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Uses of 2-Diazo-4,5,6,7-tetrahydrobenzo-[*b*]thiophene Derivatives in the Synthesis of Azoles, Azines, and Their Fused Derivatives

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ABSTRACT: *The reactions of 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene derivatives with dimeric adducts* **2a** *and* **2b** *gave the hydrazone derivatives* **3a** *and* **3b**, *respectively. The reactivity of the latter products towards various chemical reagents was studied in order to provide azole and azine derivatives incorporating the thiophene ring, and most of them showed high antimicrobial activity.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:108–115, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10003

INTRODUCTION

The reactivity of 2-diazo-4,5,6,7-tetrahydrobenzo[*b*] thiophene derivatives towards active methylene reagents, with subsequent in situ heterocyclization of the resulting adducts with various reagents has been recently studied by our research group [1–3] to make available a variety of polyfunctionaly substituted thiazole, pyridine, and pyrazole derivatives. These types of compounds are of interest because of their wide spectrum of biological properties and applications. They have been used as dihydrofolate reductase inhibitors, as well as antitumor agents. Some of them have shown diuretic properties, activity against platelet aggregation, and antidiabetic activity [4–15]. In addition, they have proved to be convenient candidates for chemical transformations into various fused heterocyclic ring systems. Prompted by our earlier promising results, we have extended our work to include the reactions of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**1**) with dimeric adducts, namely 3-amino-2,4-dicyanocroteno-nitrile (**2a**) and diethyl-3-amino-2-cyanopenten-1,5-dicarboxylate (**2b**) to give azo derivatives capable of heterocyclic transformations.

RESULTS AND DISCUSSION

The reaction of **1** with either of the dimeric adducts **2a** or **2b** gave the corresponding hydrazone derivatives **3a** and **3b**, respectively (Scheme 1). The structures of the latter products were based on analytical and spectral data. Thus, the IR spectrum of **3a** (as an example) showed NH_2 and NH stretching at $\upsilon = 3470–3320$ cm^{-1}, four CN group stretchings at $\upsilon = 2225–2220$ cm^{-1}, and the ^1H NMR spectrum showed two multiplets at $\delta = 2.22$ and 2.87 for four CH_2 groups of the cyclohexene ring, a singlet at $\delta = 4.89$ for the NH_2 group, and a singlet at $\delta = 8.69$ for the NH group. Moreover, the ^{13}C NMR spectroscopic data showed $\delta = 29.5$, 30.2 (cyclohexene C-1, C-4); 23.8, 24.9 (cyclohexene C-2, C-3); 58.4 (C=N); 102.9, 104.3 (C=C); 119.3, 119.8, 120.2, 120.7 (4 CN); 126.4, 132.0, 134.2, 138.7 (thiophene-C). The

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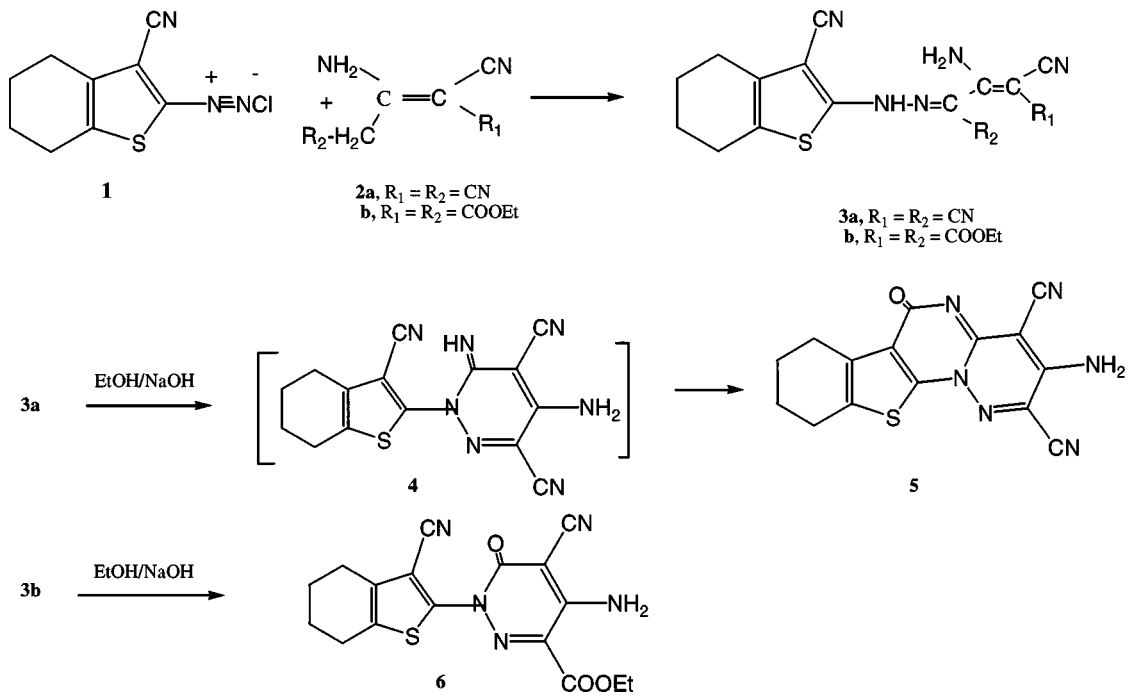


SCHEME 1

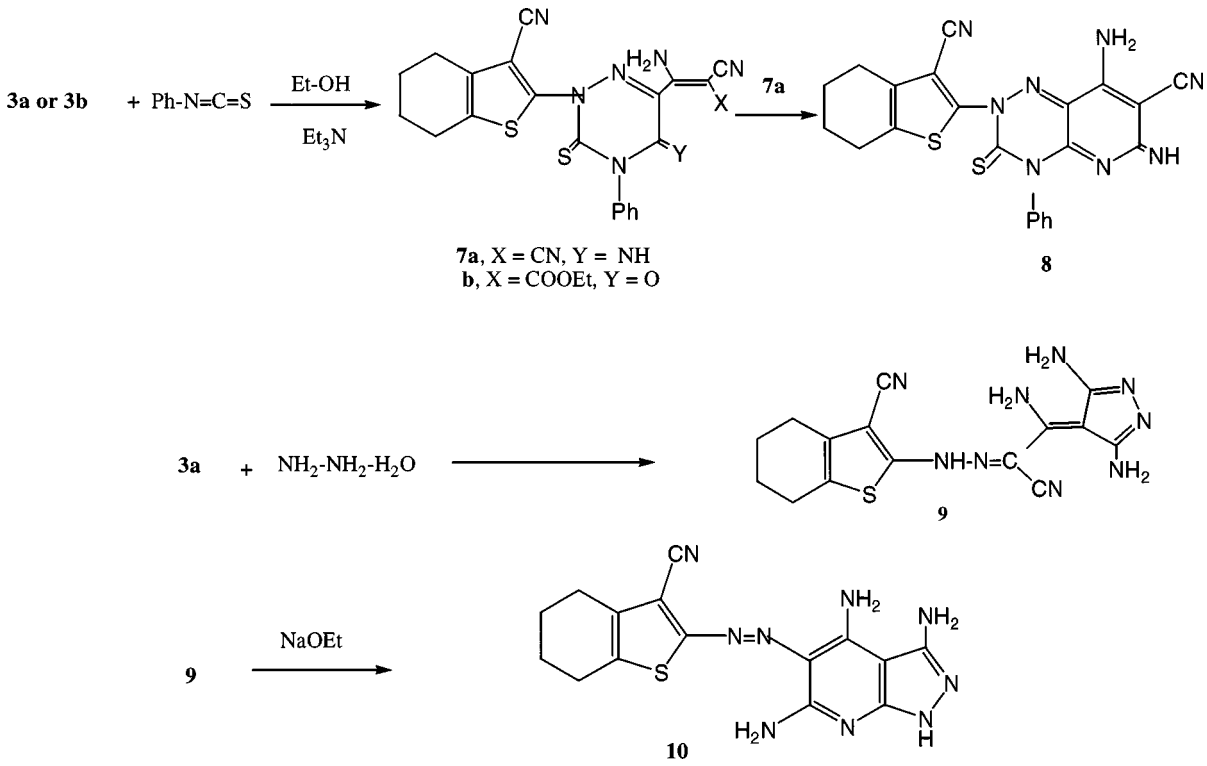
^{1}H NMR spectrum of **3b** showed, besides the cyclohexene CH_2 protons, two triplets at $\delta = 1.34$ and 1.46 for two CH_3 groups, two quartets at $\delta = 4.20$ and 4.24 for two CH_2 groups, a singlet at $\delta = 5.31$ for NH_2, and a singlet at $\delta = 9.24$ for an NH group.

Compounds **3a** and **3b** were cyclized when heated under reflux in basic ethanol solution to give annulated derivative **5** and the pyridazine derivative **6**, respectively (Scheme 1). Formation of **5** can be explained by the formation of **4** as an intermediate followed by cyclization and hydrolysis of the newly formed C=NH group to give the C=O group. Structures of compounds **5** and **6** were based on analytical and spectral data (see the Experimental section).

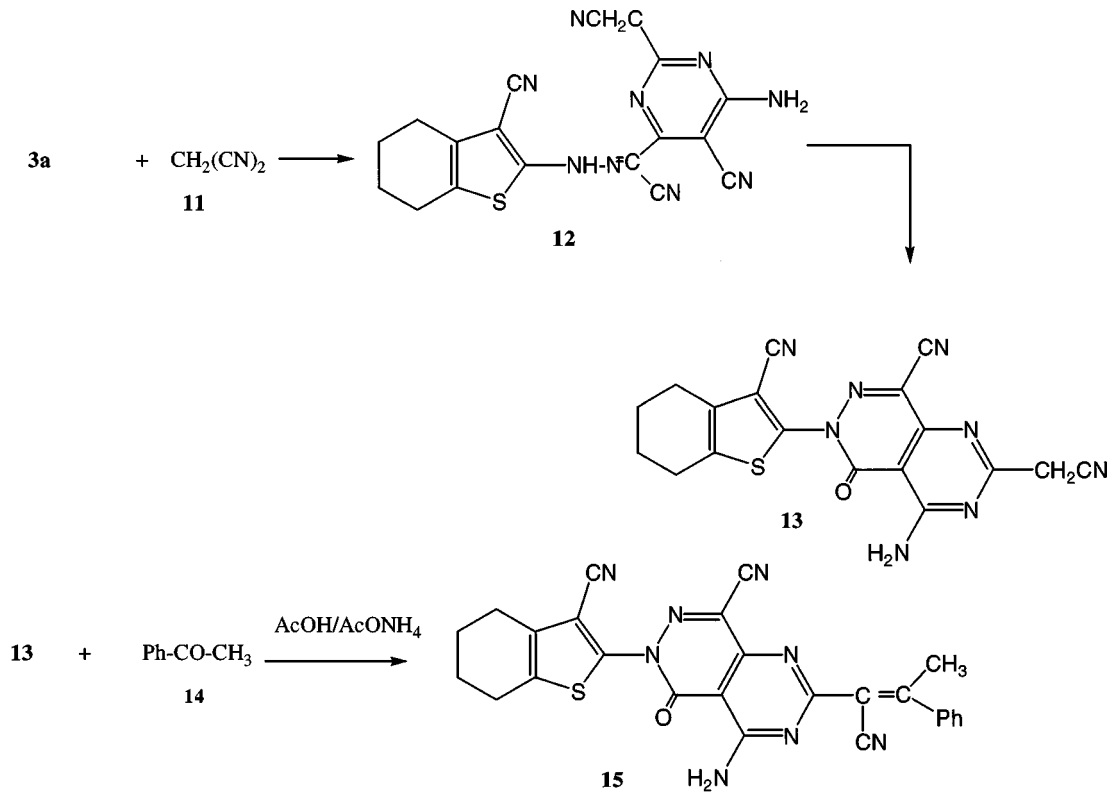
The reactions of **3a** and **3b** with phenyl isothiocyanate gave the 1,2,3-triazine derivatives **7a** and **7b**, respectively (Scheme 2). Compound **7a** underwent ready cyclization when heated in sodium ethoxide solution to give the corresponding pyrido[2,3-*e*]-1,2,4-triazine derivative **8**. The structure of **8** was established on the basis of spectral data. Thus, the IR spectrum showed NH_2, NH stretchings at $\upsilon = 3465$–3355 cm^{-1} and two CN groups stretching at $\upsilon = 2225$ and 2220 cm^{-1}. Moreover, the ^{1}H NMR spectrum showed two multiplets at $\delta = 2.24$ and 2.36 for four CH_2 groups of the cyclohexene ring, a singlet at $\delta = 4.98$ for an NH_2 group, and a singlet at $\delta = 9.38$ for an NH group.

The reaction of **3a** with hydrazine hydrate gave the pyrazole derivative **9** (Scheme 2). The cyclization of compound **9** in sodium ethoxide solution gave a single product of molecular formula $C_{15}H_{15}N_9S$. Structure **10** was indicated for this product on the basis of analytical and spectral data (see experimental section).

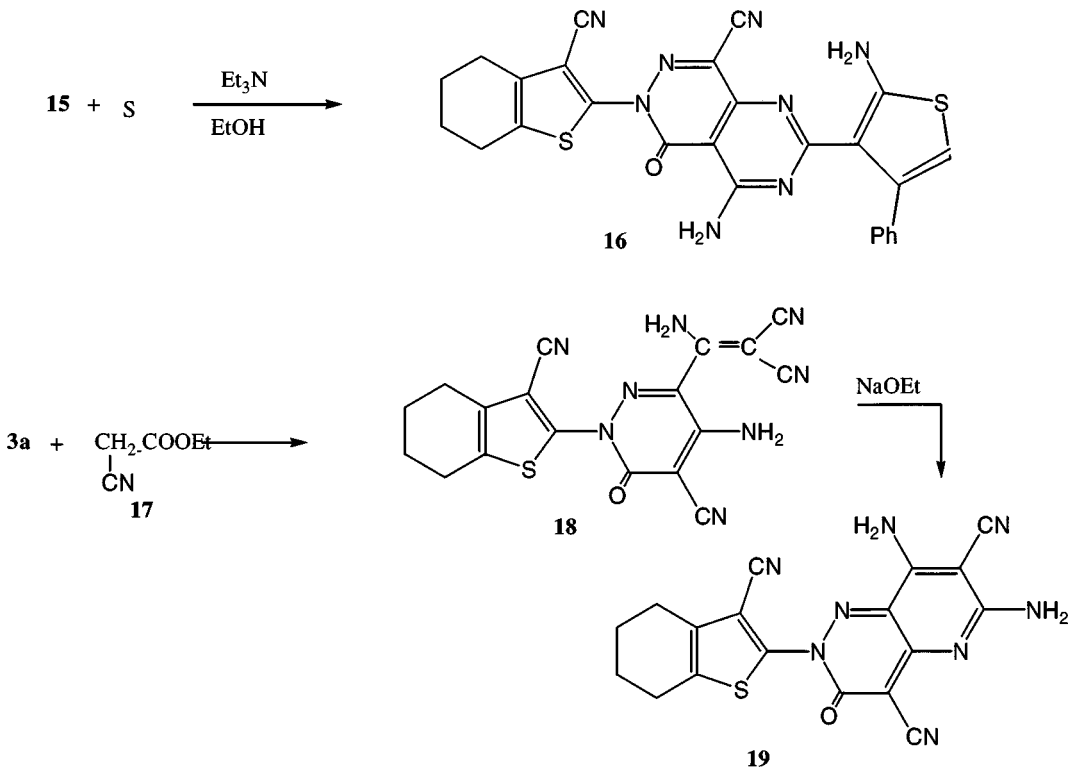
Compound **3a** reacted with malononitrile (**11**) to give the pyrimidine derivative **12**, which underwent ready cyclization in sodium ethoxide solution to give the pyrimido[5,4-*d*]pyridazine derivative **13** (Scheme 3). The structure of compound **13** was based on ^{13}C NMR data, which showed $\delta = 29.2$, 30.0 (cyclohexene C-1, C-4); 23.1, 24.5 (cyclohexene C-2, C-3); 62.2 (CH_2); 118.2, 119.0, 120.5 (3 CN); 124.4, 131.0, 133.6, 134.2, 134.9, 138.7, 138.9, 140.9, 144.1 (thiophene-C, pyridazine-C, and pyrimidine-C); 180.5 (C=O). Compound **13** reacted with acetophenone (**14**) in the presence of benzene/AcOH containing ammonium acetate to give the condensate product **15** (Scheme 3). The latter product reacted with sulfur in the presence of triethylamine to give the thiophene derivative **16** (Scheme 4). The structure of **16** was based on analytical and spectral data; thus, the IR spectrum of the reaction product showed two NH_2 stretchings at $\upsilon = 3472$–3363 cm^{-1}, two CN groups stretchings at $\upsilon = 2225$ and 2220 cm^{-1}, and the ^{1}H NMR spectrum showed two multiplets at $\delta = 2.33$ and 2.39 for four CH_2 groups of the cyclohexene ring, two singlets at $\delta = 4.75$ and 5.21 for two NH_2 groups, and a singlet at $\delta = 6.98$ for the thiazole H-5 proton.



SCHEME 2



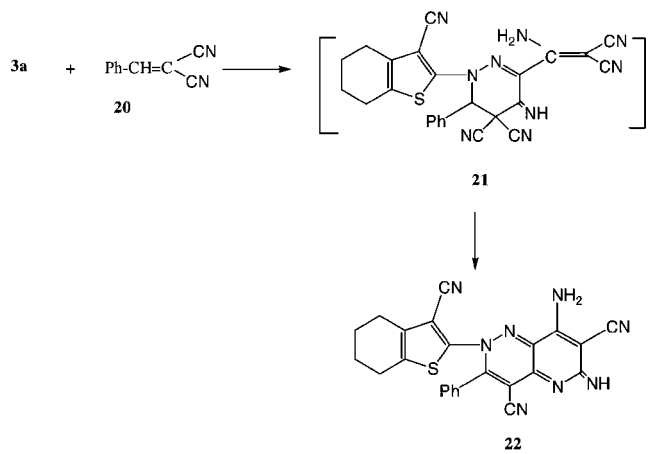
SCHEME 3



SCHEME 4

The reaction of **4a** with ethyl cyanocetate (**17**) gave the pyridazine derivative **18** (Scheme 4). Compound **18** underwent ready cyclization in sodium ethoxide solution to give the pyrido[2,1-*c*]pyridazine derivative **19**. Structures of compounds **18** and **19** were based on analytical and spectral data (see Experimental section).

The reaction of **3a** with α-cyanocinnamonitrile (**20**) gave the pyrido[2,3-*c*]pyridazine derivative **22** (Scheme 5). The reaction took place through the intermediate formation of **21**. The structure of the latter product was confirmed on the basis of analytical and spectral data (see Experimental section) (Table 1).



SCHEME 5

ANTIMICROBIAL ACTIVITY

The diverse biological activities of azole and azine derivatives prompted us to test and study the biological activities of some of the newly synthesized products. Their bactericidal and antifungal activities [16,17] were measured. A disc of blotting paper was impregnated with a known volume and an appropriate concentration of a compound to be tested, which was then placed on a sensitivity testing agar plate that was inoculated with the test organism. The compound diffused from the disc into the medium. The culture was examined for areas of no growth around the disc (zones inhibition) after overnight incubation. Growth of bacterial strains sensitive to a compound is inhibited at certain distances from the center of the disc whereas resistant strains grow up to the edge of the disc.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded for KBr disc on a Pye Unicam SP-1000

TABLE 1 In Vitro Bactericidal and Fungicidal Activity of Some of the Newly Synthesized Compounds

Compound No.	*Bacillus cerceus (Gram Positive)*	*Staphylococcus aureus (Gram Negative)*	*Escherichia coli (Gram Negative)*	*K. pneumonia (Gram Negative)*
3a	+++	++	+++	+
3b	+	+++	++	++
5	+++	++	++++	+
6	++	++	+++	+++
7a	+++	+	++	++
7b	++	++	++	++
8	+++	+++	+	++
9	++	++	+	++
10	+++	++	+++	++
12	++	+++	+++	+
13	+++	++	++	++
15	++	++	+	+++
16	+++	+++	+++	++
18	+	+++	++	+++
19	++	++	+++	+++
22	+	++	++	++

spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian EM390-300 MHz in CD_3SOCD_3 as solvent, using TMS as an internal standard, and chemical shifts are expressed as δ. Analytical data were obtained from the Microanalytical Data Unit at Cairo University, Giza, Egypt.

*3-Cyano-2-hydrazono-N-(a-cyano-b-aminocrotononitrile-y-ylideno)-4,5,6,7-tetrahydrobenzo-[b]thiophene (**3a**) and 3-Cyano-2-hydrazono-N-(a-cyano-b-ethoxycarbonyl-ethyl crotonate-y-ylideno)-4,5,6,7-tetrahydrobenzo[b]-thiophene (**3b**)*

General Procedure. To a clear solution of the diazonium salt of compound **1** [prepared by adding a cold solution of sodium nitrite (0.7 g, 0.01 mol in 10 ml water) to a cold solution of **1** in hydrochloric acid (10 ml) containing acetic acid (20 ml) with continuous stirring] either **2a** or **2b** was added. The reaction mixture in each case was stirred at 0°C for 3 h and the formed solid product, in each case, was collected by filtration.

3a: Buff crystals (from 1,4-dioxane), yield 72% (2.3 g), m.p. 110°C. IR (υ^-/cm^{-1}) = 3470–3320 (NH_2, NH); 2960 (CH_2); 2225–2220 (4 CN); 1650 (C=N); 1625 (C=C). ^{1}H NMR δ = 2.22, 2.87 (2m, 8H, 4CH_2); 4.89 (s, 2H, NH_2); 8.69 (s, br, 1H, NH). ^{13}C NMR δ = 29.5, 30.2 (cyclohexene C-1, C-4); 23.8, 24.9 (cyclohexene C-2, C-3); 58.4 (C=N); 102.9, 104.3 (C=C); 119.3, 119.8, 120.3, 120.7 (4 CN); 126.4, 132.0, 134.2, 138.7, (thiophene-C). $C_{15}H_{11}N_7S$ (321.36) = Calcd: C, 56.06; H, 3.45; N, 30.51; S, 9.98%, found: C, 56.46; H, 3.87; N, 30.99; S, 9.55%.

3b: Buff crystals (from 1,4-dioxane), yield 69% (2.9 g), m.p. 120°C. IR (υ^-/cm^{-1}) = 3480–3325 (NH_2, NH)); 2975, 2890 (CH_3, CH_2); 2225, 2220 (2 CN); 1705, 1680 (2 C=O); 1660 (C=N); 1638 (C=C). ^{1}H NMR δ = 1.34, 1.46 (2t, 6H, 2CH_3); 2.20, 2.862 (m, 8H, 4CH_2); 4.20, 4.24 (2q, 4H, 2CH_2); 5.31 (s, 2H, NH_2); 9.24 (s, br, 1H, NH). $C_{19}H_{21}N_5O_4S$ (415.47) = Calcd: C, 54.93; H, 5.10; N, 16.86; S, 7.72%, found: C, 56.46; H, 5.49; N, 16.54; S, 7.87%.

*2,4-Dicyano-3-amino-6-oxo-(4,5,6,7-tetrahydrobenzo[b]thieno[2,3:6,5]-pyridazino[6,1-a]pyrimidine (**5**) and 4-Amino-5-cyano-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thieno-2-yl)-3-ethoxycarbonyl-6-oxopyridazine (**6**)*

General Procedure. A solution of either **3a** (3.2 g, 0.01 mol) or **3b** (4.2, 0.01 mol) in ethanol (40 ml) containing sodium hydroxide (0.8 g, 0.02 mole) was heated under reflux for 2 h and then evaporated in vacuum. The remaining solid product was triturated with diethyl ether and then collected by filtration.

5: Pale yellow crystals (from acetic acid), yield 62% (2.0 g), m.p. > 300°C. IR (υ^-/cm^{-1}) = 3460, 3380 (NH_2); 2895 (CH_2); 2220, 2215 (2 CN); 1695 (C=O); 1670 (C=N); 1645 (C=C). ^{1}H NMR δ = 2.23, 2.76 (2m, 8H, 4CH_2); 5.51 (s, 2H, NH_2). $C_{15}H_{10}N_6OS$ (322.34) = Calcd: C, 55.89; H, 3.13; N, 26.07; S, 9.95%, found: C, 56.43; H, 3.45; N, 26.31; S, 9.62%.

6: Pale yellow crystals (from acetic acid), yield 59% (2.2 g), m.p. 185°C. IR (υ^-/cm^{-1}) = 3465–3380 (NH_2); 2970, 2885 (CH_2, CH_3); 2225, 2220 (2 CN); 1705, 1685 (2 C=O); 1670 (C=N); 1660 (C=C). ^{1}H NMR δ = 1.36 (t, 3H, CH_3); 2.24, 2.84 (2m, 8H, 4CH_2); 4.25 (q, 2H, CH_2); 5.30 (s, 2H, NH_2). $C_{17}H_{15}N_5O_3S$ (369.41) = Calcd: C, 55.13; H, 3.98; N, 18.91; S, 8.66%, found: C, 55.54; H, 3.98; N, 19.25; S, 8.98%.

*6-(α-Cyano-b-aminoacrylonitrilo-β-yl)-5-imino-4-phenyl-3-thioxo-2-(3-cyano-4,5,6,7-tetra-hydrobenzo[b]thieno-2-yl)-1,2,4-triazine (**7a**) and 6-(Ethyl α-cyano-β-amino-acrylat-β-yl)-5-oxo-4-phenyl-3-thioxo-2-(3-cyano-4,5,6,7-tetra-hydrobenzo[b]thieno-2-yl)-1,2,4-triazine (**7b**)*

General Procedure. To a solution of either **3a** (3.2 g, 0.01 mol) or **3b** (4.2 g, 0.01 mole) in ethanol (50 ml) containing triethylamine (0.5 ml), phenyl isothiocyanate was added. The reaction mixture was heated under reflux for 6 h. The solid product, formed in each case, upon cooling was collected by filtration.

7a: Yellowish brown crystals (from 1,4-dioxane), yield 65% (3.0 g), m.p. 140°C. IR (υ^-/cm^{-1} = 3465, 3355 (NH_2, NH); 3060 (CH aromatic); 2898 (CH_3, CH_2); 2225–2205 (3 CN); 1673 (exocyclic C=N); 1635 (C=C); 1200–1192 (C=S). ^{1}H NMR δ = 2.26, 2.75 (2m, 8H, 4CH_2); 4.84 (s, 2H, NH_2); 7.30–7.37 (m, 5H, C_6H_5); 9.22 (s, br, 1H, NH). $C_{22}H_{16}N_8S_2$ (456.54) = Calcd: C, 57.88; H, 3.53; N, 24.54; S, 14.10%, found: C, 57.46; H, 3.49; N, 24.34; S, 14.31%.

7b: Yellow crystals (from 1,4-dioxane), yield 73% (3.7 g), m.p. 130°C. IR (υ^-/cm^{-1}) = 3480, 3350 (NH_2); 3055 (CH aromatic); 2983, 2890 (CH_3, CH_2); 2225, 2210 (2 CN); 1703, 1685 (2 C=O); 1665 (C=N); 1640 (C=C); 1210–1195 (C=S). ^{1}H NMR δ = 1.13 (t, 3H, CH_3); 2.25, 2.72 (2m, 8H, 4CH_2); 4.29 (q, 2H, CH_2); 4.92 (s, 2H, NH_2); 7.34–7.39 (m, 5H, C_6H_5). $C_{24}H_{20}N_6O_3S_2$ (504.34) = Calcd: C, 57.13; H, 4.10; N, 16.66; S, 12.71%, found: C, 57.01; H, 4.49; N, 16.79; S, 12.32%.

*4-Amino-7-cyano-6-imino-2-(3-cyano-4,5,6,7-tetra hydrobenzo[b]thieno-2-yl)-4-phenyl-3-thioxopyrido[2,3-e]-1,2,4-triazine (**8**), 2,4,5-Triamino-3-(3-cyano-4,5,6,7-tetrahydrobenzo-[b]thieno-2-az)-pyrazolo[3,4-b]pyridine (**10**), 7-Amino-3-cyano-5-cyanomethyleno-1-(3-cyano-4,5,6,7-tetrahydrobenzo-[b]thieno-2-yl)-8-oxopyrimidino [4,5-d]pyridazine (**13**), and 3,5-Diamino-4,7-dicyano-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thieno-2-yl)-8-oxopyridino-[3,2-c]pyridazine (**19**)*

A suspension of either **7a** (4.56 g, 0.01 mol), **9** (3.5 g, 0.01 mol), **12** (3.87 g, 0.01 mol), or **17** (3.8 g, 0.01 mol) in sodium ethoxide solution [prepared by dissolving sodium metal (0.46 g, 0.02 mol) in absolute ethanol (50 ml)] was heated in a boiling water bath for 2 h. The solid product, formed in each case, upon pouring the reaction mixture into ice/water containing hydrochloric acid, was collected by filtration.

8: Yellowish brown crystals (from 1,4-dioxane), yield 65% (3.0 g), m.p. 180°C. IR (υ^-/cm^{-1}) = 3465, 3355 (NH_2, NH); 3050 (CH aromatic); 2983, 2890 (CH_3, CH_2); 2225, 2220 (2 CN); 1670 (exocyclic C=N); 1638 (C=C); 1200–1190 (C=S). ^{1}H NMR δ = 2.24, 2.36 (2m, 8H, 4CH_2); 4.98 (s, 2H, NH_2); 7.32–7.39 (m, 5H, C_6H_5); 9.38 (s, br, 1H, NH). $C_{22}H_{16}N_8S_2$ (456.54) = Calcd: C, 57.88; H, 3.53; N, 24.54; S, 14.10%, found: C, 57.39; H, 3.21; N, 24.67; S, 14.45%.

10: Orange crystals (from acetic acid), yield 66% (2.3 g), m.p. 230°C. IR (υ^-/cm^{-1} = 3490, 3345 (3 NH_2); 2890 (CH_2); 2220 (CN); 1655 (C=N); 1634 (C=C); 1580 (N=N). ^{1}H NMR δ = 2.26, 2.66 (2m, 8H, 4CH_2), 4.35, 4.98–5.09 (3s, 6H, 3NH_2); 6.99 (s, 1H, pyridine H-3). $C_{15}H_{15}N_9S$ (353.35) = Calcd: C, 50.99; H, 4.28; N, 35.68; S, 9.07%, found: C, 50.76; H, 4.58; N, 35.46; S, 9.45%.

13: Yellowish brown crystals (from ethanol), yield 64% (2.4 g), m.p. 240°C. IR (υ^-/cm^{-1}) = 3460, 3345 (NH_2); 2895 (CH_2); 2225, 2220–2215 (3 CN); 1685 (C=O); 1665 (C=N); 1645 (C=C). ^{1}H NMR δ = 2.21, 2.72 (2m, 8H, 4CH_2); 3.82 (s, 2H, CH_2); 5.48 (s, 2H, NH_2). ^{13}C NMR δ = 29.2, 30.0 (cyclohexene C-1, C-4); 23.1, 24.5 (cyclohexene C-2, C-3); 62.2 (CH_2); 118.2, 119.0, 120.5 (3 CN); 124.4, 131.0, 133.6, 134.2, 134.9, 138.7, 138.9, 140.9, 144.1 (thiophene-C, pyridazine-C, and pyrimidine-C); 180.5 (C=O). $C_{18}H_{12}N_8OS$ (388.41) = Calcd: C, 55.66; H, 3.11; N, 28.85; S, 8.25%, found: C, 55.22; H, 3.57; N, 28.34; S, 8.58%.

19: Pale yellow crystals (from ethanol), yield 71% (2.8 g), m.p. > 300°C. IR (υ^-/cm^{-1}) = 3460, 3340 (2 NH_2); 2865 (CH_2); 2225–2210 (3 CN); 1687 (C=O); 1655 (C=N); 1638 (C=C). ^{1}H NMR δ = 2.29, 2.70 (2m, 8H, 4CH_2); 4.81, 5.36 (2s, 4H, 2NH_2). ^{13}C NMR data which showed δ 29.3, 30.7 (cyclohexene C-1, C-4); 23.6, 24.8 (cyclohexene C-2, C-3); 118.7, 119.4, 121.0 (3 CN); 123.9, 131.9, 134.0, 134.2, 134.6, 137.8, 138.4, 140.3, 144.4, 146.6 (thiophene-C, pyridazine-C, and pyridine-C); 178.9 (C=O). $C_{18}H_{12}N_8OS$ (388.41) = Calcd: C, 55.66; H, 3.10; N, 28.85; S, 8.25%, found: C, 55.33; H, 3.29; N, 30.06; S, 8.11%.

*3-Cyano-2-hydrazono-N-[β-(aminopropiono-nitrile-a-ylideno)-β-(2,5-di-aminopyrazolo-2-ylidino)]-4,5,6,7-tetrahydrobenzo[b]thiophene (**9**)*

A solution of **3a** (3.2 g, 0.01 mol) in 1,4-dioxane (70 ml) was treated with hydrazine hydrate (0.5 g, 0.01 mol). The reaction mixture was heated under reflux for 6 h and then poured into ice/water containing a few drops of hydrochloric acid. The solid product formed upon stirring overnight was collected by filtration.

9: Buff crystals (from ethanol), yield 68% (2.3 g), m.p. 110°C. IR (υ^-/cm^{-1}) = 3468, 3340 (3 NH_2, NH); 2890 (CH_2); 2225, 2220 (2 CN); 1660 (C=N); 1640

(C=C). ^{1}H NMR $\delta = 2.23$, 2.64 (2m, 8H, $4CH_2$); 4.45, 4.85–5.01 (3s, 6H, $3NH_2$); 8.99 (s, br, 1H, NH). $C_{15}H_{15}N_9S$ (353.41) = Calcd: C, 51.10; H, 4.28; N, 35.67; S, 9.07%, found: C, 51.34; H, 4.02; N, 35.29; S, 9.35%.

*3-Cyano-2-hydrazonoacetonitrilo-α-(6-amino-5-cyano-2-cyanomethleno-4-yl)-4,5,6, 7-tetrahydrobenzo[b]thiophene (**12**)*

A solution of **3a** (3.2 g, 0.01 mol) in 1,4-dioxane (50 ml) containing a catalytic amount of triethylamine (0.5 ml) was treated with malononitrile (**11**) (0.66 g, 0.01 mol). The reaction mixture was heated under reflux for 8 h and then left to cool. The formed solid product was collected by filtration.

12: Yellowish brown crystals (from ethanol), yield 64% (2.4 g), m.p. 240°C. IR (υ^-/cm^{-1}) = 3466, 3320 (NH_2, NH); 2888 (CH_2); 2225, 2220–2215 (4 CN); 1665 (C=N); 1645 (C=C). ^{1}H NMR $\delta = 2.21$, 2.72 (2m, 8H, $4CH_2$); 3.82 (s, 2H, CH_2); 5.48 (s, 2H, NH_2). $C_{18}H_{13}N_9S$ (387.38)-Calcd: C, 55.63; H, 3.64; N, 28.83; S, 8.19%, found: C, 55.41; H, 3.91; N, 28.64; S, 8.28%.

*7-Amino-3-cyano-5-(b-phenylcrotononitrilo-a-yl)-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thieno-2-yl)-10-oxopyrimidino[4,5-d]pyridazine (**15**)*

Equimolar amounts of **13** (3.88 g, 0.01 mol) and acetophenone (**14**) (1.2 g, 0.01 mol) in benzene (50 ml) containing acetic acid (15 ml) and ammonium acetate (1.40 g, 0.02 mol) were heated under reflux for 5h, the eliminated water was separated, and then the organic mixture was evaporated in vacuum. The residual product was triturated with ethanol, and the formed solid product was collected by filtration.

15: Orange crystals (from ethanol), yield 58% (2.9 g), m.p. 220°C. IR (υ^-/cm^{-1}) = 3465, 3420 (NH_2); 3065 (CH aromatic); 2975, 2880 (CH_3, CH_2); 2225–2215 (3 CN); 1685 (C=O); 1665 (C=N); 1630 (C=C). ^{1}H NMR $\delta = 2.24$, 2.66 (2m, 8H, $4CH_2$); 2.88 (s, 3H, CH_3); 5.39 (s, 2H, NH_2), 7.31–7.38 (m, 5H, C_6H_5). $C_{26}H_{18}N_8OS$ (490.54) = Calcd: C, 63.66; H, 3.71; N, 22.84; S, 6.26%, found: C, 63.97; H, 3.45; N, 22.67; S, 6.26%.

*7-Amino-3-cyano-5-(2-amino-4-phenylthieno-3-yl)-1-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thieno-2-yl)-8-oxopyrimidino[4,5-d]pyridazine (**16**)*

A mixture of **15** (4.9 g, 0.01 mol) and sulfur (0.32 g, 0.01 mol) in ethanol 950 ml) containing triethylamine (0.5 ml) was heated under reflux for 4 h and then left to cool. The formed solid product was collected by filtration.

16: Pale yellow crystals (from ethanol), yield 73% (3.8 g), m.p. 190°C. IR (υ^-/cm^{-1}) = 3472–3363 (2 NH_2); 3065 (CH aromatic); 2860 (CH_2); 2225, 2220 (2 CN); 1685 (C=O); 1660 (C=N); 1630 (C=C). ^{1}H NMR $\delta = 2.33$, 2.39 (2m, 8H, $4CH_2$); 4.75, 5.21 (2s, 4H, $2NH_2$); 6.98 (s, 1H, thiazole H-5); 7.32–7.41 (m, 5H, C_6H_5). $C_{26}H_{18}N_8OS_2$ (522.60) = Calcd: C, 59.76; H, 3.47; N, 21.44; S, 12.27%, found: C, 57.34; H, 3.01; N, 21.78; S, 12.33%.

*3-Cyano-2-[5-amino-4-cyano-6-(α-cyano-b-aminoacrylonitrilo-β-yl)-3-oxopyridazine-2-yl] (**18**)*

A solution of **3a** (3.2 g, 0.01 mol) in dimethylformamide (20 ml) containing a catalytic amount of triethylamine (0.5 ml) was treated with ethyl cyanoacetate (**17**) (1.13 g, 0.01 mol). The reaction mixture was heated under reflux for 4 h and then left to cool. The solid product formed upon pouring the mixture into ice/water containing a few drops of hydrochloric acid was collected by filtration.

18: Yellowish brown crystals (from 1,4-dioxane), yield 65% (3.0 g), m.p. 180°C. IR (υ^-/cm^{-1}) = 3460, 3340 (2 NH_2); 2865 (CH_2); 2225–2215 (4 CN); 1680 (C=O); 1655 (C=N); 1630 (C=C). ^{1}H NMR $\delta = 2.27$, 2.72 (2m, 8H, $4CH_2$); 4.99, 5.45 (2s, 4H, $2NH_2$). $C_{18}H_{12}N_8OS$ (388.41) = Calcd: C, 55.66; H, 3.10; N, 28.85; S, 8.25%, found: C, 55.45; H, 3.35; N, 28.98; S, 8.45%.

*3-Amino-4,7-dicyano-6-imino-1-(3-cyano-4,5,6, 7-tetrahydrobenzo[b]thieno-2-yl)-8-phenylpyridino[3,2-c]pyridazine (**22**)*

A solution of **3a** (3.2 g, 0.01 mol) in dimethylformamide (20 ml) containing a catalytic amount of triethylamine (0.5 ml) was treated with α-cyanocinnamonitrile (**26**), and the reaction mixture was heated under reflux for 4 h and then left to cool. The solid product formed upon pouring the reaction mixture into ice/water mixture was collected by filtration.

22: Pale brown crystals (from acetic acid), yield 61% (2.7 g), m.p. 110°C. IR (υ^-/cm^{-1} = 3465, 3360 (NH_2, NH); 3058 (CH aromatic); 2890 (CH_2); 2225, 2210 (3 CN); 1670 (exocyclic C=N); 1638 (C=C). ^{1}H NMR $\delta = 2.24$, 2.70 (2m, 8H, $4CH_2$); 4.89 (s, 2H, NH_2); 7.32–7.39 (m, 5H, C_6H_5); 9.38 (s, br, 1H, NH). $C_{24}H_{16}N_8S$ (448.54) = Calcd: C, 64.28; H, 3.57; N, 25.00; S, 7.14%, found: C, 64.50; H, 3.21; N, 24.76; S, 7.24%.

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