Heterocyclic Syntheses from *o*-Aminonitriles. XXIX. A New Synthesis of 5-Substituted Pyrimidines[1,2]

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Reaction of 2-amino-3-cyanothiophenes with ethyl orthoformate followed by treatment of the resulting ethoxymethylenamino intermediates with ammonia yields 2-formamidino-3-cyanothiophenes, which are cyclized with sodium methoxide to thieno[2,3-*d*]pyrimidines. Desulfurization of these compounds with W-7 Raney nickel affords 5-substituted pyrimidines.

4-Amino-5-arylpyrimidines have been prepared from arylacetonitriles either by treatment with formamide at elevated temperatures[3a,b] or with trisformylaminomethane in formamide.[3c] The reaction fails with nitriles in which the α-methylene grouping is insufficiently activated, *e.g.*, alkyl nitriles. We wish to describe in this paper an alternate and potentially versatile route to 4-amino-5-substituted pyrimidines which allows the preparation of both 5-alkyl and 5-aryl derivatives. This new procedure, based upon the known propensity of substituted thiophenes to undergo reductive desulfurization,[4] involves the preparation of a number of thieno[2,3-*d*]pyrimidines from 2-amino-3-cyanothiophenes and their subsequent desulfurization to give the desired 5-substituted pyrimidine.[5]

The synthesis of 2-amino-3-cyanothiophenes may be readily achieved by condensation of an α-mercaptoaldehyde or ketone with malononitrile[6a-c] or by reaction of an aldehyde or ketone with malononitrile and elemental sulfur,[6d] both in the presence of amine catalysts. Thus, the reaction of cyclohexanone with malononitrile and sulfur, using morpholine as catalyst, gave 2-amino-3-cyano-4,5,6,7-tetrahydrothianaphthene (**1a**);[6d] treatment of this compound with excess ethyl orthoformate at reflux for 5 hr gave the intermediate 2-ethoxymethylenamino derivative which, without isolation, was treated with ethanolic ammonia. The resulting 2-formamidino compound, upon treatment with sodium methoxide in methanol, underwent intramolecular cyclization to give the desired condensed thienopyrimidine (**3a**).[7]

Desulfurization of **3a** was effected by heating at reflux in ethanolic solution with a fourfold excess of freshly prepared W-7 Raney nickel. Examination of the desulfurization product by nmr showed it to be a mixture of 4-amino-5-(1-cyclohexenyl)pyrimidine (**4a**) and the corresponding 5-cyclohexyl compound (**4b**). Thus, the spectrum of the mixture showed a vinylic multiplet centered at τ 4.12 and a methyl proton attributable to **4b** at τ 7.25. Integration of the areas under these peaks indicated that some 20–25% of **4b** was present, although in one run almost none was formed and the product proved to be almost pure **4a**. Surprisingly, attempts to reduce mixtures of **4a** and **4b** to give pure **4b**, using W-2 Raney nickel at pressures up to 400 psi, proved fruitless. Desulfurization of the 7-methoxy analog (**3b**) of **3a** yielded 4-amino-5-(4-methoxy-1-cyclohexyl)pyrimidine; its nmr spectrum showed vinylic absorption at τ 4.25 and no detectable methinyl absorption.

Condensation of mercaptoacetone[8] with malononitrile afforded 2-amino-3-cyano-4-methylthiophene (**1c**), which was smoothly converted to **3c**. Subsequent desulfurization over W-7 Raney nickel gave a mixture of **4d** (65%) and **4e** (35%). The isopropyl group of **4d** showed (nmr) a methyl peak (doublet) at τ 8.72 and a single proton methine signal (heptet) at τ 7.21 (J = 6.0 cps). Contributions to the spectrum from **4e** were observed at τ 7.91 (J = 1.0 cps) assigned to the vinylic methyl group and at τ 4.62 (J = 1.0 cps, *trans*-H) and τ 4.80 (J = 0 cps, *cis*-H). In contrast to the case mentioned above, this mixture of **4d** and, **4e** could readily be hydrogenated to homogeneous **4d** over W-2 Raney nickel at 50 psi of hydrogen.

Condensation of β-tetralone with malononitrile and sulfur in the presence of morpholine gave a fair yield of a pale yellow crystalline solid. Although this reaction could have led either to the angular (**1d**) or the linear product (**1d'**), its nmr spectrum showed a symmetrical A_2B_2 multiplet centered at τ 7.13 compatible only with **1d**. Conversion of **1d** into **3d** proceeded smoothly, but initial attempts to aromatize **3d** with sulfur or with chloranil failed. Aromatization was achieved, however, by the following method. Initial acetylation of **3d** with a mixture of acetic anhydride and pyridine gave the diacetyl derivative **5** which was converted with N-bromosuccinimide into a bromination product (**6**), very likely a mixture of isomers. Treatment of **6** without isolation with alcoholic potassium hydroxide effected simultaneous dehydrobromination and deacetylation to give **3e**[9] (Scheme I). Finally, desulfurization of **3e** gave 4-amino-5-(2-naphthyl)pyrimidine (**4f**) identical with the product obtained by treatment of 2-naphthylacetonitrile with formamide at 180°.[3a]

Reaction of tetracyanoethylene with hydrogen sulfide is known to give 2,5-diamino-3,4-dicyanothiophene[10]

(1) For part XXVIII, see E. C. Taylor, A. McKillop, Y. Shvo, and G. H. Hawks, *Tetrahedron*, **23**, 2081 (1967).

(2) This work was supported by Grant No. CA-02551 to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(3) (a) W. H. Davies and H. A. Piggott, *J. Chem. Soc.*, 347 (1945); (b) W. H. Davies, A. W. Johnson, and H. A. Piggott, *ibid.*, 352 (1945); (c) G. Tsatsaronis and F. Effenberger, *Chem. Ber.*, **94**, 2876 (1961).

(4) G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 356 (1962).

(5) For a preliminary report of this work, see E. C. Taylor and J. G. Berger, *Angew. Chem.*, **78**, 144 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 131 (1966).

(6) (a) K. Gewald, *Angew. Chem.*, **73**, 114 (1961); (b) *Z. Chem.*, **2**, 305 (1962); (c) *Chem. Ber.*, **98**, 3571 (1965); (d) K. Gewald, E. Schinke, and H. Bottcher, *ibid.*, **99**, 94 (1966).

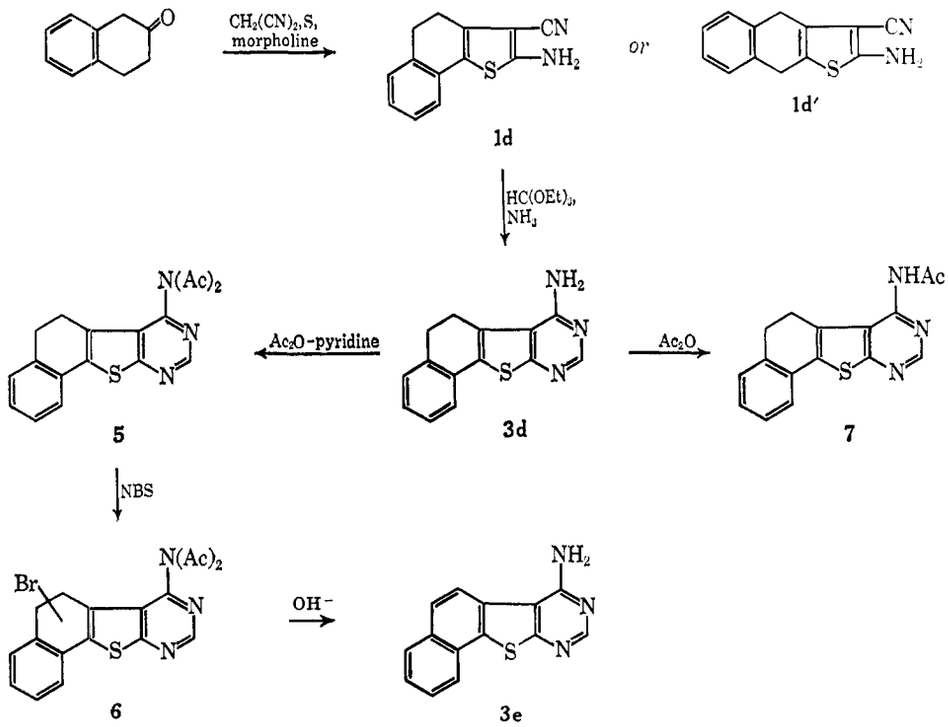
(7) For a discussion of this route to fused 4-aminopyrimidines from *o*-aminonitriles, see E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **87**, 1995 (1965), and previous papers in this series.

(8) O. Hromatka and E. Engel, *Monatsh.*, **78**, 32 (1948).

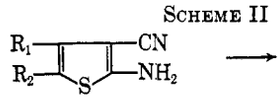
(9) Treatment of **3d** with acetic anhydride alone gave a monoacetyl derivative (**7**). The striking similarity of the ultraviolet spectra of **7** and **5** indicates that the latter probably possesses the structure assigned rather than one involving acetylation on either the N_1 or N_3 ring nitrogens.

(10) W. J. Middleton, V. A. Engelhart, and B. S. Fisher, *J. Am. Chem. Soc.*, **80**, 2822 (1958).

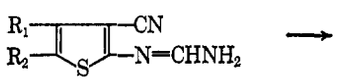
SCHEME I



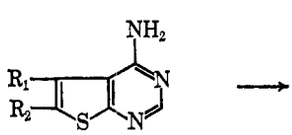
SCHEME II



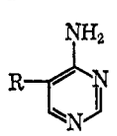
1a, $R_1, R_2 = -(CH_2)_4-$
b, R_1, R_2 = 6-methoxytetrahydrobenzo-
c, $R_1 = CH_3$; $R_2 = H$
d, R_1, R_2 = 3,4-dihydronaphtho[1,2]-
e, $R_1 = CN$; $R_2 = NH_2$



2



3a, $R_1, R_2 = -(CH_2)_4-$
b, R_1, R_2 = 7-methoxytetrahydrobenzo-
c, $R_1 = CH_3$; $R_2 = H$
d, R_1, R_2 = 3,4-dihydronaphtho[1,2]-
e, R_1, R_2 = naphtho[1,2]-
f, R_1, R_2 = 4-aminopyrimido[4,5]-



4a, R = cyclohexenyl[11]
b, R = cyclohexyl
c, R = 4-methoxy-1-cyclohexenyl
d, R = isopropyl
e, R = isopropenyl
f, R = 2-naphthyl
g, R = 4-amino-5-pyrimidinyl

(11) It has recently come to our attention that the desulfurization of **3a** with W-2 Raney nickel to give **4a** has be encarried out independently (A. M. Chacko, Ph.D. Thesis, University of North Carolina, Chapel Hill, N. C., 1965).

(**1e**), which possesses two symmetrically placed *o*-aminonitrile groupings. Both reacted normally when **1e** was heated with ethyl orthoformate followed by treatment with alcoholic ammonia. The bisformamidino derivative (**2e**) thus formed was cyclized by sodium methoxide in dimethylformamide to 4,5-diaminodipyrimido[4,5-*b*][4′,5′-*d*]thiophene (**3f**). Desulfurization then gave 4-amino-5-(4-amino-5-pyrimidinyl)-pyrimidine (**4g**). (See Scheme II.)

Experimental Section[12]

2-Amino-3-cyano-4-methylthiophene (**1c**) was prepared from mercaptoacetone and malononitrile with piperidine as catalyst according to the procedure of Gewald.[6a,c] **2-Amino-3-cyano-6-methoxy-4,5,6,7-tetrahydrothianaphthene** (**1b**) was prepared in 45% yield from 4-methoxycyclohexanone,[13] malononitrile, and sulfur (morpholine catalyst) by the procedure of Gewald,[6b,d] mp 120–120.5°.

Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.68; H, 5.81; N, 13.46; S, 15.21. Found: C, 57.45; H, 5.68; N, 13.16; S, 14.94.

2-Amino-3-cyano-4,5-dihydrobenzo[*g*]thianaphthene (**1d**).—Morpholine (5 ml) was added to a mixture of β-tetralone (22.5 g), malononitrile (10.5 g), and S (7.2 g) in 75 ml of absolute ethanol. Warming resulted within 1–2 min. After 5–10 min, the mixture was heated to reflux for 5 min and another 75 ml of ethanol was added. The hot solution was filtered, the filtrate cooled, and the yellow crystals dissolved in acetone and filtered to remove some residual sulfur. Evaporation of the extracts gave 11.9 g (34%) of a pale yellow solid, mp 193–196°. The analytical sample was recrystallized from ethanol (charcoal) as long white needles: mp 195–197°; infrared spectrum, 3405, 3310, 3205, and 2210 cm^{-1}; nmr, τ 7.13 (A_2B_2 multiplet, 4 H), 5.10 (broad singlet, 2 H); 2.86 (multiplet, 4 H).

Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.01; H, 4.46; N, 12.38; S, 14.14. Found: C, 69.02; H, 4.44; N, 12.38; S, 14.14.

(12) Melting points are uncorrected. The nmr spectra were taken in $DCCl_3$ (TMS as internal standard) on a Varian A-60A spectrometer. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer. Infrared spectra were determined by the Nujol mull technique on a Perkin-Elmer Model 237B Grating Infracord. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

(13) D. S. Noyce and B. N. Bastian, *J. Am. Chem. Soc.*, **82**, 1248 (1960).

4-Amino-5,6,7,8-tetrahydropyrimido[4,5-*b*]thianaphthene (3a).—The following procedure is illustrative of the preparation of the condensed thienopyrimidines. 2-Amino-3-cyano-4,5,6,7-tetrahydrothianaphthene[6d] (20 g) was heated under reflux with 250 ml of ethyl orthoformate for 5 hr. Excess ethyl orthoformate was removed *in vacuo* and the residue, which in this case solidified, was treated with 300 ml of ethanol saturated with ammonia at 0°. The solid dissolved to give a yellow-orange solution and within 5 min the bright yellow *o*-formamidinonitrile separated. The mixture was stirred overnight, the ethanol removed *in vacuo*, and the residue dissolved in 300 ml of DMF. Sodium methoxide (7.0 g) was added and the stirred solution was heated to 80–120° for 1 hr. The solution was concentrated under reduced pressure, the residue treated with warm water, and the product filtered. It was washed with cold ethanol, which removed tarry material, and the crude light brown product (20 g) was sublimed at 190–200° (0.005 mm) to give 17.7 g (77%) of pale yellow crystals, mp 271.5–273.5°.

Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.50; H, 5.40; N, 20.47; S, 15.62. Found: C, 58.10; H, 5.47; N, 20.47; S, 15.44.

4-Amino-7-methoxy-5,6,7,8-tetrahydropyrimido[4,5-*b*]thianaphthene (3b).—White plates from ethanol, mp 174.5–175°, were obtained in 68% yield.

Anal. Calcd for $C_{11}H_{13}N_3OS$: C, 56.16; H, 5.57; N, 17.86; S, 13.60. Found: C, 56.02; H, 5.57; N, 17.72; S, 13.25.

4-Amino-5-methylthieno[2,3-*d*]pyrimidine (3c).—Yellow needles from ethanol, mp 241–243°, were obtained in 82% yield.

Anal. Calcd for $C_7H_7N_3S$: C, 50.89; H, 4.27; N, 25.44; S, 19.41. Found: C, 50.65; H, 4.32; N, 25.91; S, 18.65.

4-Amino-5,6-dihydropyrimido[4,5-*b*]benzo[*g*]thianaphthene (3d).—White microcrystals from xylene, mp 257–258.5°, were obtained in 74% yield: λ_{max}^{EtOH} mμ (log ε) 224 (4.45), 249 (4.13), 258 (3.92), 318 (4.21), 332 (4.38), 347 (4.31).

Anal. Calcd for $C_{14}H_{11}N_3S$: C, 66.39; H, 4.38; N, 16.59; S, 12.64. Found: C, 66.24; H, 4.27; N, 16.66; S, 12.56.

4-Acetamido-5,6-dihydropyrimido[4,5-*b*]benzo[*g*]thianaphthene (7).—The above material (0.55 g) was heated to boiling with 12 ml of Ac_2O to give a yellow solution. Within 1 min, long needles began to form. After cooling in ice, the product was filtered off and recrystallized from benzene–pentane to give 0.40 g (62%): mp 238–239°; λ_{max}^{EtOH} mμ (log ε) 237.5 (4.40), 265 (4.25), 277 (4.31), 330.5 (4.32), 343.5 (4.24).

Anal. Calcd for $C_{16}H_{13}N_3OS$: C, 65.08; H, 4.44; N, 14.32; S, 10.83. Found: C, 65.22; H, 4.61; N, 13.96; S, 10.66.

4-Diacetylamino-5,6-dihydropyrimido[4,5-*b*]benzo[*g*]thianaphthene (5).—A solution of 8.1 g of **3d** in 50 ml of pyridine and 25 ml of Ac_2O was heated under reflux for 45 min. Excess reagents were removed *in vacuo* and the residue was recrystallized from 20 ml of xylene to give 9.6 g (89%) of pale yellow needles of **5**: mp 198.5–200°; λ_{max}^{EtOH} mμ (log ε) 237 (4.16), 268 (4.23), 275 (4.32), 334 (4.22), 344 (4.19).

Anal. Calcd for $C_{18}H_{15}N_3O_2S$: C, 64.09; H, 4.48; N, 12.46; S, 9.48. Found: C, 63.74; H, 4.48; N, 12.79; S, 9.15.

4-Aminopyrimido[4,5-*b*]benzo[*g*]thianaphthene (3e).—The diacetyl derivative **5** (8.1 g) and N-bromosuccinimide (5.1 g) were dissolved in 250 ml of CCl_4 and *ca.* 10 mg of benzoyl peroxide was added. Upon heating to reflux, the mixture turned orange and a vigorous reaction ensued. Within 3–5 min, the color discharged, an orange solid deposited from solution, and the reaction subsided. Reflux was continued for 1.5 hr, solvent was removed *in vacuo*, and the yellow powdery residue was heated at reflux with 10 g of KOH in 200 ml of ethanol. Within 15 min, a voluminous crop of needles began to deposit from solution and more ethanol was added to maintain fluidity. After 3 hr at reflux, the mixture was concentrated to dryness and diluted with water. The solid was collected by filtration and washed with water followed by cold ethanol: yield 5.9 g (98%), mp 308–309° (recrystallization from ethanol raised the melting point to 312–313°); λ_{max}^{EtOH} mμ (log ε) 220 (4.57), 249 (sh), 256 (4.58), 272 (4.45), 280.5 (4.52), 311 (4.13), 317 (4.17), 323 (4.15), 330 (4.10), 345 (3.64).

Anal. Calcd for $C_{14}H_9N_3S$: C, 66.92; H, 3.61; N, 16.73; S, 12.74. Found: C, 66.62; H, 3.95; N, 16.44; S, 12.41.

4,5-Diaminodipyrimido[4,5-*b*][4′,5′-*d*]thiophene (3f).—Yellow needles from aqueous DMF, mp 324–325° dec, were obtained in 30% yield.

Anal. Calcd for $C_8H_6N_6S$; C, 44.04; H, 2.77; N, 38.52; S, 14.67. Found: C, 43.70; H, 2.92; N, 38.12; S, 14.35.

Desulfurization of Thienopyrimidines.—The general procedure is illustrated by the preparation of 4-amino-5-isopropylpyrimidine (**4d**). A solution of this compound (3.0 g) in *ca.* 200 ml of ethanol was heated at reflux, with vigorous stirring, for 16 hr with 12.5 g of freshly prepared W-7 Raney nickel (from 25 g of alloy). The hot mixture was filtered and the nickel washed with hot ethanol. The combined filtrates were evaporated to dryness. Sublimation of the residue gave 1.25 g of product which was shown by nmr to be a mixture of **4d** (65%) and **4e** (35%) (see discussion). Hydrogenation over W-2 Raney nickel in ethanol at 50 psi of hydrogen gave pure **4d**, white needles from benzene: mp 140–141.5°; λ_{max}^{EtOH} mμ (log ε) 236 (4.05), 274 (3.70).

Anal. Calcd for $C_7H_{11}N_3$: C, 61.27; H, 8.08; N, 30.63. Found: C, 61.45; H, 2.06; N, 30.91.

4-Amino-5-(1-cyclohexenyl)pyrimidine (4a).—Desulfurization of **3a** in ethanol using a sixfold excess of W-7 Raney nickel gave 30–40% of a mixture of **4a** (~80%) and **4b** (~20%): **4a**, mp 156–158.5° (lit.[11] mp 163.5°); λ_{max}^{EtOH} mμ (log ε) 240 (3.93), 278 (3.66).

Anal. Calcd for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.15; H, 7.48; N, 23.67.

4-Amino-5-(4-methoxy-1-cyclohexenyl)pyrimidine (4c).—Desulfurization of **3b** in ethanol using a fourfold excess of W-7 Raney nickel gave a poor yield of **4c**, white needles from benzene: mp 146–147°; λ_{max}^{EtOH} mμ (log ε) 240.5 (3.94), 280 (3.69).

Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.36; H, 7.37; N, 20.47. Found: C, 64.25; H, 7.39; N, 20.17.

4-Amino-5-(2-naphthyl)pyrimidine (4f).—Desulfurization of **3e** in DMF at 85–90° for 2.5 days with a twelvefold excess of W-7 Raney nickel gave **4f**: mp 180.5–182.5° (yield 15%); λ_{max}^{EtOH} mμ (log ε) 223 (4.85), 250 (4.23), 280 (4.12).

Anal. Calcd for $C_{14}H_{14}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 75.85; H, 5.12; N, 19.14.

This product was identical (melting point, mixture melting point, infrared spectrum) with an authentic sample prepared by treatment of 2-naphthylacetonitrile with formamide at 180° under a stream of ammonia.[3a]

4-Amino-5-(4-amino-5-pyrimidinyl)pyrimidine (4g).—Desulfurization of **3f** in DMF at 100° for 19 hr using a sixfold excess of W-7 Raney nickel gave **4g**: mp 356° dec (yield 17%); λ_{max}^{EtOH} mμ (log ε) 232 (4.15), 284 (3.80).

Anal. Calcd for $C_8H_8N_6$: C, 51.05; H, 4.28; N, 44.66. Found: C, 51.28; H, 4.49; N, 43.80.

Registry No.—**1b**, 13145-85-2; **1d**, 13145-86-3; **3a**, 4994-88-1; **3b**, 13145-88-5; **3c**, 13145-89-6; **3d**, 13131-89-0; **3e**, 13145-90-9; **3f**, 13145-91-0; **4a**, 13145-92-1; **4c**, 13145-93-2; **4d**, 5000-30-6; **4f**, 5000-31-7; **4g**, 5000-32-8; **5**, 13145-97-6; **7**, 13145-98-7.