Studies of Thieno[2,3-*b*]pyrazines in Preparation of Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines and Related Molecules (1)

S. W. Schneller and F. W. Clough*

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

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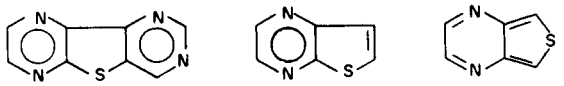
A variety of 2,3-disubstituted derivatives of the previously unknown thieno[2,3-*b*]pyrazine ring system have been employed as a synthetic foundation for pyrazino[2′,3′:4,5]thieno[3,2-*d*]-pyrimidine and several of its derivatives.

As part of a program of investigating the biosignificant pyrimidine nucleus as part of tricyclic heterocyclic arrays, the ring system **1** possessing the thieno[2,3-*b*]pyrazine moiety was considered an important link in this study. The literature contains no report of the thieno[2,3-*b*]pyrazine ring (**2**) (2) although the isomeric thieno[3,4-*b*]pyrazine (**3**) is well-analyzed (3). To circumvent the previous difficulty in preparing **2** and its derivatives (*i.e.*, the unattractive



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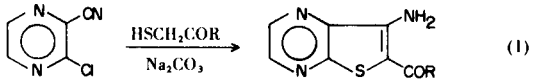
accessibility of 2,3-diaminothiophene for condensation with α-dicarbonyl compounds) construction of the thiophene ring onto the preformed pyrazine nucleus was pursued.

The most direct and versatile route into ring system **2**, which would also avail the necessary functionality for fusion of the desired pyrimidine ring, was found to be *via* ethyl 3-aminothieno[2,3-*b*]pyrazine-2-carboxylate (**4**). Compound **4** was prepared utilizing the sodium carbonate mediated (4) reaction of ethyl α-mercaptoacetate with 2-



(1)

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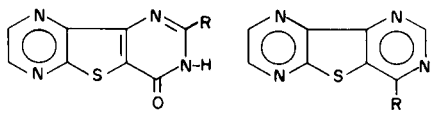
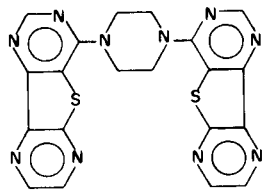
4, R = OC_2H_5
5, R = NH_2

chloro-3-cyanopyrazine (**6**) (5,6) as shown in equation (1). Subsequent treatment of **4** with formamide yielded the pyrimidinone **7** (7), which, in turn, was converted by phosphorus oxychloride into 4-chloropyrazino[2′,3′:4,5]-thieno[3,2-*d*]pyrimidine (**8**), a fruitful precursor for the desired molecules.



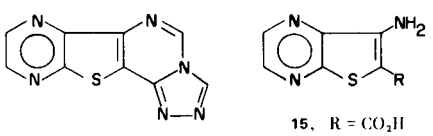
7, R = H
17, R = CH_3

8, R = Cl
9, R = OCH_3
10, R = SH
11, R = $NHNH_2$
13, R = N-morpholino



14

Reaction of **8** with sodium methoxide in methanol produced the 4-methoxy derivative (**9**) while treatment with thiourea resulted in the 4-mercapto system (**10**). Compounds **7** and **10** were found to be intractable to simple base promoted methylation. The 4-hydrazino derivative (**11**), prepared by the reaction of **8** with hydrazine hydrate, permitted the preparation of the fused s-triazole (**12**) upon treatment with formic acid. The parent ring, pyrazino-[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**1**), was prepared *via* direct catalytic reduction of **8** or by bubbling oxygen through a sodium ethoxide/ethanol solution of **11**. By analogy with hydrazine **8** also reacts with representative amines to form **13** (morpholine) and **14** (piperazine).



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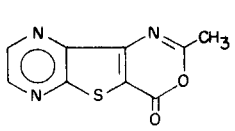
15, R = CO_2H
18, R = CN

Saponification of the ethyl ester **4** with potassium hydroxide in absolute ethanol yielded 3-aminothieno[2,3-*b*]pyrazine-2-carboxylic acid (**15**). Reaction of **15** with acetic anhydride formed the oxazinone (**16**) which, upon reaction with ammonium hydroxide, produced the 2-methylpyrimidinone **17**.

When α-mercaptoacetamide was employed in equation (1) rather than ethyl α-mercaptoacetate 3-aminothieno-[2,3-*b*]pyrazine-2-carboxamide (**5**) was isolated. The corresponding 2-carbonitrile (**18**), was readily available by phosphorus oxychloride dehydration of **5**. Treatment of **5** with ethyl chloroformate in pyridine resulted in the pyrimidinedione **19** which was also available from fusion of the amino acid **15** or the amino amide **5** with urea.



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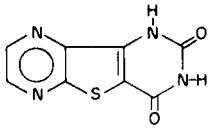


19

EXPERIMENTAL (8)

Ethyl 3-Aminothieno[2,3-*b*]pyrazine-2-carboxylate (**4**).

To 7.5 g. (53.7 mmoles) of 2-chloro-3-cyanopyrazine (**6**) (5,6) in 150 ml. of absolute ethanol was added 6.48 g. (54.0 mmoles) of ethyl α-mercaptoacetate and 5.73 g. (54.0 mmoles) of anhydrous sodium carbonate and the mixture was refluxed for 4.5 hours. After cooling the reaction mixture was filtered. The residue was stirred with 200 ml. of water, filtered and the insoluble material recrystallized from aqueous ethanol to give 9.3 g. (77.6%), m.p. 114-116°; ir (potassium bromide): 2.9 μ (NH), 6.0 μ (C=O); ^{1}H nmr (deuteriochloroform): δ 1.42 (t, CH_3), δ 4.45 (q, CH_2), δ 8.32 (q, H-5, H-6), δ 6.3 (bs, NH_2); mass spectrum m/e (relative abundance): 223 (69, M^+), 195 (20), 178 (23), 177 (100), 151 (11), 150 (14), 149 (32), 123 (14), 122 (13), 72 (15), 52 (10), 45 (13), 29 (15), 18 (21).

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.41; H, 4.06. Found: C, 48.23; H, 4.14.

Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)one (**7**).

A mixture of 5.0 g. (22.4 mmoles) of **4** in 150 ml. of formamide (9) was refluxed for 8 hours. Upon cooling a light yellow precipate resulted which was filtered and recrystallized from 1-butanol to yield 2.8 g. (61%) of white crystals, m.p. > 390°; ir (potassium bromide): 2.90 μ (NH), 5.90 μ (C=O).

Anal. Calcd. for $C_8H_4N_4OS$: C, 47.05; H, 1.97. Found: C, 46.99; H, 2.27.

4-Chloropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**8**).

To 10 ml. of phosphorus oxychloride was added 0.5 g. (2.45 mmoles) of **7** and the resulting mixture was refluxed for 3.5 hours. After cooling the reaction mixture was poured with vigorous stirring over ice. The tan crystals that resulted were filtered, dried, and then sublimed (150°/1.5 mm.) to give 0.38 g. (70%) of white crystals, m.p. 175-177°; ir (potassium bromide): 6.45 μ (C=N); mass spectrum m/e (relative abundance): 224 (37), 223 (10), 222 (100), 187 (85), 160 (17).

Anal. Calcd. for $C_8H_3ClN_4S$: C, 43.05; H, 1.34. Found: C, 43.01; H, 1.14.

4-Methoxypyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**9**).

A solution containing 0.3 g. (1.34 mmoles) of **8** and 0.05 g. of sodium in 15 ml. of absolute methanol was refluxed for 3 hours. The solution was cooled, evaporated to dryness and the resulting residue treated with water. The insoluble material was filtered, air dried and then sublimed (140°/1.5 mm.) to give 0.1 g. (34%) of white crystals, m.p. 216-218°; ir (potassium bromide): 6.40 μ (C=N).

Anal. Calcd. for $C_9H_6N_4OS$: C, 49.54; H, 2.75. Found: C, 49.61; H, 2.86.

4-Mercaptopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**10**).

A solution of 0.7 g. (3.15 mmoles) of **8** and 0.608 g. (8.0 mmoles) of thiourea in 30 ml. of absolute ethanol was refluxed for 3 hours. After cooling, the yellow-orange mixture was filtered and the precipitate was recrystallized from a large volume of methanol to yield 0.66 g. (94%) of yellow crystals, m.p. dec., 365-367°; ir (potassium bromide): 6.30 μ (C=N); mass spectrum m/e (relative abundance): 220 (100, M^+), 193 (22), 187 (28), 28 (13), 18 (29).

Anal. Calcd. for $C_8H_4N_4S_2 \cdot \frac{1}{2}H_2O$: C, 42.10; H, 2.19. Found: C, 42.02; H, 2.17.

4-Hydrazinopyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**11**).

To 0.5 g. (2.25 mmoles) of **8** in 20 ml. of absolute ethanol was added 2 ml. of 97% hydrazine and the mixture was refluxed for 12 hours. After cooling, the orange mixture was filtered and the precipitate recrystallized from absolute ethanol to give 0.45 g. (91.7%) of the white product, m.p. 256-258°; ir (potassium bromide): 3.05 μ (NH), 3.15 μ (NH_2), 6.31 μ (C=N); mass spectrum m/e (relative abundance): 218 (100, M^+), 188 (17), 161 (26).

Anal. Calcd. for $C_8H_6N_6S$: C, 44.02; H, 2.77. Found: C, 44.23; H, 2.91.

s-Triazolo[4,3-*c*]pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**12**).

A solution of 0.2 g. (0.92 mmole) of **11** and 15 ml. of formic acid was refluxed for 4 hours. After cooling the formic acid was removed *in vacuo*. The residue was sublimed (220°/1.5 mm.) to yield 0.08 g. (37%) of a white product, m.p. 274-276°, which appeared to be hydgroscopic when exposed to air; ir (potassium bromide): 5.92 μ (C=N).

Anal. Calcd. for $C_9H_4N_6S \cdot \frac{1}{2}H_2O$: C, 45.56; H, 2.09. Found: C, 45.81; H, 2.12.

Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**1**).

Method A.

Oxygen was bubbled through a 40 ml. absolute ethanolic solution of 0.2 g. (0.0086 g-atoms) of sodium and 0.2 g. (0.917 mmole) of **11** for 3 hours. Dilute hydrochloric acid was added until the solution was slightly acidic and then sodium bicarbonate was carefully added to achieve neutrality. The resulting solution was extracted with ether (4 x 40 ml.) and the ether extracts were combined and dried over anhydrous sodium sulfate. The ether was removed to leave a green-brown residue which was sublimed (160°/1.5 mm.) to give 0.14 g. (81.4%) of white crystals, m.p. 192-195°; ir (potassium bromide): 6.30 μ (C=N); ^{1}H nmr (hexadeuterodimethylsulfoxide): δ 8.84 (d, 7-H or 8-H), δ 8.97 (d, 7-H or 8-H), δ 9.33 (s, 2-H or 4-H), δ 9.63 (s, 2-H or 4-H).

Anal. Calcd. for $C_8H_4N_4S$: C, 51.05; H, 2.14. Found: C, 50.99; H, 2.33.

Method B.

A 35 ml. ethanolic solution of 0.1 g. (0.45 mmole) of **8** containing 50 mg. of palladium on charcoal and 60 mg. of magnesium

oxide was treated with an atmospheric pressure of hydrogen for four days. Following this exposure, the solution was filtered, the catalyst washed with warm ethanol and the ethanolic filtrate evaporated. The residue was treated with water, extracted with ether (2 x 25 ml.), the ether extracts combined and dried over anhydrous magnesium sulfate and evaporated to yield after purification, 0.05 g. (60%) of white crystals identical to that described in method A.

4-(*N*-Morpholino)pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**13**).

A solution of 0.1 g. (0.44 mole) of **8** and 1 ml. of morpholine in 7 ml. of absolute ethanol was refluxed for 10 hours. The solution was cooled, the ethanol evaporated and the product obtained by filtering the residue. The collected material was washed with water, air dried and purified by vacuum sublimation (150°/1.5 mm.) to give 0.06 g. (50%) of white crystals, m.p. 206-208°; ir (potassium bromide): 6.45 μ (C=N).

Anal. Calcd. for $C_{12}H_{11}N_5OS$: C, 52.75; H, 4.03. Found: C, 52.68; H, 4.24.

N,N′-Bis(pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)piperazine (**14**).

To 5 ml. of absolute ethanol was added 0.1 g. (0.45 mmole) of **8** and 0.02 g. (0.23 mmole) of piperazine and the mixture was refluxed for 10 hours. Upon cooling the precipitate was collected and recrystallized from dimethylformamide to yield 0.1 g. (48%), m.p. 336° dec.; ir (potassium bromide): 6.50 μ (C=N).

Anal. Calcd. for $C_{20}H_{14}N_{10}S_2 \cdot 2H_2O$: C, 48.58; H, 3.62. Found: C, 48.21; H, 3.92.

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

A mixture of 2.0 g. (8.96 mmoles) of **4** and 1.2 g. (21.4 mmoles) of potassium hydroxide in 50 ml. of absolute ethanol was refluxed for 1 hour. After cooling the precipitate was filtered, dissolved in water, and then acetic acid was added until precipitation was complete. The product was filtered and air dried to yield 1.2 g. (68.6%) of light yellow crystals, m.p. 218-220°; ir (potassium bromide): 2.92 μ (NH), 3.10 μ (OH), 5.95 μ (C=O); mass spectrum m/e (relative abundance): 195 (100, M^+), 178 (10), 177 (100), 149 (45), 123 (11), 122 (30), 105 (11), 72 (15), 52 (21), 45 (40), 28 (20), 18 (12).

Anal. Calcd. for $C_7H_5N_3O_2S$: C, 43.07; H, 2.56. Found: C, 43.19; H, 2.69.

2-Methyl-4*H*-pyrazino[2′,3′:4,5]thieno[3,2-*d*][3,1]oxazin-4-one (**16**).

A solution of 0.7 g. (3.68 mmoles) of **15** in 15 ml. of acetic anhydride was refluxed for 3 hours. After cooling to room temperature a white precipitate had formed, which was filtered and recrystallized from absolute ethanol to yield 0.5 g. (64%) as white crystals, m.p. 198-202°; ir (potassium bromide): 5.75 μ (C=O), 6.20 μ (C=N).

Anal. Calcd. for $C_9H_5N_3O_2S$: C, 49.31; H, 2.29. Found: C, 49.55; H, 2.46.

2-Methylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)one (**17**).

In 7 ml. of 95% ethanol was mixed 0.2 g. (0.91 mmole) of **16** and 2 ml. of concentrated ammonium hydroxide and the solution was refluxed for 4 hours. The yellow solution was cooled to room temperature and filtered to yield a white precipitate which was recrystallized from absolute ethanol to give 0.18 g. (90%) of white crystals, m.p. 243-244°; ir (potassium bromide): 5.95 μ (C=O), 6.25 μ (C=N).

Anal. Calcd. for $C_9H_6N_4OS \cdot \frac{1}{2}H_2O$: C, 47.57; H, 3.08. Found: C, 47.81; H, 3.22.

3-Aminothieno[2,3-*b*]pyrazine-2-carboxamide (**5**).

A mixture of 1.5 g. (10.8 mmoles) of 2-chloro-3-cyanopyrazine (**6**) (5,6), 0.98 g. (10.8 mmoles) of α-mercaptoacetamide and 1.48 g. (13.9 mmoles) of sodium carbonate in 25 ml. of absolute ethanol was refluxed for 2 hours, cooled, and then filtered to give a greenish-yellow precipitate. The precipitate was mixed with water, filtered and then recrystallized from methanol to yield 2.0 g. (96%) of a yellow product, m.p. 284-286°; ir (potassium bromide): 2.90 μ (NH), 3.00 μ (NH), 5.99 μ (C=O); ^{1}H nmr (hexadeuterodimethylsulfoxide): δ 6.88 (b, NH_2), δ 7.34 (b, NH_2), δ 8.70 (d, 5-H or 6-H), δ 8.81 (d, 5-H or 6-H); mass spectrum m/e (relative abundance): 194 (100, M^+), 178 (13), 177 (76), 150 (13), 149 (38), 123 (16), 122 (20), 106 (10), 72 (17.5), 52 (20), 45 (24), 44 (20), 28 (17), 18 (22).

Anal. Calcd. for $C_7H_6N_4OS$: C, 43.27; H, 3.11. Found: C, 43.41; H, 3.31.

3-Amino-2-cyanothieno[2,3-*b*]pyrazine (**18**).

To 10 ml. of phosphorus oxychloride was added 1.0 g. (5.15 mmoles) of **5** and the mixture was refluxed for 5 hours. After cooling, the mixture was carefully poured over ice and then filtered to yield a brown cake which was dried and sublimed (180°/1.5 mm.) to yield 0.8 g. (88%) of yellow crystals, m.p. 204-206°; ir (potassium bromide): 4.55 μ (C≡N), 6.10 μ (C=N).

Anal. Calcd. for $C_7H_4N_4S$: C, 47.71; H, 2.28. Found: C, 47.99; H, 2.27.

Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-2,4(1*H*,3*H*)dione (**19**).

Method A.

To a mixture of 15 ml. of pyridine and 0.5 g. (2.58 mmoles) of **5** was carefully added 2 ml. of ethyl chloroformate and the mixture was refluxed for 48 hours. After cooling, the solution was concentrated and then water was added to produce a yellow precipitate (0.4 g., 70%) which was filtered and purified by repeated dissolution in aqueous base and precipitation by dilute acid, m.p. >340°; ir (potassium bromide): 2.95 μ (NH), 5.85 μ (C=O), 5.95 μ (C=O).

Anal. Calcd. for $C_8H_4N_4O_2S \cdot H_2O$: C, 40.33; H, 2.52. Found: C, 40.46; H, 2.43.

Method B.

A finely ground mixture of 0.4 g. of **5** or **15** (2.1 mmoles) and 0.8 g. of urea were heated at 180° for 20 minutes. At this temperature the mixture melted and resolidified. The solid mass was extracted with warm 5% sodium hydroxide, filtered and the cooled filtrate acidified with acetic acid to yield, upon filtering and air drying, a yellow product (60-70% yield) identical to that described in method A.

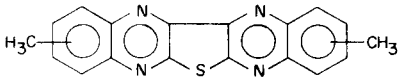
Acknowledgments.

The assistance of Mr. Omar Richany in the preparation of **6** and Professor E. E. Campainge of Indiana University for obtaining the mass spectral data reported in the Experimental Section is gratefully appreciated. We are also indebted to Professor T. W. G. Solomons for his kind consent to use the facilities of his laboratory during the execution of this research.

REFERENCES

(1) A preliminary account of this work was presented at the 168th American Chemical Society Meeting, September 8-13, 1974, Atlantic City, New Jersey.

(2) Compound *i* has been obtained from the photochemical reaction of the pesticide Morestan (W. F. Gray, I. R. Pomerantz



i

and R. D. Ross, *J. Heterocyclic Chem.*, **9**, 707 (1972).

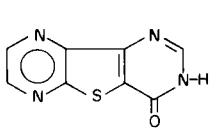
(3a) R. Motoyama and E. Imoto, *Nippon Kagaku Zasshi*, **78**, 793 (1957); *Chem. Abstr.*, **54**, 22560f (1960); (b) S. Nishimura, A. Sakumoto, and E. Imoto, *ibid.*, **82**, 1540 (1961); *Chem. Abstr.*, 57, 15051g (1962); (c) S. Nishimura and E. Imoto, *ibid.*, **82**, 1680 (1961); *Chem. Abstr.*, 59, 1619e (1963); (d) W. J. Evers, I. Katz, R. A. Wilson, and E. T. Theimer, U. S. Patent 3,767,426 (1970); *Chem. Abstr.*, **80**, 27295p (1974).

(4) A. A. Santilli, D. H. Kim, and S. V. Wanser, *J. Heterocyclic Chem.*, 8, 445 (1971).

(5) M. Asai, *Yakugaku Zasshi*, **81**, 1475 (1961); *Chem. Abstr.*, 56, 8711h (1962).

(6) The precursor to **6**, 2-hydroxy-3-carboxamidopyrazine, has been reported by F. L. Muehlmann and A. R. Day, *J. Am. Chem. Soc.*, 78, 242 (1956).

(7) The absence of a hydroxyl band in the infrared spectrum of **7** ruled out tautomer *iv* but it was not possible to discern which of the remaining two significant tautomers (*ii* or *iii*) was predominant. (see W. L. F. Armarego in "Fused Pyrimidines," Part I, Ed. D. J. Brown, Wiley-Interscience, New York, 1967, pp. 102-104 and references cited therein).



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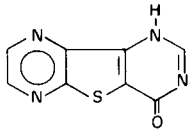

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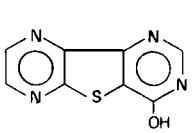

iv

(8) Melting points were taken on a Mel-Temp Capillary melting point apparatus and are uncorrected. The nmr spectrum was obtained on a Varian A-60 spectrometer using TMS as an internal standard. Ir spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. The mass spectra were determined on a Varian MAT CH-7 at Indiana University, Bloomington, Indiana. The microanalyses were performed by Het-Chem-Co., Harrisonville, Missouri.

(9) The use of freshly distilled formamide is essential for optimum yields.