd. for $C_9H_7ClN_2O_2S \cdot H_2O$: C, 41.69; H, 3.47. Found: C, 41.67; H, 3.51.

7-Chlorothieno[2,3-*b*]pyrazine (**6**).

A mixture of 0.8 g. (3.85 mmoles) of **5** and 0.73 g. of potassium hydroxide in 30 ml. of absolute ethanol was refluxed for 1.5 hours. After removing the ethanol under vacuum, water was added to dissolve the residue and the aqueous solution was acidified with glacial acetic acid to yield a white precipitate which was filtered, air dried and recrystallized from aqueous ethanol to give 0.3 g. (44%), m.p. 248-250°, of 7-chlorothieno[2,3-*b*]pyrazine-6-carboxylic acid [ir (potassium bromide): 6.00 μ (C=O)].

A mixture of 0.25 g. (1.39 mmoles) of this carboxylic acid and 0.329 g. (0.00518 g.-atom) of copper powder was heated over an open flame as previously described for the preparation of **1**. A white solid was obtained after extraction of the residue and it was sublimed (50°/2.0 mm.) to give 0.19 g. (quantitative) of **6** as white crystals, m.p. 70-72°.

Anal. Calcd. for $C_6H_3ClN_2S$: C, 42.23; H, 1.77. Found: C, 42.00; H, 1.62.

7-Aminothieno[2,3-*b*]pyrazine (**8**).

A mixture of 1.0 g. (5.13 mmoles) of **7** (2a) and 1.21 g. (0.101 g.-atom) of copper powder in a 50 ml. flask fitted with a condenser was heated with an open flame for 5 minutes. Liquefaction occurred and gas was vigorously evolved. After cooling the entire apparatus was thoroughly rinsed with ether, the ether was then extracted with 10% sodium bicarbonate (2 x 20 ml.), dried over anhydrous sodium carbonate and then removed to yield a residue which was sublimed (78-80°/3.0 mm.) to produce 0.5 g. (64.6%) of **8** as light yellow crystals, m.p. 81-82°; ir (potassium bromide): 2.95 μ and 3.08 μ (NH_2), 6.25 μ (C=N); ^{1}H nmr (deuteriochloroform): δ 4.15 (broad, NH_2), δ 6.70 (s, H-6), δ 8.60 (d, J = 2 Hz, H-2 or H-3), δ 8.71 (d, J = 2 Hz, H-2 or H-3).

Anal. Calcd. for $C_6H_5N_3S$: C, 47.66; H, 3.33. Found: C, 47.40; H, 3.28.

Ethyl Thieno[2,3-*b*]pyridine-2-carboxylate (**13**).

Sodium nitrite (2.0 g., 23.5 mmoles) dissolved in 10 ml. of water was added dropwise over a 10 minute period to a stirred, ice cooled solution of 2.0 g. (9.0 mmoles) of ethyl 3-aminothieno-[2,3-*b*]pyridine-2-carboxylate (**12**) (6) in 50 ml. of 75% sulfuric acid. After the addition and following stirring of the solution in an ice bath for 30 minutes, it was poured into 80 ml. of pre-chilled 50% hypophosphorus acid. Considerable frothing ensued while the stirring was continued in the ice bath for an additional 30 minutes after which the solution was placed in a refrigerator for

6 hours. The reaction mixture was then neutralized with solid sodium bicarbonate and the resultant solution extracted with ether (10 x 150 ml.). The combined extracts were dried over anhydrous magnesium sulfate and then the ether was removed on the rotoevaporator to yield a green solid which was purified by vacuum sublimation (90°/2 mm.) to yield **13** as white crystals (37.5%), m.p. 57-58°; ir (potassium bromide): 5.80 μ (C=O); ^{1}H nmr (deuteriochloroform): δ 1.41 (t, J = 7.5 Hz, CH_3), δ 4.42 (q, J = 7.5 Hz, CH_2), δ 7.34 (d of d, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 4.5 Hz, H-5), δ 7.90 (s, H-3), δ 8.12 (d of d, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 1.5 Hz, H-4), δ 8.62 (d of d, $J_{5,6}$ = 4.5 Hz, $J_{4,6}$ = 1.5 Hz, H-6).

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.92; H, 4.34. Found: C, 58.20; H, 4.44.

Thieno[2,3-*b*]pyridine-2-carboxylic Acid (**14**).

After dissolving 0.1 g. (0.48 mmole) of **13** in 3 ml. of absolute ethanol, 0.5 g. (8.9 mmoles) of potassium hydroxide was added and within seconds a white precipitate formed (10). The heterogeneous reaction solution was refluxed for 25 minutes and upon cooling the resultant white solid was obtained by filtration and dissolved in 3 ml. of water. Acidification of the aqueous solution with glacial acetic acid resulted in precipitation of **14** which was filtered and purified by vacuum sublimation (165°/2 mm.) to yield white needles (35.9%), m.p. 311-312°; ir (potassium bromide): 5.85-5.90 μ (C=O); ^{1}H nmr (hexadeuterodimethylsulfoxide): δ 7.50 (d of d, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 4.5 Hz, H-5), δ 8.09 (s, H-3), δ 8.39 (d of d, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 1.5 Hz, H-4), δ 8.59 (d of d, $J_{5,6}$ = 4.5 Hz, $J_{4,6}$ = 1.5 Hz, H-6).

Anal. Calcd. for $C_8H_5NO_2S$: C, 53.66; H, 2.79. Found: C, 53.45; H, 2.78.

Thieno[2,3-*b*]pyridine (**9**).

A mixture of 0.15 g. (0.84 mmole) of **14** and 0.2 g. (0.0031 g.-atom) of copper powder were mixed together in a 25 ml. round bottom flask equipped with a microdistillation apparatus. The mixture was heated with an open flame during which time the mixture darkened and a liquid began to condense on the inside of the apparatus. After heating for 3 minutes, the flame was removed and the reaction mixture allowed to cool. The entire apparatus was then extracted with ether and the combined ether extracts were washed with 10% sodium bicarbonate solution. After drying over anhyhrous sodium sulfate, the ether was removed (rotoevaporator) to leave an oil which crystallized when placed in the refrigerator. The ^{1}H nmr spectrum of this product and its melting point were identical with that reported (11) for **9**. The yield was 0.1 g. (87%).

3-Aminothieno[2,3-*b*]pyridine-2-carboxylic Acid (**15**).

A solution of 3.0 g. (13.5 mmoles) of **12** in 75 ml. of absolute ethanol containing 1.8 g. (32.1 mmoles) of potassium hydroxide was refluxed for 45 minutes. Compound **12** was not initially soluble in the ethanolic solution but slowly dissolved upon reflux and the corresponding potassium salt began to precipitate. After cooling to room temperature, the insoluble potassium salt obtained by filtering the solution was dissolved in 200 ml. of water and the aqueous solution acidified with glacial acetic acid to yield **15**, following recrystallization from ethanol, as yellow crystals (87.8%), m.p. 160°; ir (potassium bromide): 2.87 μ (NH), 2.97 μ (OH), 6.02 μ (C=O); ^{1}H nmr (hexadeuterodimethylsulfoxide): δ 7.52 (d of d, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 5.0 Hz, H-5), δ 8.58 (d of d, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 1.5 Hz, H-4), δ 8.76 ($J_{5,6}$ = 5.0 Hz, $J_{4,6}$ = 1.5 Hz H-6).

Anal. Calcd. for $C_8H_6N_2O_2S$: C, 49.48; H, 3.09. Found: C, 49.62; H, 3.29.

Acknowledgement.

We gratefully acknowledge the Beta Lambda Chapter of Phi Beta Psi for their partial support of this research endeavor.

REFERENCES AND NOTES

(1) S. W. Schneller and F. W. Clough, presented to the Division of Medicinal Chemistry at 168th American Chemical Society Meeting, Atlantic City, New Jersey, September 8-13, 1974, MEDI-32.

(2) For example, see (a) S. W. Schneller and F. W. Clough, *J. Heterocyclic Chem.*, **12**, 513 (1975); (b) W. F. Gray, I. H. Pomerantz, and R. D. Ross, *ibid.*, **9**, 707 (1972).

(3) M. Goto, A. Sakurai, K. Ohta, and H. Yamakami, *Tetrahedron Letters*, 4507 (1967); A. Sakurai and M. Goto, *ibid.*, 2941 (1968).

(4) A. Burger in "Medicinal Chemistry," Part I, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, p. 77.

(5) S. W. Schneller, *Int. J. Sulfur Chem., B*, **7**, 309 (1972).

(6) S. W. Schneller and F. W. Clough, *J. Heterocyclic Chem.*, **11**, 975 (1974).

(7) L. H. Klemm, R. Zell, I. T. Barnish, R. A. Klemm, C. E. Klopfenstein, and D. R. McCoy, *ibid.*, **7**, 373 (1970).

(8) Following separation with boiling cyclohexane, the soluble portion (in very small amounts) was found to have properties (infrared and melting point) consistent with those of **16** reported elsewhere (7) while the insoluble portion is **17** by the same physical property (7) correlations.

(9) Melting points were taken on Mel-Temp and Thomas Hoover Capillary melting point apparatuses and are uncorrected. The nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ir spectra were recorded on a Perkin Elmer Model 337 spectrophotometer. The microanalyses were performed by Het-Chem-Co., Harrisonville, Missouri.

(10) The white solid was believed to be potassium thieno-[2,3-*b*]pyridine-2-carboxylate based on its infrared spectral properties [(potassium bromide) 6.32 μ and 7.10 μ (carboxylate group)].

(11) L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R. McCoy, and R. A. Klemm, *J. Org. Chem.*, **34**, 347 (1969).