Heteroatom Chemistry
Volume 12, Number 3, 2001

The Reaction of 2-Amino-3-cyano-4,5,6,7-Tetrahydrobenzo[*b*]-thiophene with Diethyl Malonate: Synthesis of Coumarin, Pyridine, and Thiazole Derivatives

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Received 22 November 2000; revised 29 December 2000

ABSTRACT: *The reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene (***1***) with diethyl malonate (***2***) gave two products:* **3** *and* **4**. *The reactivity of* **3** *toward a variety of chemical reagents was studied to give azoles, azines, and their fused derivatives.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:168–175, 2001

INTRODUCTION

Over recent years we have been involved in a comprehensive program aimed at investigating the reactions of 4,5,6,7-tetrahydrobenzo[*b*]thiophene derivatives with a variety of chemical reagents with subsequent heterocyclization of the products to form pyridines, pyrimidines, and pyridazines [1–3]. The importance of such compounds is due to their diverse pharmaceutical activities including antibacterial [4], antidiabetic [5], anti-inflammatory [6], and antiviral [7,8], and as antiplatelet activating factors [9].

RESULTS AND DISCUSSION

In this article, we report the reaction of 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene **1** with diethyl malonate **2** to form 2-amidothiophene derivatives capable of heterocyclization when reacted with a variety of chemical reagents. Thus, the reaction of **1** with **2** in an oil bath at 140°C gave two products, each with the molecular formula $C_{14}H_{16}N_2SO_3$. Their separation was based on the greater solubility of one of the products over the other in ethanol. The ethanol soluble product was identified to be compound **3**, based on analytical and spectral data. Thus, the IR spectrum showed the CN group stretching at 2225 cm^{-1}, together with two very strong C=O stretching signals at 1745 and 1695 cm^{-1}. Moreover, the ^{13}C NMR data showed the presence of δ 28.4 (ester CH_3), 29.7, 30.6 (cyclohexene C-1, C-4), 24.1, 24.7 (cyclohexene C-2, C-3), 52.9 (ester CH_2), 58.6 (CH_2), 119.9 (CN), 126.6, 132.1, 132.7, 138.0 (thiophene-C), 178.9 and 181.0 (2 C=O). The ethanol insoluble product (low yield) was identified to be the tetrahydrobenzo[*b*]thieno[5,4:2,3]pyridine derivative **4**. The IR spectrum of the latter compound showed no CN stretching. Moreover, the ^1H NMR spectrum showed, in addition to the characteristic signals of the tetrahydrobenzene ring, a triplet at δ 1.33 for the CH_3 group, a quartet at δ 4.28 for the ester CH_2 group, and a singlet (D_2O exchangeable) at δ 5.23 corresponding to the NH_2 group. Moreover, the ^{13}C NMR data showed δ 27.8 (ester CH_3), 29.5, 30.2 (cyclohexene C-1, C-4), 23.8, 24.9 (cyclohexene C-2, C-3), 53.2 (ester CH_2), 120.7 (CN), 126.4, 132.0, 132.2, 134.2, 134.9, 138.7, 138.9, 140.2 (thiophene-

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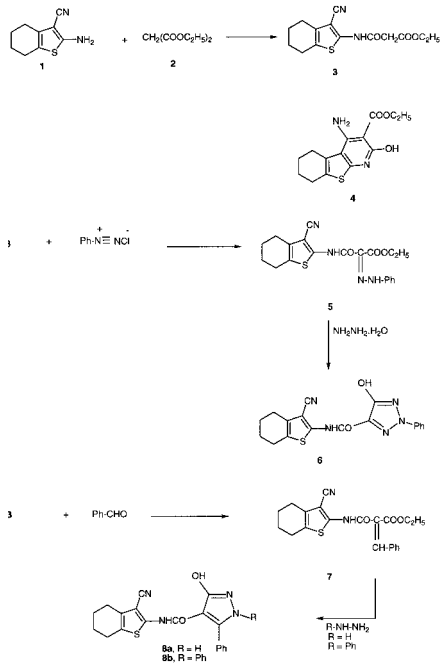
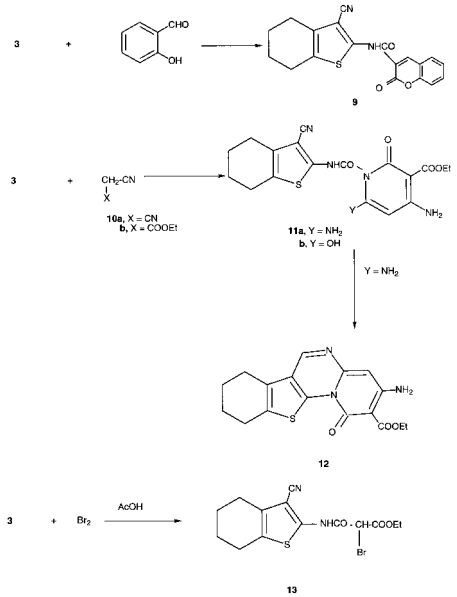
C, pyridine-C), and 181.7 (C=O). Compound **3** showed interesting reactivity toward a variety of chemical reagents. Thus, it reacted with benzenediazonium chloride at 0°C to give the corresponding hydrazone derivative **5**. The latter reacted with hydrazine hydrate to give the 5-hydroxy-1,2,3-triazole derivative **6**. The structure of compound **6** was based on analytical and spectral data (see Experimental section). The reaction of compound **3** with benzaldehyde gave the benzal derivative **7**. The latter reacted with hydrazine hydrate and phenylhydrazine to give the 3-hydroxypyrazole derivatives **8a** and **8b**, respectively, (Scheme 1). The reaction of **3** with salicylaldehyde gave the coumarin derivative **9**, the formation of which took place through first a condensation followed by ethanol elimination (Scheme 2).

The reactivity of compound **3** toward cyanomethylene reagents was studied. Thus, with either malononitrile (**10a**) or ethyl cyanoacetate (**10b**), the corresponding 2-pyridinyl-4,5,6,7-tetrahydrobenzo [*b*]thiophene derivatives **11a** and **11b**, respectively, were formed. Compound **11a** underwent ready cyclization when heated in a boiling water bath with sodium ethoxide solution to give the annulated compound, which was identified as the tetrahydrobenzo[*b*]thieno[2,3:4,5]pyrimidino[3,2:1,2]pyridine derivative **12**. The structure of compound **12** was identified on the basis of the disappearance of CN group stretching in the IR spectrum, and the ^{13}C NMR data showed δ 26.3 (ester CH_3), 29.3, 30.7 (cyclohexane C-1, C-4), 22.7, 25.4 (cyclohexane C-2, C-3), 55.2 (ester CH_2), 125.2, 131.5, 132.8, 133.1, 133.6, 136.2, 138.9, 140.5, 143.2, 143.7 (thiophene-C, pyrimidine-C, pyridine-C), 179.6, and 180.4 (2 C=O) (Scheme 2).

Compound **3** reacted with bromine in hot acetic acid solution to give the monobromo derivative **13** (Scheme 2). The latter reacted with potassium cyanide in ethanol solution to give the tetrahydrobenzo[*b*]thieno[2,3-*b*]pyridine derivative **15**. Compound **15** was formed through the intermediate formation of **14** followed by cyclization. The IR spectrum of **15** showed only one CN group stretching at υ^- 2225 cm^{-1} and two C=O group stretchings at υ^- 1715 and υ^- 1683 cm^{-1}. The reaction of compound **13** with thiourea gave the 2-aminothiazole derivative **16**, the structure of which was established on the basis of analytical and physical data (see Experimental section. Compound **16** underwent ready cyclization when heated in ethanolic sodium hydroxide solution to give the tetrahydrobezo[*b*] thieno[5,4:2,3]pyridino[6,5;4,5]-thiazolidene derivative **18**. Formation of the latter product took place through the intermediate formation of **17** followed by ester hydrolysis and decarboxylation. ^{13}C NMR data confirm its structure; thus, δ 26.9 (ester CH_3), 29.2, 30.9 (cyclohexene C-1, C-4), 24.2, 24.5 (cyclohexene C-2, C-3), 52.9 (ester CH_2), 119.2 (CN), 124.5, 130.7, 131.9, 134.9, 140.2, 142.8 (thiophene-C, pyridine-C), 179.8, 180.7 (2 C=O) (Scheme 3).



SCHEME 1



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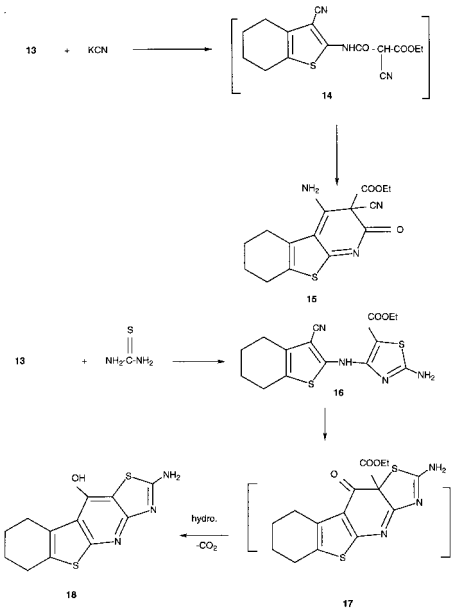
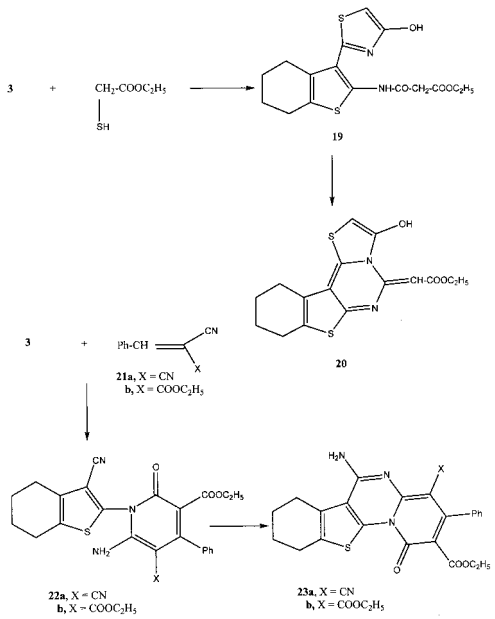


SCHEME 3



SCHEME 4

Compound **3** reacted with thioglycolic acid to give the thiazole derivative **19**. The latter product underwent ready cyclization when heated in dimethylformamide solution containing a catalytic amount of triethylamine to give the tetrahydrobenzo[*b*]thieno[5,4:4,5]pyrimidino[6,1:2,3]thiazole derivative **20**. Moreover, the reaction of compound **3** with cinnamonitrile derivatives was studied. Thus, the reaction of **3** with either *α*-cyanocinnamonitrile (**21a**) or *α*-ethoxycarbonyl cinnamonitrile (**21b**) gave the 2-pyridino-4,5,6,7-tetrahydrobenzo[*b*]thiophene derivatives **22a** and **22b**, respectively. The latter products underwent ready cyclization when heated in sodium ethoxide solution to give the tetrahydrobenzo[*b*]thieno[5,4:4,5]pyrimidino[3,2:1,2pyridine derivatives **23a** and **23b**, respectively. The structures of compounds **22a,b** and **23a,b** were based on analytical and spectral data (see Experimental section) (Scheme 4).

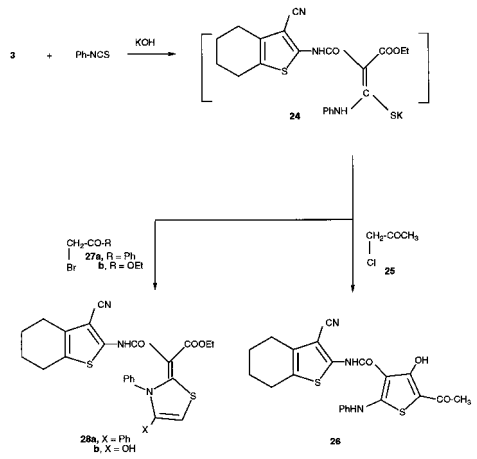
Our research group has studied the reaction of active methylene reagents with phenyl isothiocyanate in basic dimethylformamide/KOH solution, followed by heterocyclization with *α*-halocarbonyl compounds to give either thiophene or thiazole derivatives [10–13]. The nature of the products depends on the *α*-halocarbonyl compound used. In a similar way, the reaction of compound **3** with phenyl isothiocyanate in basic dimethylformamide solution gave the intermediate potassium sulfide salt **24**. The reaction of **24** with chloroacetone **25** gave the thiophene derivative **26**. Its structure was based on ^{1}H NMR spectral data that showed, in addition to the expected signal of the cyclohexene ring, a singlet at δ 2.20 for the CH_3 group, a multiplet at δ 7.29–7.34 attributable to the phenyl protons, two singlets (D_2O exchangeable) at δ 8.45 and 8.59 for two NH groups, and a singlet at δ 10.62 for an OH group. Moreover, the ^{13}C NMR data showed δ 29.2, 31.0 (cyclohexene C-1, C-4), 24.3, 24.8 (cyclohexene C-2, C-3), 120.1 (CN), 122.0, 122.9, 124.4, 130.8, 131.6, 132.7, 134.9, 136.7, 136.9, 140.0 (two thiophene-C, benzene-C), 178.9, and 180.4 (C=O). However, the reaction of **24** with either phenacyl bromide **27a** or ethyl bromoacetate **27b** gave the thiazole derivatives **28a** and **28b**, respectively. The structures of the latter products were based on analytical and spectral data (see Experimental section) (Scheme 5).

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr) on a Pye Unicam Sp-1000 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian EM-390 90 Mhz spectrometer in DMSO-d6 as solvent and TMS as an internal reference. Chemical shifts were expressed as δ. Analytical data were carried out at the Microanalytical Data Unit at Cairo University.

3-Cyano-2-(ethoxycarbonylacetamido-N-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene **3** *and 4-Amino-3-ethoxycabonyl-2-hydroxy-4,5,6,7-tetrahydro[b]thieno[5,4:2,3]pyridine* **4**

General Procedure. To the dry solid **1** (1.78 g, 0.01 mol), diethyl malonate (1.52 g, 0.01 mol) was



SCHEME 5

added. The reaction mixture was heated in an oil bath at 140°C for 2 hours and then left to cool. Ethanol (50 mL, 95%) was added to the reaction mixture, and the whole mixture was heated and filtered. The ethanol-soluble product was collected from the filtrate, precipitated upon addition of ice containing a few drops of hydrochloric acid, and identified. This solid product was identified as compound **1**. The ethanol insoluble product was identified as compound **4**.

3: Yellowish white crystals (from ethanol), yield 76% (2.21 g), m.p. 220–222°C. IR (υ^{-}/cm^{-1}) = 3450–3230 (NH), 2986, 2960 (CH_3, CH_2), 2225 (CN), 1745, 1695 (2 C=O), 1645 (C=C). ^{1}H NMR δ = 1.31 (t, 3H, CH_3), 2.24, 2.78 (2m, 8H, 4CH_2), 4.25 (q, 2H, CH_2), 5.67 (s, 2H, CH_2), 8.89 (s, 1H, NH). ^{13}C NMR δ = 28.4 (ester CH_3), 29.7, 30.6 (cyclohexene C-1, C-4), 24.1, 24.7 (cyclohexene C-2, C-3), 52.9 (ester CH_2), 58.6 (CH_2) 119.9 (CN), 126.6, 132.1, 132.7, 138.0 (thiophene-C), 178.9, 181.0 (2 C=O). $C_{14}H_{16}N_2O_3S$ (292.34): Calcd: C, 57.52; H, 5.51; N, 9.59; S, 10.97; found: C, 57.31; H, 5.59, N, 9.23; S, 11.21.

4: Yellow crystals (from 1,4-dioxane), yield 15% (0.43 g), m.p. > 300°C. IR (υ^{-}/cm^{-1}) = 3570–3330 (OH, NH_2), 2980, 2973 (CH_3, CH_2), 1680 (C=O), 1640 (C=C). ^{1}H NMR δ = 1.33 (t, 3H, CH_3), 2.23, 2.74 (2m, 8H, 4CH_2), 4.28 (q, 2H, CH_2), 5.32 (s, 2H, NH_2), 10.21 (s, 1H, OH). ^{13}C NMR δ = 27.8 (ester CH_3), 29.5, 30.2 (cyclohexene C-1, C-4), 23.8, 24.9 (cyclohexene C-2, C-3), 53.2 (ester CH_2), 120.7 (CN), 126.4, 132.0, 132.2, 134.2, 134.9, 138.7, 138.9, 140.2 (thiophene-C, pyridine-C), 181.7 (C=O). $C_{14}H_{16}N_2O_3S$ (292.34): Calcd: C, 57.52; H, 5.51; N, 9.59; S, 10.97; found: C, 57.20; H, 5.42, N, 9.69; S, 10.77.

3-Cyano-2-[α-ethoxycarbonyl-α-phenylhydrazoactamido-N-yl]-4,5,6,7-tetrahydrobenzo[b]thiophene **5**

To a cold solution (0–5°C) of **3** (2.92 g, 0.01 mol) in ethanol (40 mL), a cold solution of benzenediazonium chloride (0.01 mol) (prepared by adding cold sodium nitrilte solution [0.7 g, 0.01 mol] to a cold suspension [0–5°C] of aniline [0.92 g, 0.01 mol] in concentrated hydrochloric acid [8 ml] with stirring) was added with continuous stirring. The whole reaction mixture was left at room temperature for 4 hours, and the formed solid product was collected by filtration.

5: Red crystals (from ethanol), yield 80% (3.16 g), m.p. 165°C. IR (υ^{-}/cm^{-1}) = 3460–3310 (NH), 2980, 2970 (CH_3, CH_2), 2220 (CN), 1705, 1685 (2 C=O), 1640 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, CH_3), 2.26, 2.79 (2m, 8H, 4CH_2), 4.23 (q, 2H, CH_2), 8.99, 9.67 (2s, 2H, 2NH). $C_{20}H_{20}N_4O_3S$ (396.44); Calcd: C, 60.59; H, 5.08; N, 14.13; S, 8.09; found: C, 60.46; H, 4.87, N, 14.45; S, 7.77.

3-Cyano-2-aminocarbonyl[4-hydroxy-2-phenyl-1,2,3-triazol-5-yl]-4,5,6,7-tetrahydrobenzo[b]thiophene **6**

To a solution of **5** (3.96 g, 0.01 mol) in 1,4-dioxane (50 mL), hydrazine hydrate (0.5 ml, 0.01 mol) is added. The reaction mixture was heated under reflux for 5 hours and evaporated in a vacuum, and the remaining product was triturated with ethanol. The formed solid product was collected by filtration.

6: Yellow crystals (from acetic acid), yield 66% (2.40 g), m.p. 185°C. IR (υ^{-}/cm^{-1}) = 3530–3300 (OH, NH), 3060 (CH aromatic), 2976 (CH_2), 2220 (CN), 1690 (C=O), 1655, 1635 (C=C). ^{1}H NMR δ = 2.25, 2.69 (2m, 8H, 4CH_2), 7.32–7.39 (m, 5H, C_6H_5), 8.53 (1s, 1H, NH). $C_{18}H_{15}N_5O_2S$ (365.39): Calcd: C, 59.17; H, 4.14; N, 19.16; S, 8.78; found: C, 59.46; H, 4.86, N, 19.45; S, 9.01.

3-Cyano-2-[α-ethoxycarbonyl-α-benzalactamido-N-yl]-4,5,6,7-tetrahydrobenzo[b]thiophene **7** *and 3-Cyano-2-aminocarbonyl[coumarin-3-yl]-4,5,6,7-tetrahydrobenzo[b]thiophene* **9**

General Procedure. To a solution of **3** (2.92 g, 0.01 mol) in 1,4-dioxane (50 mL) containing piperidine (0.5 mL), either benzaldehyde (1.02 g, 0.01 mol) or salicylaldehyde (1.18 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 4 hours and then evaporated in a vacuum.

The remaining product was triturated with diethyl ether, and the formed solid product was collected by filtration.

7: White crystals (from ethanol), yield 71% (2.69 g), m.p. 265–267°C IR (υ^{-}/cm^{-1}) = 3500–3350 (NH), 3065 (CH aromatic), 2979, 2880 (CH_3, CH_2), 2222 (CN), 1705, 1685 (2 C=O), 1645 (C=C). ^{1}H NMR δ = 1.37 (t, 3H, CH_3), 2.27, 2.70 (2m, 8H, $4CH_2$), 4.23 (q, 2H, CH_2), 6.67 (s, 1H, CH=C), 7.30–7.37 (m, 5H, C_6H_5), 8.75 (s, 1H, NH). $C_{21}H_{20}N_2O_3S$ (380.44): Calcd: C, 66.30; H, 5.30; N, 7.36; S, 8.43%, found: C, 66.01; H, 4.96, N, 7.21; S, 9.30%.

9: Yellow crystals (from 1,4-dioxane), yield 90% (3.15 g), m.p. 230–234°C. IR (υ^{-}/cm^{-1}) = 3500–3310 (NH), 3066 (CH aromatic), 2976 (CH_2), 2223 (CN), 1708, 1685 (2 C=O), 1648 (C=C). ^{1}H NMR δ = 2.27, 2.73 (2m, 8H, $4CH_2$), 6.99 (s, 1H, coumarin H-9), 7.33–7.41 (m, 4H, C_6H_4), 8.83 (1s, 1H, NH). $C_{19}H_{14}N_2O_3S$ (350.37): Calcd: C, 65.13; H, 4.03; N, 7.99; S, 9.15; found: C, 65.09; H, 4.47, N, 8.51; S, 9.47.

3-Cyano-2-aminocarbonyl[3-hydroxy-5-phenylpyrazol-4-yl]-4,5,6,7-tetrahydrobenzo[b]thiophene **8a** *and 3-Cyano-2-aminocarbonyl[3-hydroxy-1,5-diphenylpyrazol-4-yl]-4,5,6,7-tetrahydrobenzo[b]thiophene* **8b**

General Procedure. To a solution of **7** (3.80 g, 0.01 mol) in dimethylformamide (30 mL), either hydrazine hydrate (0.5 mL, 0.01 mol) or phenylhydrazine (1.10 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 hours and then poured into ice containing a few drops of hydrochloric acid. The solid product, formed in each case, was collected by filtration,

8a: Orange crystals (from acetic acid), yield 78% (3.03 g), m.p. 145°C. IR (υ^{-}/cm^{-1}) = 3560–3340 (OH, NH), 3058 (CH aromatic), 2979 (CH_2), 2220 (CN), 1693 (C=O), 1660 (C=N), 1646 (C=C), ^{1}H NMR δ = 2.25, 2.71 (2m, 8H, $4CH_2$), 7.29–7.35 (m, 5H, C_6H_5), 8.79, 9.41 (2s, 2H, 2NH), 10.63 (s, 1H, OH). $C_{19}H_{16}N_4O_2S$ (364.41): Calcd: C, 62.62; H, 4.43; N, 15.37; S, 8.79; found: C, 62.39; H, 4.17, N, 15.61; S, 9.20.

8b: Orange crystals (from acetic acid), yield 63% (2.78g), m.p. 188°C. IR (υ^{-}/cm^{-1}) = 3557–3321 (OH, NH), 3060 (CH aromatic), 2982 (CH_2), 2225 (CN), 1687 (C=O), 1666 (C=N), 1642 (C=C). ^{1}H NMR δ = 2.22, 2.76 (2m, 8H, $4CH_2$), 7.31–7.39 (m, 10H, $2C_6H_5$), 9.21 (s, H, NH), 10.57 (s, 1H, OH). $C_{25}H_{20}N_4O_2S$ (440.51): Calcd: C, 68.16; H, 4.57; N, 12.72; S, 7.28; found: C, 68.40; H, 4.35, N, 12.59; S, 7.48.

3-Cyano-2-(2,4-diamino-5-ethoxycarbonyl-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene **11a**, *3-Cyano-2-(4-amino-5-ethoxycarbonyl-2-hydroxy-6-oxopyridine-1-yl)-4,5,6,7-tetrahydro-benzo[b]thiophene* **11b**, *3-Cyano-2-(2-amino-3-cyano-5-ethoxycarbonyl-4-phenyl-6-oxopyridine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene* **22a**, *and 3-Cyano-2-(2-amino-3,5-diethoxycarbonyl-4-phenyl-6-oxopyridine-1-yl)-4,5,6,7-tetrahydro-benzo[b]thiophene* **22b**

General Procedure. A solution of **3** (2.92 g, 0.01 mol) in dimethylformamide (40 mL) containing triethylamine (0.5 mL) was treated with either malononitrile (0.66 g, 0.01 mol), ethyl cyanoacetate (1.13 g, 0.01 mol), α-cyanocinnamonitrile (1.74 g, 0.01 mol), or α-ethoxycarbonyl cinnamonitrile (2.21 g, 0.01 mol). The reaction mixture, in each case, was heated under reflux for 6 hours and then poured into ice/water containing a few drops of hydrochloric acid. The solid product, formed in each case, was collected by filtration.

11a: Orange crystals (from acetic acid), yield 86% (3.01 g), m.p. 240–243°C. IR (υ^{-}/cm^{-1}) = 3480–3320 (2 NH_2), 3030 (CH pyridine), 2980, 2880 (CH_3, CH_2), 2225 (CN), 1690, 1680 (2 C=O), 1640 (C=C). ^{1}H NMR δ = 1.31 (t, 3H, CH_3), 2.21, 2.69 (2m, 8H, $4CH_2$), 4.21 (q, 2H, CH_2), 4.68, 5.62 (2s, 4H, $2NH_2$), 6.99 (s, 1H, pyridine H-3), $C_{17}H_{18}N_4O_3S$ (358.39): Calcd: C, 56.97; H, 5.06; N, 15.63; S, 8.94; found: C, 56.75; H, 4.77, N, 15.61; S, 9.23.

11b: Orange crystals (from acetic acid), yield 60% (2.15 g), m.p. 155–157°C. IR (υ^{-}/cm^{-1}) = 3580–3300 (OH, NH_2), 3036 (CH pyridine), 2988, 2889 (CH_3, CH_2), 2222 (CN), 1694 (C=O), 1648 (C=C). ^{1}H NMR δ = 1.33 (t, 3H, CH_3), 2.25, 2.65 (2m, 8H, $4CH_2$), 4.25 (q, 2H, CH_2), 5.62 (s, 2H, NH_2), 7.03 (s, 1H, pyridine H-5), $C_{17}H_{17}N_3O_4S$ (359.38): Calcd: C, 56.81; H, 4.76; N, 11.69; S, 8.92; found: C, 56.77; H, 4.79, N, 11.68; S, 9.09.

22a: Yellow crystals (from 1,4-dioxane), yield 82% (3.64 g), m.p. 220–223°C. IR (υ^{-}/cm^{-1}) = 3420, 3380 (NH_2), 3050 (CH aromatic), 2988, 2870 (CH_3, CH_2), 2225, 2220 (2 CN), 1695, 1687 (2 C=O), 1644 (C=C). ^{1}H NMR δ = 1.33 (t, 3H, CH_3), 2.26, 2.71 (2m, 8H, $4CH_2$), 4.25 (q, 2H, CH_2), 4.55 (s, 2H, NH_2), 7.32–7.37 (m, 5H, C_6H_5), $C_{24}H_{20}N_4O_3S$ (444.64): Calcd: C, 64.86; H, 4.53; N, 12.60; S, 7.21; found: C, 64.77; H, 4.67, N, 12.67; S, 7.09.

22b: Orange crystals (from ethanol), yield 65% (2.88 g), m.p. 266–268°C. IR (υ^{-}/cm^{-1}) = 3460, 3360 (NH_2), 3055 (CH aromatic), 2983, 2877 (CH_3, CH_2), 2220 (CN), 1695–1680 (3 C=O), 1641 (C=C). ^{1}H NMR δ = 1.33, 1.40 (2t, 6H, $2CH_3$), 2.25, 2.70 (2m,

8H, 4CH_2), 4.20, 4.25 (2q, 4H, 2CH_2), 4.58 (s, 2H, NH_2), 7.30–7.38 (m, 5H, C_6H_5), $C_{26}H_{25}N_3O_5S$ (491.53): Calcd: C, 63.56; H, 5.08; N, 8.55; S, 6.67; found: C, 63.28; H, 5.39, N, 8.69; S, 6.49.

4,7-Diamino-3-ethoxycarbonyl-2-oxo-4,5,6,7-tetrahydrobenzo-[b]thieno[5,4:4,5]-pyrimidino[3,2:1,2]pyridine **12**, *7-Amino-5-cyano-3-ethoxycarbonyl-2-oxo-4-phenyl-4,5,6,7-tetrahydrobenzo-[b]thieno[5,4:4,5]-pyrimidino[3,2:1,2]pyridine* **23a**, *7-Amino-3,5-diethoxycarbonyl-2-oxo-4-phenyl-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:4,5]-pyrimidino [3,2:1,2]pyridine* **23b**

General Procedure. A suspension of either **11a** (3.58 g, 0.01 mol), **22a** (4.44 g, 0.01 mol) or **22b** (4.91 g, 0.01 mol) in sodium ethoxide (prepared by dissolving sodium metal [0.46 g, 0.02 mol] in absolute ethanol [50 mL]) was heated in a boiling water bath for 6 hours. The solid product formed, in each case upon pouring the mixture into ice/water containing hydrochloric acid (to pH 6) was collected by filtration.

12: Pale yellow crystals (from 1,4-dioxane), yield 56% (2.0 g), m.p. 220–223°C. IR (υ^-/cm^{-1}) = 3475–3346 (2 NH_2), 3038 (CH pyridine), 2988, 2895 (CH_3, CH_2), 1693, 1684 (2 C=O), 1633 (C=C). ^{1}H NMR δ = 1.35 (t, 3H, CH_3), 2.28, 2.71 (2m, 8H, 4CH_2), 4.24 (q, 2H, CH_2), 4.99, 5.41 (2s, 4H, 2NH_2), 7.09 (s, 1H, pyridine H-5). ^{13}C NMR δ = 26.3 (ester CH_3), 29.3, 30.7 (cyclohexene C-1, C-4), 22.7, 25.4 (cyclohexene C-2, C-3), 55.2 (ester CH_2), 125.2, 131.5, 132.8, 133.1, 133.6, 136.2, 138.9, 140.5, 143.2, 143.7 (thiophene-C, pyrimidine-C, pyridine-C), 179.6, 180.4 (2 C=O). $C_{17}H_{18}N_3O_3S$ (358.39): Calcd: C, 56.97; H, 5.06; N, 15.63; S, 8.94; found: C, 57.33; H, 4.89, N, 15.29; S, 9.41.

23a: Yellow crystals (from DMF), yield 60% (2.66 g), m.p. 186–189°C. IR (υ^-/cm^{-1}) = 3444, 3360 (NH_2), 3055 (CH aromatic), 2983, 2879 (CH_3, CH_2), 2222 (CN), 1690, 1685 (2 C=O), 1640 (C=C). ^{1}H NMR δ = 1.34 (t, 3H, CH_3), 2.25, 2.73 (2m, 8H, 4CH_2), 4.23 (q, 2H, CH_2), 4.60 (s, 2H, NH_2), 7.31–7.40 (m, 5H, C_6H_5), $C_{24}H_{20}N_4O_3S$ (444.64): Calcd: C, 64.86; H, 4.53; N, 12.60; S, 7.21; found: C, 64.69; H, 4.67, N, 12.77; S, 7.13.

23b: Pale yellow crystals (from DMF), yield 65% (2.88 g), m.p. 135°C. IR (υ^-/cm^{-1}) = 3469, 3354 (NH_2), 3050 (CH aromatic), 2989, 2865 (CH_3, CH_2), 1700–1680 (3 C=O), 1648 (C=C). ^{1}H NMR δ = 1.36, 1.42 (2t, 6H, 2CH_3), 2.22, 2.74 (2m, 8H, 4CH_2), 4.23, 4.27 (2q, 4H, 2CH_2), 4.66 (s, 2H, NH_2), 7.32–7.42 (m, 5H, C_6H_5), $C_{26}H_{25}N_3O_5S$ (491.53): Calcd: C, 74.43; H, 6.01; N, 8.55; S, 7.64; found: C, 74.61; H, 5.54, N, 8.70; S, 7.69.

3-Cyano-2-aminoccarbonyl(ethyl α-bromoacetat-α-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene **13**

To a hot solution of **3** (2.92 g, 0.01 mol) in acetic acid (40 mL), bromine (0.5 mL, 0.01 mol) in acetic acid (10 mL) was added dropwise with continues stirring. The reaction mixture was left at room temperature for 3 hours and then poured into ice/water. The solid product formed was collected by filtration.

13: Pale yellow crystals (from acetic acid), yield 60% (2.23 g), m.p. 180–184°C. IR (υ^-/cm^{-1}) = 3420–3380 (NH), 2979, 2883 (CH_3, CH_2), 2220 (CN), 1696, 1680 (2 C=O), 1645 (C=C). ^{1}H NMR δ = 1.33 (t, 3H, CH_3), 2.27, 2.74 (2m, 8H, 4CH_2), 4.22 (q, 2H, CH_2), 9.21 (s, 1H, NH). $C_{14}H_{15}N_2O_3SBr$ (371.45): Calcd: C, 45.27; H, 4.07; N, 7.54; S, 8.63; Br, 21.54; found: C, 47.33; H, 4.89, N, 15.29; S, 9.41.

4-Amino-3-cyano-3-ethoxycarbonyl-2-oxo-4,5,6,7-tetrahydrobenzo[b]thieno[2,3-b]pyridine **15**

To a hot solution of **13** (3.71 g, 0.01 mol) in ethanol (60 mL), potassium cyanide (0.76 g, 0.01 mol) solution (in 10 mL water) was added dropwise with stirring. The reaction mixture was left at room temperature for 3 hours and then poured into ice/water containing hydrochloric acid (to pH 6), and the formed solid product was collected by filtration.

15: Yellow crystals (from acetic acid), yield 70% (2.20 g), m.p. 160–163°C IR (υ^-/cm^{-1}) = 3480–3351 (NH_2), 2974, 2881 (CH_3, CH_2), 2225 (CN), 1715, 1682 (2 C=O), 1635 (C=C). ^{1}H NMR δ = 1.32 (t, 3H, CH_3), 2.25, 2.69 (2m, 8H, 4CH_2), 4.23 (q, 2H, CH_2), 5.44 (s, 2H, NH_2), $C_{15}H_{15}N_3O_3S$ (317.35): Calcd: C, 56.77; H, 4.76; N, 13.24; S, 10.10; found: C, 56.38; H, 4.66, N, 14.21; S, 10.09.

2-Amino-(2-amino-5-ethoxycarbonylthiazole-4-yl)-3-cyano-4,5,6,7-tetrahydrobenzo[b] thiophene **16**

A solution of **13** (3.71 g, 0.01 mol) in absolute ethanol (60 mL) was treated with thiourea (0.76 g, 0.01 mol). The reaction mixture was heated under reflux for 3 hours and then poured into ice/water. The solid product, so formed, was collected by filtration.

16: Orange crystals (from acetic acid), yield 81% (3.33 g), m.p. 120–122°C. IR (υ^-/cm^{-1}) = 3475–3321 (2 NH_2), 2994, 2871 (CH_3, CH_2), 2222 (CN), 1695 (C=O), 1660 (CN) 1645 (C=C). ^{1}H NMR δ = 1.35 (t, 3H, CH_3), 2.27, 2.71 (2m, 8H, 4CH_2), 4.25 (q, 2H, CH_2), 4.89 (s, 2H, NH_2), 8.99 (s, 1H, NH)

$C_{15}H_{16}N_4O_2S_2$ (348.34): Calcd: C, 51.73; H, 4.60; N, 16.12; S, 18.39; found: C, 51.66; H, 4.62, N, 16.28; S, 18.44.

2-Amino-4-hydroxy-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:2,3]-pyridino[6,5:4,5]thiazole **18**

A solution of **16** (4.12 g, 0.01 mol) in ethanol (50 mL) containing sodium hydroxide (0.5 g) was heated under reflux for 5 hours and then poured into ice/water containing hydrochloric acid (to pH 6). The formed solid product was collected by filtration.

18: Orange crystals (from DMF), yield 60% (1.67 g), m.p. 230–234°C. IR (υ^-/cm^{-1}) = 3555–3331 (OH, NH_2), 1666 (C=N) 1638 (C=C). ^{1}H NMR δ = 2.27, 2.71 (2m, 8H, $4CH_2$), 5.49 (s, 2H, NH_2), 10.31 (s, 1H, OH). ^{13}C NMR δ = 26.9 (ester CH_3), 29.2, 30.9 (cyclohexene C-1, C-4), 24.2, 24.5 (cyclohexene C-2, C-3), 52.9 (ester CH_2), 119.2 (CN), 124.5, 130.7, 131.9, 134.9, 140.2, 142.8 (thiophene-C, pyridine-C), 179.8, 180.7 (2 C=O). $C_{12}H_{11}N_3OS_2$ (277.36): Calcd: C, 51.96; H, 3.99; N, 15.15; S, 23.12; found: C, 51.87; H, 4.04, N, 14.87; S, 23.09.

2-Ethoxycarbonylacetamido-N-yl-3-(4-hydroxythiazol-2-y)-4,5,6,7-tetrahydrobenzo[b]thiophene **19**

To a solution of **3** (2.92 g, 0.01 mol) in acetic acid (60 mL), thioglycolic acid (1.20 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3 hours and then evaporated in vacuum. The remaining semisolid product was tritutrated with ethanol. The formed solid product was collected by filtration.

19: Pale yellow crystals (from acetic acid), yield 73% (2.67 g), m.p. 168–70°C. IR (υ^-/cm^{-1}) = 3580–3355 (OH, NH), 1685, 1680 (2 C=O), 1660 (C=N) 1644 (C=C). ^{1}H NMR δ = 1.38 (t, 3H, CH_3), 2.26, 2.73 (2m, 8H, $4CH_2$), 4.24 (q, 2H, CH_2), 4.56 (s, 2H, CH_2), 8.88 (s, 1H, NH), 10.01 (s, 1H, OH) $C_{16}H_{18}N_2O_4S_2$ (366.43): Calcd: C, 52.44; H, 4.95; N, 7.64; S, 17.50; found: C, 52.77; H, 5.04, N, 7.67; S, 17.32.

3-Hydroxy-4-ethoxycarbonylcarboylidieno-4,5,6,7-tetrahydrobenzo[b]thieno[5,4:4,5]pyrimidino[6,1:2,3]thiazole **20**

A solution of **19** (3.66 g, 0.01 mol) in dimethylformamide (30 mL) containing a catalytic amount of triethylamine (0.5 mL) was heated under reflux for 6 hours and then evaporated in a vacuum. The remaining product was triturated with diethyl ether, and the formed solid product was collected by filtration.

20: White crystals (from acetic acid), yield 56% (2.5 g), m.p. 222–224°C. IR (υ^-/cm^{-1}) = 3585–3325 (OH), 1660 (C=N) 1638 (C=C). ^{1}H NMR δ = 1.35 (t, 3H, CH_3), 2.24, 2.72 (2m, 8H, $4CH_2$), 4.26 (q, 2H, CH_2), 6.77 (s, 1H, CH=C), 10.31 (s, 1H, OH). $C_{16}H_{16}N_2O_3S_2$ (348.42): Calcd: C, 55.15; H, 4.63; N, 8.07; S, 18.41; found: C, 55.29; H, 5.01, N, 7.88; S, 18.33.

2-Aminocarbonyl(5-acetyl-4-hydroxy-2-phenylaminothiophene-3-yl)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene **26***, 2-Aminocarbonylethyl acetato-α-ylidieno-α-(3,4-diphenylthiazol-2-ylidieno)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene* **28a***, and 2-Aminocarbonylethyl acetato-α-ylidieno-α-(4-hydroxy-3-phenylthiazol-2-ylidieno)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene* **28b**

General Procedure. To a solution of **3** (2.77 g, 0.01 mol) in dimethylformamide (30 mL) containing solid potassium hydroxide (0.4 g, 0.01 mol), phenyl isothiocyanate (1.30 g, 0.01 mol) was added. The reaction mixture was stirred at room temperature overnight. Either chloroacetone (0.93 g, 0.01 mol), phenacylbromide (2.0 g, 0.01 mol), or ethyl bromoacetate (1.06 g, 0.01 mol) was added, and the reaction mixture, in each case, was stirred at room temperature overnight. The solid product formed upon pouring the mixture into ice/water containing hydrochloric acid (to pH 6) was collected by filtration.

26: Yellow crystals (from ethanol), yield 66% (2.87 g), m.p. 140°C. IR (υ^-/cm^{-1}) = 3590–3320 (OH, 2 NH), 3050 (CH aromatic), 2223 (CN), 1695, 1683 (2 C=O), 1660 (C=N) 1638 (C=C). ^{1}H NMR δ = 2.20 (s, 3H, CH_3), 2.23, 2.73 (2m, 8H, $4CH_2$), 7.29–7.34 (m, 5H, C_6H_5), 8.45, 8.59 (2s, 2H, 2NH), 10.07 (s, 1H, OH). ^{13}C NMR δ = 29.2, 31.0 (cyclohexene C-1, C-4), 24.3, 24.8 (cyclohexene C-2, C-3), 120.1 (CN), 122.0, 122.9, 124.4, 130.8, 131.6, 132.7, 134.9, 136.7, 136.9, 140.0 (two thiophene-C, benzene-C), 178.9, and 180.4 (C=O). $C_{22}H_{19}N_3O_3S_2$ (437.52): Calcd: C, 60.39; H, 4.37; N, 9.60; S, 14.66; found: C, 60.44; H, 4.01, N, 9.79; S, 14.39.

28a: Yellow crystals (from ethanol), yield 77% (4.06 g), m.p. 150°C. IR (υ^-/cm^{-1}) = 3445–3368 (NH), 3055 (CH aromatic), 2220 (CN), 1695, 1683 (2 C=O), 1660 (C=N) 1638 (C=C). ^{1}H NMR δ = 1.33 (t, 3H, CH_3), 2.22, 2.70 (2m, 8H, $4CH_2$), 4.23 (q, 2H, CH_2), 7.31–7.39 (m, 10H, 2 C_6H_5), 8.48 (s, H, NH), $C_{29}H_{25}N_3O_3S_2$ (527.64): Calcd: C, 66.01; H, 4.77; N, 7.96; S, 12.15; found: C, 66.34; H, 4.61, N, 7.77; S, 11.89.

28b: Yellow crystals (from ethanol), yield 59% (2.75 g), m.p. 177–180°C. IR (υ^-/cm^{-1}) = 3545–3350

(OH, NH), 3050 (CH aromatic), 2220 (CN), 1690, 1681 (2 C=O), 1665 (C=N) 1640 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, CH_3), 2.25, 2.73 (2m, 8H, $4CH_2$), 4.27 (q, 2H, CH_2), 7.28–7.36 (m, 5H, C_6H_5), 8.71 (s, H, NH), 10.27 (s, 1H, OH). $C_{23}H_{21}N_3O_4S_2$ (467.54): Calcd: C, 59.08; H, 4.53; N, 8.99; S, 13.72; found: C, 58.84; H, 4.68, N, 9.29; S, 13.86.

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