Synthesis of 2-Amino-6,7-dihydrothieno-[3′,2′:5,6]pyrido[2,3-*d*]pyrimidin-4-one

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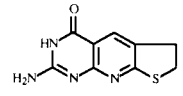
2-Amino-6,7-dihydrothieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidin-4-one (**1**) was prepared in three steps from *S*-(3-butynyl)thiosemicarbazide hydroiodide (**3**) and diethyl ketomalonate. The featured step in this synthetic sequence was an intramolecular Diels-Alder reaction of the *in situ* generated 3-(3-butynylthio)-6-carboethoxy-5-chloro-1,2,4-triazine (**9**) to provide the key intermediate 5-carboethoxy-6-chloro-2,3-dihydrothieno-[2,3-*b*]pyridine (**6**). In the course of studies directed toward the preparation of **1**, thermolysis of 3-(3-butynylthio)-6-carboethoxy-1,2,4-triazin-5(2*H*)-one (**2**) was found to involve competitive intramolecular Diels-Alder and intramolecular coplanar cycloamination processes, providing the 2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one (**4**) and the 1,3-thiazino[3,2-*b*]-1,2,4-triazin-3-one (**5**) derivatives, respectively.

J. Heterocyclic Chem., **25**, 1733 (1988).

Intramolecular Diels-Alder reactions of 3-(3-butynylthio)-1,2,4-triazines have been shown by our group and others to lead conveniently to thieno[2,3-*b*]pyridines [1]. Our long standing interest in thienopterins such as urothione and Form B of the molybdenum cofactor [2] has led us to extend this concept to the first preparation of members of the closely related 6,7-dihydrothieno[3′,2′:5,6]-pyrido[2,3-*d*]pyrimidin-4-one ring system (**1**).



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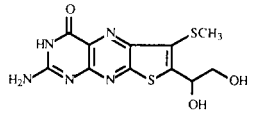
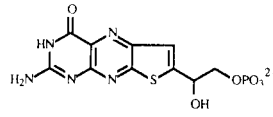


Urothione

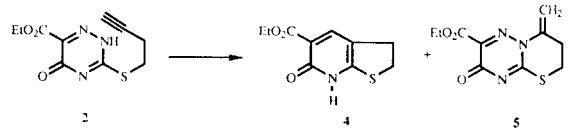


Molybdenum Cofactor Form B

A straightforward strategy for the preparation of this ring system would appear to involve the preparation of a suitably functionalized 3-(3-butynylthio)-1,2,4-triazine precursor which, after undergoing an intramolecular Diels-Alder reaction to give a 2,3-dihydrothieno[2,3-*b*]pyridine intermediate (such as **4**, Scheme 2), could be cyclized with guanidine to yield the final target ring system. We anticipated that the 6-carboethoxy-1,2,4-triazin-5(2*H*)-one (**2**) would serve this purpose. Ample precedent [1f,m,6] appeared to support the possibility of direct alkylation of the preformed 1,2,4-triazin-5(2*H*)-one-3(4*H*)-thione [3] with 4-iodo-1-butyne [4] (Scheme 1). However, all attempts toward this end met with failure. Alkylations of this type are normally carried out in aqueous sodium hydroxide, but under these conditions, hydrolysis of the ester functionality was the only observable reaction. Utilization of organic bases such as triethylamine apparently promoted ring alkylation [5]. Ultimately, it was discovered that condensation of *S*-(3-butynyl)thiosemicarbazide hydroiodide (**3**) [1f] with diethyl ketomalonate smoothly provided **2** in high yield (Scheme 1).

Heating **2** in refluxing nitrobenzene (bp 210°) produced the desired 2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one (**4**) in 59% yield. A consistent by-product obtained in 28% yield was the intramolecular coplanar cycloamination product **5**, formed by intramolecular nucleophilic attack on the internal acetylene carbon by the N-2 nitrogen of the 1,2,4-triazine ring (Scheme 2) [6].

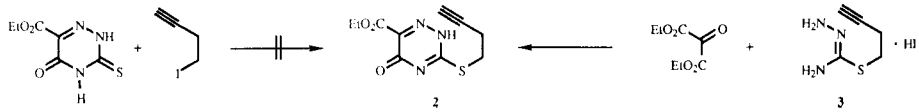
Scheme 2



2 4 5

The conversion of **4** to 5-carboethoxy-6-chloro-2,3-dihydrothieno[2,3-*b*]pyridine (**6**) (the projected intermediate for guanidine cyclization) was without success under a variety of chlorinating conditions (refluxing phosphorus oxychloride, refluxing phosphorus oxychloride in the pres-

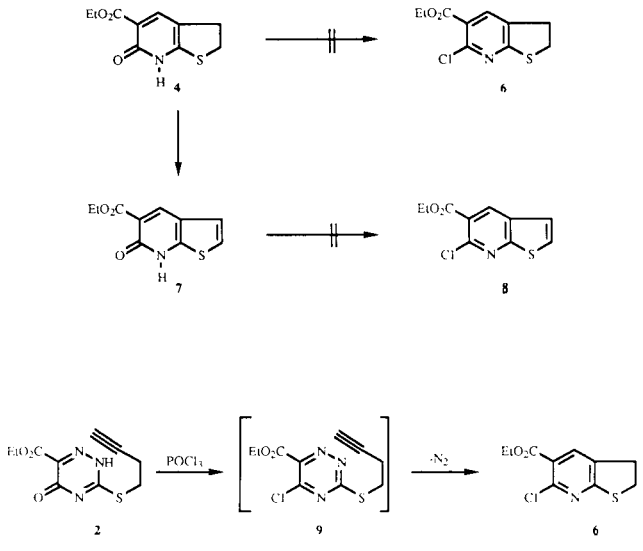
Scheme 1



2 3

ence of benzyltriethylammonium chloride and *N,N*-diethylaniline, and refluxing thionyl chloride). Alternatively, compound **4** was oxidized with 2,3-dichloro-5,6-dicyanoquinone (DDQ) to the fully aromatic thieno[2,3-*b*]-pyridin-6-one (**7**). As the case of compound **4**, however, this compound also resisted chlorination to its corresponding 6-chloro derivative (**8**) (Scheme 3).

Scheme 3

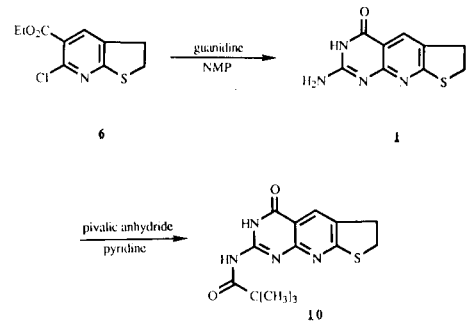


In order to circumvent these problems, we attempted to chlorinate the triazinone **2** *prior* to cycloaddition by heating with phosphorus oxychloride. To our surprise, **6** was directly obtained in 88% yield, presumably through initial chlorination of **2** followed by an intramolecular Diels-Alder reaction of the intermediate **9** (Scheme 3). Initial triazine chlorination would preclude the possibility of any competitive coplanar cycloamination leading to by-products such as **5**.

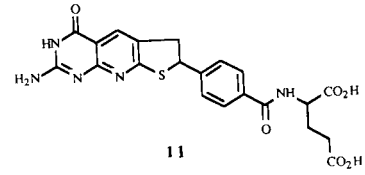
The fused chloropyridine **6** has proven to be exceptionally stable to nucleophilic displacement of the chloro substituent [7]. Attempted cyclization with guanidine in refluxing *t*-butyl alcohol (bp 82°) resulted merely in hydrolysis of the ester functionality while leaving the chloro substituent intact. In refluxing 1-octanol (bp 194°), guanidine cyclization was successful albeit in meager yield. When refluxing *N*-methyl-2-pyrrolidone (bp 210°) was utilized as solvent for the guanidine cyclization reaction, however, the desired 2-amino-6,7-dihydrothieno[3′,2′:5,6]pyrido-[2,3-*d*]-pyrimidin-4-one (**1**) was isolated in 42% yield.

Thorough characterization of **1** was not trivial as this compound is virtually insoluble in all organic solvents, a trait common to most pterins and deazapterins. However, treatment of compound **1** with pivalic anhydride in refluxing pyridine provided the 2-pivaloyl derivative **10** which, because of its ready solubility (even in methylene chloride), was readily characterized (Scheme 4) [8].

Scheme 4



We are currently investigating applications of the above reaction sequence to the synthesis of selected potential inhibitors (*e.g.*, **11**) of the folate family of enzyme cofactors.



EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The ^{1}H nmr data were obtained with a General Electric QE300 300 MHz instrument and chemical shifts are reported in ppm relative to residual nondeuterated solvent. Mass spectral data were obtained by Dr. Dorothy Little on a Kratos MS50TC spectrometer. Elemental analyses were performed by Eli Lilly and Co., Indianapolis, Indiana. Column chromatography was performed on Merck silica gel 60 (240-400) mesh; silica gel plates were routinely used for tlc determinations. Commercial reagents were utilized without further purification.

3-(3-Butynylthio)-6-carboethoxy-1,2,4-triazin-5(2*H*)-one (**2**).

A solution of *S*-(3-butynyl)thiosemicarbazide hydroiodide (**3**) (5.12 g, 19 mmoles), diethyl ketomalonate (3.3 g, 19 mmoles) and sodium bicarbonate (1.6 g, 19 mmoles) in 25 ml of ethanol was heated at reflux for 6 hours and stirred at room temperature overnight. The ethanol was evaporated under reduced pressure, and the residue was triturated with aqueous ethanol to give a yellow solid. Recrystallization from aqueous ethanol gave 4.20 g (88%) of a white solid, mp 131-132°; ^{1}H nmr (deuteriochloroform): δ 1.40 (t, J = 7.1 Hz, 3H), 2.07 (t, J = 2.5 Hz, 1H), 2.63 (dt, J_1 = 7.0 Hz, J_2 = 2.5 Hz, 2H), 3.34 (t, J = 7.0 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H).

Anal. Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.43; H, 4.38; N, 16.59; S, 12.66. Found: C, 47.51; H, 4.30; N, 16.48; S, 12.60.

Thermolysis of 3-(3-Butynylthio)-6-carboethoxy-1,2,4-triazin-5(2*H*)-one (**2**). Synthesis of 5-Carboethoxy-2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one (**4**) and 2-Carboethoxy-7,8-dihydro-8-methylene-3*H*,6*H*-1,3-thiazino-[3,2-*b*]-1,2,4-triazin-3-one (**5**).

A stirred suspension of 3-(3-butynylthio)-6-carboethoxy-1,2,4-triazin-5(2*H*)-one (**2**) (1.00 g, 3.95 mmoles) in nitrobenzene (16 ml) was heated at reflux for 1 hour. After this period, the reaction mixture was filtered through a pad of silica gel and washed with methylene chloride to remove nitrobenzene solvent. Subsequent elution with 1:1 hexanes/ethyl

acetate (750 ml) provided 0.52 g (59%) of 5-carboethoxy-2,3-dihydrothieno[2,3-*b*]pyridin-6(7*H*)-one (**4**) as tan crystals, R_f = 0.55 (1:1 ethyl acetate/methylene chloride), mp 105-107°; ^{1}H nmr (deuteriochloroform): δ 1.41 (t, J = 7.3 Hz, 3H), 3.27 (t, J = 7.6 Hz, 2H), 3.44 (t, J = 7.2 Hz, 2H), 4.40 (q, J = 7.3 Hz, 2H), 7.82 (d, J = 1.23 Hz, 1H); hrms, Calcd. for $C_{10}H_{11}NO_3S$: m/z 225.0460; Found: m/z 225.0458.

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22; S, 14.23; Found: C, 53.57; H, 4.94; N, 6.23; S, 14.21.

Further elution of the silica gel pad with 1:1 ethyl acetate/methylene chloride (300 ml) afforded 0.28 g (28%) of 2-carboethoxy-7,8-dihydro-8-methylene-3*H*,6*H*-1,3-thiazino[3,2-*b*]-1,2,4-triazin-3-one (**5**) as a white solid, R_f = 0.31, mp 173.5-174.5°; ^{1}H nmr (deuteriochloroform): δ 1.41 (t, J = 7.3 Hz, 3H), 3.06-3.11 (m, 2H), 3.21-3.16 (m, 2H), 4.47 (q, J = 7.1 Hz, 2H), 4.99 (d, J = 1.2 Hz, 1H), 5.71 (d, J = 1.2 Hz, 1H); hrms, Calcd. for $C_{10}H_{11}N_3O_3S$: m/z 253.0521; Found: m/z 253.0536.

Anal. Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.42; H, 4.38; N, 16.59; S, 12.66. Found; C, 47.64; H, 4.52; N, 16.41; S, 12.80.

5-Carboethoxy-6-chloro-2,3-dihydrothieno[2,3-*b*]pyridine (**6**).

A suspension of 3-(3-butynylthio)-6-carboethoxy-1,2,4-triazin-5(2*H*)-one (**2**) (3.04 g, 12.02 mmoles) in 80 ml of phosphorus oxychloride was heated at reflux under nitrogen for 10 hours. After this period, the reaction mixture was evaporated under reduced pressure, and the residual black gum was taken up in methylene chloride and filtered through a silcia gel pad, eluting with 1:1 hexanes/ethyl acetate. The filtrate was evaporated under reduced pressure to yield 2.58 g (88%) of a pale sienna oil; ^{1}H nmr (deuteriochloroform): δ 1.40 (t, J = 7.2 Hz, 3H), 3.36 (t, J = 7.7 Hz, 2H), 3.53 (t, J = 7.7 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 7.91 (s, 1H); hrms, Calcd. for $C_{10}H_{10}ClNO_2S$: m/z 243.0121; Found: m/z 243.0114.

Anal. Calcd. for $C_{10}H_{10}ClNO_2S$: C, 49.28; H, 4.14; N, 5.75; S, 13.16; Cl, 14.55. Found: C, 49.00; H, 4.13; N, 5.87; S, 13.02; Cl, 14.30.

5-Carboethoxythieno[2,3-*b*]pyridin-6(7*H*)-one (**7**).

A 25 ml flask charged with 5-carboethoxy-2,3-dihydrothieno[2,3-*b*]-pyridin-6(7*H*)-one (**4**) (0.32 g, 1.42 mmoles), 2,3-dichloro-5,6-dicyanoquinone (0.34 g, 1.49 mmoles), and *p*-dioxane (11 ml) was stirred under nitrogen for 3 hours. After this period, the reaction mixture was evaporated under reduced pressure, and the residual black gum was taken up in methylene chloride (10 ml) and filtered through a silica gel pad, eluting with 1:1 hexanes/ethyl acetate. The filtrate was evaporated under reduced pressure to afford 0.24 g (76%) of white needles, mp 128-129°; ^{1}H nmr (deuteriochloroform): δ 1.47 (t, J = 7.2 Hz, 3H), 4.50 (q, J = 7.2 Hz, 2H), 7.21 (d, J = 6.0 Hz, 1H), 7.34 (s, J = 6.0 Hz, 1H), 8.61 (s, 1H), 11.57 (bs, 1H); hrms, Calcd. for $C_{10}H_9NO_3S$: m/z 233.0303; Found: m/z 223.0304.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27; S, 14.36. Found: C, 53.60; H, 4.21; N, 6.01; S, 14.36.

2-Amino-6,7-dihydrothieno[3',2':5,6]pyrido[2,3-*d*]pyrimidin-4-one (**1**).

To a stirred solution of guanidine hydrochloride (1.96 g, 20.53 mmoles) in *N*-methyl-2-pyrrolidone (20 ml) was added sodium methoxide (1.16 g, 21.47 mmoles) at once, and the resulting suspension was stirred under nitrogen for 10 minutes. After this period, a solution of 5-carboethoxy-6-chloro-2,3-dihydrothieno[2,3-*b*]pyridine (**6**) (2.50 g, 10.27 mmole) in *N*-methylpyrrolidone (15 ml) was added to the reaction mixture, which was subsequently heated at reflux under nitrogen for 3 hours. After this period, the reaction mixture was cooled (ice bath) and then poured into vigorously stirred chilled water (60 ml) acidified with 2 drops of concentrated hydrochloric acid. Vacuum filtration (washing liberally with water) afforded 0.95 g (42%) of 2-amino-6,7-dihydrothieno[3',2':5,6]pyrido-[2,3-*d*]pyrimidin-4-one (**1**) as a pale yellow powder, mp >300°; ^{1}H nmr (dimethylsulfoxide-d_6 with trifluoroacetic acid-d): δ 3.32 (t, J = 7.9 Hz, 2H), 3.49 (t, J = 7.8 Hz, 2H), 7.98 (s, 1H); hrms, Calcd. for $C_9H_8N_4OS$: m/z 220.0419; Found: m/z 220.0418.

2-Pivaloylamino-6,7-dihydrothieno[3',2':5,6]pyrido[2,3-*d*]pyrimidin-4-one (**10**).

A stirred suspension of 2-amino-6,7-dihydrothieno[3',2':5,6]pyrido-[2,3-*d*]pyrimidin-4-one (**1**) (0.30 g, 1.4 mmoles), pivalic anhydride (0.6 g, 3.2 mmoles) and pyridine (1.5 g, 19 mmoles) was heated in an oil bath at 150° for 5 hours. The cooled mixture was diluted with aqueous methanol and the solid collected *via* vacuum filtration. Recrystallization from methanol gave 0.25 g (60%) of a white solid, mp 266-267°; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 9H), 3.42 (t, J = 6.3, 2H), 3.48 (t, J = 6.3, 2H), 8.08 (s, 1H); hrms, Calcd. for $C_{14}H_{16}N_4O_2S$: m/z 304.0994; Found: m/z 304.0996.

Anal. Calcd. for $C_{14}H_{16}N_4O_2S$: C, 55.25; H, 5.30; N, 18.41; S, 10.53. Found: C, 54.96; H, 5.24; N, 18.05; S, 10.29.

REFERENCES AND NOTES

[1] For references to intramolecular Diels-Alder reactions of monocyclic 1,2,4-triazines, see the following: Dienophilic substituent tethered to positions 3 or 6 (nitrogen extrusion): [a] E. C. Taylor and J. E. Macor, *Tetrahedron Letters*, **26**, 2419 (1985); [b] E. C. Taylor and J. E. Macor, *Tetrahedron Letters*, **27**, 431 (1986); [c] E. C. Taylor and L. G. French, *Tetrahedron Letters*, **27**, 1967 (1986); [d] E. C. Taylor and J. E. Macor, *Tetrahedron Letters*, **27**, 2107 (1986); [e] E. C. Taylor and J. L. Pont, *Tetrahedron Letters*, **28**, 379 (1987); [f] E. C. Taylor and J. E. Macor, *J. Org. Chem.*, **52**, 4280 (1987); [g] E. C. Taylor, J. E. Macor and J. L. Pont, *Tetrahedron*, **43**, 5145 (1987); [h] E. C. Taylor, J. L. Pont and J. C. Warner, *Tetrahedron*, **43**, 5159 (1987); [i] G. Seitz and S. Dietrich, *Arch. Pharm.*, **317**, 379 (1984); [j] G. Seitz, L. Gorge and S. Dietrich, *Tetrahedron Letters*, **26**, 4355 (1985); [k] G. Seitz and S. Dietrich, *Arch. Pharm.*, **318**, 1048 and 1051 (1985); [l] G. Seitz, S. Dietrich, L. Gorge and J. Richter, *Tetrahedron Letters*, **27**, 2747 (1986). E. C. Taylor and L. G. French, *J. Org. Chem.*, in press. Dienophilic substituent tethered to position 5 (nitrile extrusion): [m] E. C. Taylor and J. L. Pont, *J. Org. Chem.*, **52**, 4287 (1987).

[2a] E. C. Taylor and L. A. Reiter, *J. Org. Chem.*, **47**, 528 (1982); [b] E. C. Taylor and L. A. Reiter, *J. Am. Chem. Soc.*, in press.

[3] R. B. Barlow and A. D. Welch, *J. Am. Chem. Soc.*, **78**, 1258 (1956).

[4] G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

[5a] J. Lee and W. W. Paudler, *J. Heterocyclic Chem.*, **9**, 995 (1972); [b] J. Daunis, *Bull. Soc. Chim. France*, 2126 (1973).

[6] This finding is not unprecedented; see [a] T. Sasaki and I. Shimizu, *Heterocycles*, **22**, 1225 (1984), and [b] E. Rougeot, H. Moskowitz and M. Miocque, *J. Heterocylic Chem.*, **20**, 1407 (1983). We have thoroughly explored the effects of solvent and temperature on this competitive process which we have described in the following paper: [c] E. C. Taylor, J. L. Pont and J. C. Warner, *J. Org. Chem.*, in press.

[7] T. V. Sycheva, O. S. Anisimova and L. N. Yakhontov, *Khim. Geterosikl. Soedin.*, 91 (1986).

[8] This pivaloylation technique for the solubilization of pterins and related fused 2-aminopyrimidin-4-ones has been described previously: E. C. Taylor, K. F. McDaniel and J. C. Warner, *Tetrahedron Letters*, **28**, 1977 (1987); E. C. Taylor and P. S. Ray, *J. Org. Chem.*, **52**, 3997 (1987).