

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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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 C₁₄H₁₆N₂SO₃. 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 ¹³C NMR data showed the presence of δ 28.4 (ester CH₃), 29.7, 30.6 (cyclohexene C-1, C-4), 24.1, 24.7 (cyclohexene C-2, C-3), 52.9 (ester CH₂), 58.6 (CH₂), 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 CH₃ group, a quartet at δ 4.28 for the ester CH₂ group, and a singlet (D₂O exchangeable) at δ 5.23 corresponding to the NH₂ group. Moreover, the ¹³C NMR data showed δ 27.8 (ester CH₃), 29.5, 30.2 (cyclohexene C-1, C-4), 23.8, 24.9 (cyclohexene C-2, C-3), 53.2 (ester CH₂), 120.7 (CN), 126.4, 132.0, 132.2, 134.2, 134.9, 138.7, 138.9, 140.2 (thiophene-

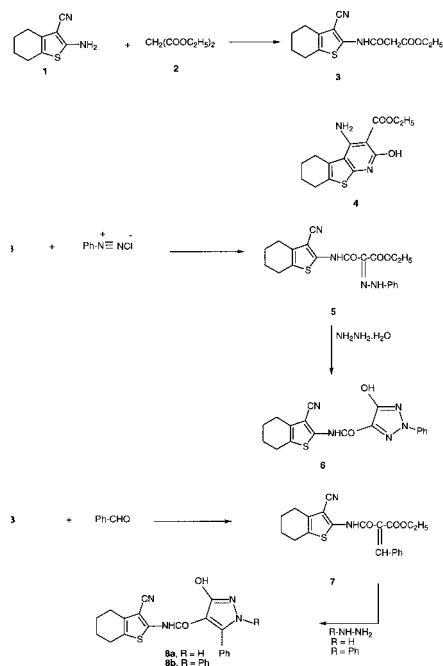
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C, pyridine-C), and 181.7 (C=O). Compound 3 showed interesting reactivity toward a variety of chemical reagents. Thus, it reacted with benzenediazonium chloride at 0°C to give the corresponding hydrazone derivative 5. The latter reacted with hydrazine 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).

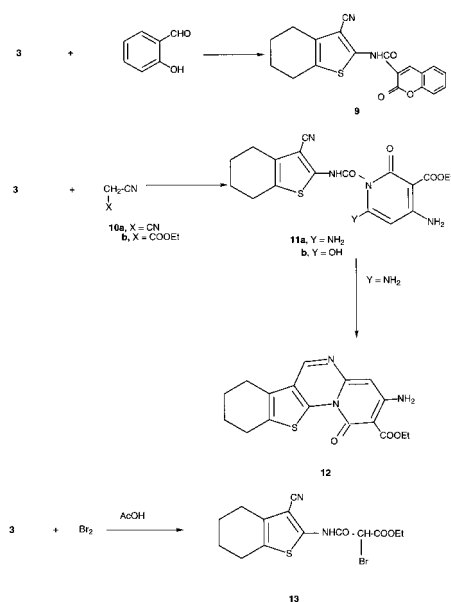
The reactivity of compound 3 toward cyanomethylene reagents was studied. Thus, with either malononitrile (10a) or ethyl cyanoacetate (10b), the corresponding 2-pyridinyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene derivatives 11a and 11b, respectively, were formed. Compound 11a underwent ready cyclization 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 ¹³C

NMR data showed δ 26.3 (ester CH₃), 29.3, 30.7 (cyclohexane C-1, C-4), 22.7, 25.4 (cyclohexane C-2, C-3), 55.2 (ester CH₂), 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).

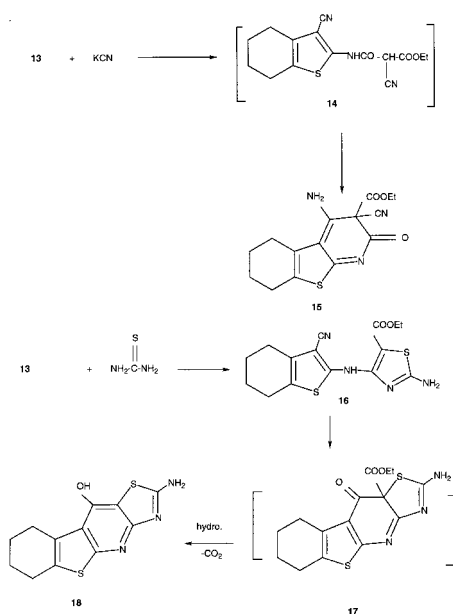
Compound 3 reacted with bromine in hot acetic acid solution to give the monobromo derivative 13 (Scheme 2). The latter reacted with potassium cyanide in ethanol solution to give the tetrahydrobenzo[*b*]thieno[2,3-*b*]pyridine derivative 15. Compound 15 was formed through the intermediate formation of 14 followed by cyclization. The IR spectrum of 15 showed only one CN group stretching at ν 2225 cm⁻¹ and two C=O group stretchings at ν 1715 and ν 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 tetrahydrobenzo[*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. ¹³C NMR data confirm its structure; thus, δ 26.9 (ester CH₃), 29.2, 30.9 (cyclohexene C-1, C-4), 24.2, 24.5 (cyclohexene C-2, C-3), 52.9 (ester CH₂), 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



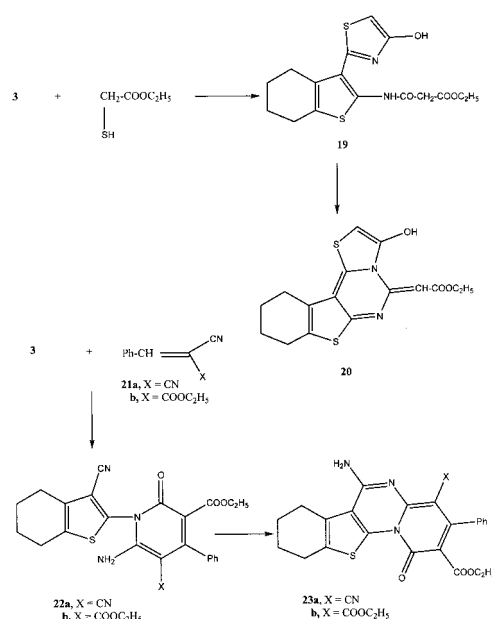
SCHEME 2



SCHEME 3

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 cinnamionitrile derivatives was studied. Thus, the reaction of 3 with either α -cyanocinnamionitrile (21a) or α -ethoxycarbonyl cinnamionitrile (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[3,2:1,2]pyridine 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 ^1H NMR spectral data that showed, in addition to the



SCHEME 4

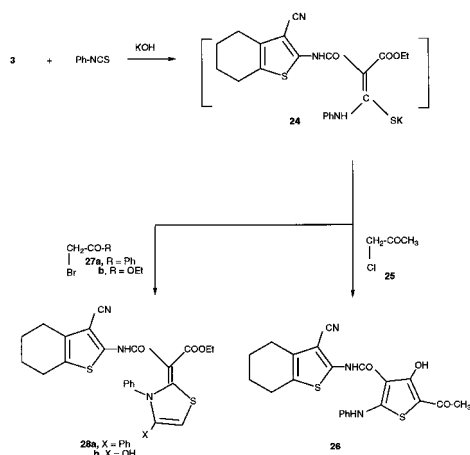
expected signal of the cyclohexene ring, a singlet at δ 2.20 for the CH_3 group, a multiplet at δ 7.29–7.34 attributable to the phenyl protons, two singlets (D_2O exchangeable) at δ 8.45 and 8.59 for two NH groups, and a singlet at δ 10.62 for an OH group. Moreover, the ^{13}C NMR data showed δ 29.2, 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. ^1H NMR and ^{13}C NMR spectra were measured on a Varian EM-390 90 Mhz spectrometer in DMSO-d_6 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-ethoxycarbonyl-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. $220\text{--}222^\circ\text{C}$. IR (ν/cm^{-1}) = 3450–3230 (NH), 2986, 2960 (CH_3 , CH_2), 2225 (CN), 1745, 1695 (2 C=O), 1645 (C=C). ^1H NMR δ = 1.31 (t, 3H, CH_3), 2.24, 2.78 (2m, 8H, 4 CH_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). $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ (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. $> 300^\circ\text{C}$. IR (ν/cm^{-1}) = 3570–3330 (OH, NH), 2980, 2973 (CH_3 , CH_2), 1680 (C=O), 1640 (C=C). ^1H NMR δ = 1.33 (t, 3H, CH_3), 2.23, 2.74 (2m, 8H, 4 CH_2), 4.28 (q, 2H, CH_2), 5.32 (s, 2H, NH), 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). $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$ (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 ($0\text{--}5^\circ\text{C}$) 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 nitrite solution [0.7 g, 0.01 mol] to a cold suspension [$0\text{--}5^\circ\text{C}$] 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 (ν/cm^{-1}) = 3460–3310 (NH), 2980, 2970 (CH_3 , CH_2), 2220 (CN), 1705, 1685 (2 C=O), 1640 (C=C). ^1H NMR δ = 1.36 (t, 3H, CH_3), 2.26, 2.79 (2m, 8H, 4 CH_2), 4.23 (q, 2H, CH_2), 8.99, 9.67 (2s, 2H, 2NH). $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$ (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 (ν/cm^{-1}) = 3530–3300 (OH, NH), 3060 (CH aromatic), 2976 (CH_2), 2220 (CN), 1690 (C=O), 1655, 1635 (C=C). ^1H NMR δ = 2.25, 2.69 (2m, 8H, 4 CH_2), 7.32–7.39 (m, 5H, C_6H_5), 8.53 (1s, 1H, NH). $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$ (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 (ν -cm⁻¹) = 3500–3350 (NH), 3065 (CH aromatic), 2979, 2880 (CH₃, CH₂), 2222 (CN), 1705, 1685 (2 C=O), 1645 (C=C). ¹H NMR δ = 1.37 (t, 3H, CH₃), 2.27, 2.70 (2m, 8H, 4CH₂), 4.23 (q, 2H, CH₂), 6.67 (s, 1H, CH=C), 7.30–7.37 (m, 5H, C₆H₅), 8.75 (s, 1H, NH). C₂₁H₂₀N₂O₃S (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 (ν -cm⁻¹) = 3500–3310 (NH), 3066 (CH aromatic), 2976 (CH₂), 2223 (CN), 1708, 1685 (2 C=O), 1648 (C=C). ¹H NMR δ = 2.27, 2.73 (2m, 8H, 4CH₂), 6.99 (s, 1H, coumarin H-9), 7.33–7.41 (m, 4H, C₆H₄), 8.83 (1s, 1H, NH). C₁₉H₁₄N₂O₃S (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 (ν -cm⁻¹) = 3560–3340 (OH, NH), 3058 (CH aromatic), 2979 (CH₂), 2220 (CN), 1693 (C=O), 1660 (C=N), 1646 (C=C), ¹H NMR δ = 2.25, 2.71 (2m, 8H, 4CH₂), 7.29–7.35 (m, 5H, C₆H₅), 8.79, 9.41 (2s, 2H, 2NH), 10.63 (s, 1H, OH). C₁₉H₁₆N₄O₂S (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 (ν -cm⁻¹) = 3557–3321 (OH, NH), 3060 (CH aromatic), 2982 (CH₂), 2225 (CN), 1687 (C=O), 1666 (C=N), 1642 (C=C). ¹H NMR δ = 2.22, 2.76 (2m, 8H, 4CH₂), 7.31–7.39 (m, 10H, 2C₆H₅), 9.21 (s, H, NH), 10.57 (s, 1H, OH). C₂₅H₂₀N₄O₂S (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-tetrahydro-benzo[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 -cyanocinnamionitrile (1.74 g, 0.01 mol), or α -ethoxycarbonyl cinnamionitrile (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 (ν -cm⁻¹) = 3480–3320 (2 NH₂), 3030 (CH pyridine), 2980, 2880 (CH₃, CH₂), 2225 (CN), 1690, 1680 (2 C=O), 1640 (C=C). ¹H NMR δ = 1.31 (t, 3H, CH₃), 2.21, 2.69 (2m, 8H, 4CH₂), 4.21 (q, 2H, CH₂), 4.68, 5.62 (2s, 4H, 2NH₂), 6.99 (s, 1H, pyridine H-3), C₁₇H₁₈N₄O₃S (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 (ν -cm⁻¹) = 3580–3300 (OH, NH₂), 3036 (CH pyridine), 2988, 2889 (CH₃, CH₂), 2222 (CN), 1694 (C=O), 1648 (C=C). ¹H NMR δ = 1.33 (t, 3H, CH₃), 2.25, 2.65 (2m, 8H, 4CH₂), 4.25 (q, 2H, CH₂), 5.62 (s, 2H, NH₂), 7.03 (s, 1H, pyridine H-5), C₁₇H₁₇N₃O₄S (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 (ν -cm⁻¹) = 3420, 3380 (NH₂), 3050 (CH aromatic), 2988, 2870 (CH₃, CH₂), 2225, 2220 (2 CN), 1695, 1687 (2 C=O), 1644 (C=C). ¹H NMR δ = 1.33 (t, 3H, CH₃), 2.26, 2.71 (2m, 8H, 4CH₂), 4.25 (q, 2H, CH₂), 4.55 (s, 2H, NH₂), 7.32–7.37 (m, 5H, C₆H₅), C₂₄H₂₀N₄O₃S (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 (ν -cm⁻¹) = 3460, 3360 (NH₂), 3055 (CH aromatic), 2983, 2877 (CH₃, CH₂), 2220 (CN), 1695–1680 (3 C=O), 1641 (C=C). ¹H NMR δ = 1.33, 1.40 (2t, 6H, 2CH₃), 2.25, 2.70 (2m,

8H, 4CH₂), 4.20, 4.25 (2q, 4H, 2CH₂), 4.58 (s, 2H, NH₂), 7.30–7.38 (m, 5H, C₆H₅), C₂₆H₂₅N₃O₅S (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]thienof[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]thienof[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]thienof[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 (ν -cm⁻¹) = 3475–3346 (2 NH₂), 3038 (CH pyridine), 2988, 2895 (CH₃, CH₂), 1693, 1684 (2 C=O), 1633 (C=C). ¹H NMR δ = 1.35 (t, 3H, CH₃), 2.28, 2.71 (2m, 8H, 4CH₂), 4.24 (q, 2H, CH₂), 4.99, 5.41 (2s, 4H, 2NH₂), 7.09 (s, 1H, pyridine H-5). ¹³C NMR δ = 26.3 (ester CH₃), 29.3, 30.7 (cyclohexene C-1, C-4), 22.7, 25.4 (cyclohexene C-2, C-3), 55.2 (ester CH₂), 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). C₁₇H₁₈N₃O₃S (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 (ν -cm⁻¹) = 3444, 3360 (NH₂), 3055 (CH aromatic), 2983, 2879 (CH₃, CH₂), 2222 (CN), 1690, 1685 (2 C=O), 1640 (C=C). ¹H NMR δ = 1.34 (t, 3H, CH₃), 2.25, 2.73 (2m, 8H, 4CH₂), 4.23 (q, 2H, CH₂), 4.60 (s, 2H, NH₂), 7.31–7.40 (m, 5H, C₆H₅), C₂₄H₂₀N₄O₃S (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 (ν -cm⁻¹) = 3469, 3354 (NH₂), 3050 (CH aromatic), 2989, 2865 (CH₃, CH₂), 1700–1680 (3 C=O), 1648 (C=C). ¹H NMR δ = 1.36, 1.42 (2t, 6H, 2CH₃), 2.22, 2.74 (2m, 8H, 4CH₂), 4.23, 4.27 (2q, 4H, 2CH₂), 4.66 (s, 2H, NH₂), 7.32–7.42 (m, 5H, C₆H₅), C₂₆H₂₅N₃O₅S (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-aminocarbonyl(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 (ν -cm⁻¹) = 3420–3380 (NH), 2979, 2883 (CH₃, CH₂), 2220 (CN), 1696, 1680 (2 C=O), 1645 (C=C). ¹H NMR δ = 1.33 (t, 3H, CH₃), 2.27, 2.74 (2m, 8H, 4CH₂), 4.22 (q, 2H, CH₂), 9.21 (s, 1H, NH). C₁₄H₁₅N₂O₃SBr (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 (ν -cm⁻¹) = 3480–3351 (NH₂), 2974, 2881 (CH₃, CH₂), 2225 (CN), 1715, 1682 (2 C=O), 1635 (C=C). ¹H NMR δ = 1.32 (t, 3H, CH₃), 2.25, 2.69 (2m, 8H, 4CH₂), 4.23 (q, 2H, CH₂), 5.44 (s, 2H, NH₂), C₁₅H₁₅N₃O₃S (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 (ν -cm⁻¹) = 3475–3321 (2 NH₂), 2994, 2871 (CH₃, CH₂), 2222 (CN), 1695 (C=O), 1660 (CN) 1645 (C=C). ¹H NMR δ = 1.35 (t, 3H, CH₃), 2.27, 2.71 (2m, 8H, 4CH₂), 4.25 (q, 2H, CH₂), 4.89 (s, 2H, NH₂), 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 (ν /cm⁻¹) = 3555–3331 (OH, NH₂), 1666 (C=N) 1638 (C=C). ¹H NMR δ = 2.27, 2.71 (2m, 8H, 4CH₂), 5.49 (s, 2H, NH₂), 10.31 (s, 1H, OH). ¹³C NMR δ = 26.9 (ester CH₃), 29.2, 30.9 (cyclohexene C-1, C-4), 24.2, 24.5 (cyclohexene C-2, C-3), 52.9 (ester CH₂), 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-yl)-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 triturated 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 (ν /cm⁻¹) = 3580–3355 (OH, NH), 1685, 1680 (2 C=O), 1660 (C=N) 1644 (C=C). ¹H NMR δ = 1.38 (t, 3H, CH₃), 2.26, 2.73 (2m, 8H, 4CH₂), 4.24 (q, 2H, CH₂), 4.56 (s, 2H, CH₂), 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-ethoxycarbonylcarbonylidieno-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 (ν /cm⁻¹) = 3585–3325 (OH), 1660 (C=N) 1638 (C=C). ¹H NMR δ = 1.35 (t, 3H, CH₃), 2.24, 2.72 (2m, 8H, 4CH₂), 4.26 (q, 2H, CH₂), 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-Aminocarbonyl-ethyl acetato- α -ylidieno- α -(3,4-diphenylthiazol-2-ylidieno)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene 28a, and 2-Amino-carbonyl-ethyl 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 (ν /cm⁻¹) = 3590–3320 (OH, 2 NH), 3050 (CH aromatic), 2223 (CN), 1695, 1683 (2 C=O), 1660 (C=N) 1638 (C=C). ¹H NMR δ = 2.20 (s, 3H, CH₃), 2.23, 2.73 (2m, 8H, 4CH₂), 7.29–7.34 (m, 5H, C₆H₅), 8.45, 8.59 (2s, 2H, 2NH), 10.07 (s, 1H, OH). ¹³C 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 (ν /cm⁻¹) = 3445–3368 (NH), 3055 (CH aromatic), 2220 (CN), 1695, 1683 (2 C=O), 1660 (C=N) 1638 (C=C). ¹H NMR δ = 1.33 (t, 3H, CH₃), 2.22, 2.70 (2m, 8H, 4CH₂), 4.23 (q, 2H, CH₂), 7.31–7.39 (m, 10H, 2 C₆H₅), 8.48 (s, 1H, 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 (ν /cm⁻¹) = 3545–3350

(OH, NH), 3050 (CH aromatic), 2220 (CN), 1690, 1681 (2 C=O), 1665 (C=N) 1640 (C=C). ^1H NMR δ = 1.36 (t, 3H, CH₃), 2.25, 2.73 (2m, 8H, 4CH₂), 4.27 (q, 2H, CH₂), 7.28–7.36 (m, 5H, C₆H₅), 8.71 (s, H, NH), 10.27 (s, 1H, OH). C₂₃H₂₁N₃O₄S₂ (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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