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Thiophenylhydrazonoacetates in Heterocyclic Synthesis

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ABSTRACT: *Benzo[b]thiophen-2-yl-hydrazonoesters* **4** *were synthesized by coupling of 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (***1***) with either ethyl cyanoacetate or ethyl acetoacetate. The reactivity of* **4** *toward a variety of nitrogen nucleophiles was investigated to yield pyrazole, isoxazole, pyrimidine, triazine, pyrazolopyridine, and pyrazolopyrimidine derivatives.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:15–20, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10205

INTRODUCTION

Over recent years, there has been an increasing interest in the chemistry of thiophenes because of their biological significance. Many of them have been widely investigated for therapeutic uses, especially as antifungal [1,2], antibacterial [3], anti-inflammatory [4], anticonvulsant [5], antiasthmatic [6], and analgesic [7] agents. They also were known to show anti-HIV [8], antiproliferative [9], germicidal [10], and D2 dopaminergic [11] activities. Moreover, they were reported to act as selective type 4 phosphodiesterase inhibitors [12], inhibitors of the response to oxytocin [13], and high-affinity retinoic acid receptor antagonists [14]. As a continuation of our systematic investigations dealing with application of 2-aminothiophenes in the synthesis of polyfunctionally substituted heterocycles [15–18], we have decided to synthesize a series of novel tetrahydrobenzo[*b*]thiophene-3-carboxamide derivatives with potential wide spectrum of bioresponses.

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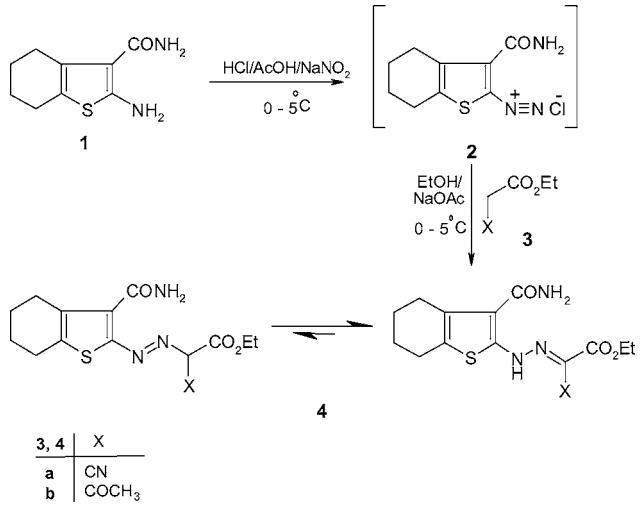
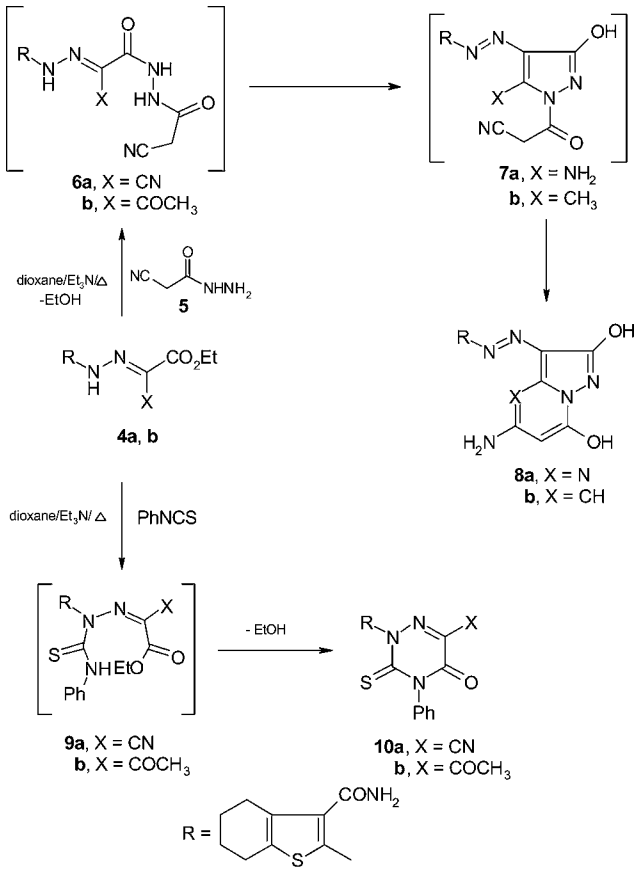
RESULTS AND DISCUSSION

2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**1**), required for the synthesis of the title precursors **4**, was prepared by condensation of cyclohexanone, elemental sulfur, and cyanoacetamide as described [19]. The β-enaminoamide **1**, in which an amino group is adjacent to the electron-withdrawing amide group, could be easily diazotized [20,21] to afford the diazonium salt **2**. Coupling of **2** with either ethyl cyanoacetate (**3a**) or ethyl acetoacetate (**3b**) afforded **4a,b**, respectively, in good yields (Scheme 1). Elemental analyses and spectral data studies were used to establish both structures. The IR spectrum of **4a** revealed the presence of NH_2 and NH groups stretching at 3419–3197 cm^{-1}, CN group stretching at 2220 cm^{-1}, and two C=O groups stretching at 1718 and 1664 cm^{-1}. Also, its ^1H NMR spectrum showed, besides the expected signals for the tetrahydrobenzo[*b*]thiophene moiety, a triplet at δ 1.32 ppm due to ester CH_3 group, a quartet at δ 4.13 ppm for ester CH_2 group, and two D_2O-exchangeable singlets at δ 6.53 (2H) and δ 8.29 (1H) ppm corresponding to NH_2 and



SCHEME 1



SCHEME 2

NH protons, respectively. The IR spectrum of **4b** indicated the presence of bands for NH_2, NH, and three C=O groups. The ^{1}H NMR spectrum was also in accordance with the proposed structure (see Experimental section).

The behavior of **4a,b** toward cyanoacetohydrazide (**5**) was examined with respect to the synthesis of pyrazoloazines (Scheme 2). Compound **4a** reacted with **5** in refluxing 1,4-dioxane containing a catalytic amount of triethylamine, to yield a single product. Structure **8a** could be assigned for it based on analytical and spectral data. Thus, its IR spectrum showed the absence of any CN stretching absorption that might be expected to appear at the range of ν 2210–2225 cm^{-1}, while it showed only the presence of one C=O group stretching at 1666 cm^{-1}. Additionally, its ^{1}H NMR spectrum showed the presence of a pyrimidine H-5 proton at δ 7.41 ppm together with four D_2O-exchangeable singlets at δ 5.55 (2H), δ 6.22 (2H), δ 8.99 (1H), and δ 0.98 (1H) ppm corresponding to two NH_2 and two OH protons, respectively, besides the expected signals for the tetrahydrobenzene moiety. We suggest a mechanism for the formation of **8a** in which the intermediate **6a** is obtained first. Then, an internal nucleophilic attack by the NH group on the cyano group takes place, accompanied by a migration of both of the two NH protons to the negatively charged nitrogen atom to yield the nonisolable aminocyanoacetylpyrazole derivative **7a**. The latter can cyclize also via nucleophilic attack by the NH_2 group on the cyano group of cyanoacetyl moiety, forming the final isolable pyrazolopyrimidine derivative **8a**. Similarly, **4b** reacted with **5** to afford **8b**, most likely formed via intermediacy of **6b** and **7b**. Assignment of structure **8b** was based on analytical and spectral data. Thus, its IR spectrum revealed the presence of absorption at ν 3520–3205 owing to the stretching vibrations of the two OH and two NH_2 functions as well as only one stretching absorption peak at ν 1663 for the C=O function. Moreover, its ^{1}H NMR spectrum exhibited, in addition to the expected agreeable signals, the presence of two pyridine H-3 and H-5 protons at δ 7.12 and 7.25 ppm, together with four D_2O-exchangeable protons at δ 5.12 (2H), δ 6.41 (2H), δ 9.10 (1H), and δ 11.09 (1H) ppm corresponding to two NH_2 and two OH groups, respectively. The latter reactions constitute a facile and convenient one-pot reaction leading to fused heterocyclic derivatives, which are otherwise difficult to access.

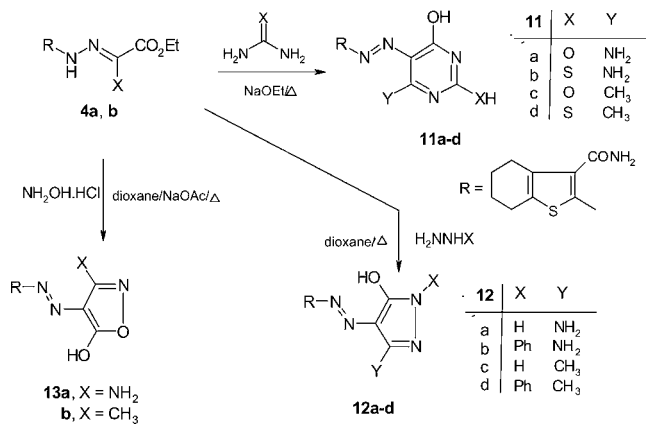
The behavior of **4** toward phenyl isothiocyanate was also studied with respect to the synthesis of highly substituted triazines. Thus, **4a,b** reacted with phenyl isothiocyanate, in refluxing 1,4-dioxane-triethylamine solutions, to afford the corresponding 1,2,4-triazine derivatives **10a,b** (Scheme 2). Compound **10** was assumed to be formed via an initial nucleophilic attack by the NH group in **4** on the isothiocyanate moiety, affording the adducts **9**, which cyclized via ethanol elimination. The structures

of **10a,b** were assigned on the basis of their elemental analyses and spectral data. Thus, the IR spectrum of **10a** indicated the presence of NH_2 group stretching at 3370 and 3200 cm^{-1}, CN group stretching at 2218 cm^{-1}, and two C=O groups stretching at 1708 and 1664 cm^{-1}. Moreover, its ^1H NMR spectrum showed, besides the expected signals, a multiplet at δ 7.21–7.42 ppm for C_6H_5 protons.

The reaction of **4a,b** with equimolar amounts of urea or thiourea, in refluxing ethanolic sodium ethoxide solutions, provided the corresponding 4-hydroxypyrimidines **11a–d** (Scheme 3). Similarly, compounds **4a,b** reacted with equimolar amounts of hydrazine hydrate (98%) or phenylhydrazine, in refluxing 1,4-dioxane, to afford the corresponding 4-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)azo]-5-hydroxypyrazole derivatives **12a–d**. Analogous synthesis of pyrimidines and pyrazoles, from 3-oxonitriles and 1,3-dicarbonyl compounds, has been reported previously [22,23]. The structures of the latter products were based on analytical and spectral data (see Experimental section). Reaction of **4a,b** with hydroxylamine hydrochloride, in refluxing 1,4-dioxane containing sodium acetate solutions, afforded the 4-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)azo]-5-hydroxy-isoxazoles **13a,b** (Scheme 3). The structures of the latter products were based on analytical and spectral data. Thus, the ^1H NMR spectrum of **13b** exhibited, besides the expected signals, two D_2O-exchangeable singlets at δ 7.17 (2H) and δ 9.87 (1H) ppm corresponding to NH_2 and OH protons, respectively.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam Sp-1000 spectrophotometer. ^1H NMR spectra were obtained on a Varian EM-390 90 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts δ are expressed in ppm. 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (**1**) was prepared according to the literature procedure [19].



SCHEME 3

*Ethyl α-(3-Carbamoyl-4,5,6,7-tetrahydrobenzo-[b]thiophen-2-yl-hydrazono)cyanoacetate (**4a**) and Ethyl α-(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl-hydrazono)acetoacetate (**4b**)*

Compound **1** (0.05 mol) was dissolved in concentrated hydrochloric acid (100 ml) containing glacial acetic acid (15 ml) by warming and the solution was then cooled to 0–5°C. Sodium nitrite (0.05 mol) in water (10 ml) was then added to this solution dropwise with vigorous stirring, during about 2 h, while cooling at 0–5°C. The clear diazonium salt solution was then added dropwise to a solution of ethyl cyanoacetate (**3a**) or ethyl acetoacetate (**3b**) (0.05 mol) in ethanol (50 ml) containing sodium acetate (4 g) at 0–5°C. The pH of the coupling mixture, in each case, was maintained at 5–6 through the coupling process by adding sodium acetate. After the complete addition of the diazonium salt, the reaction mixture was stirred at room temperature overnight. The precipitated products separated upon dilution with cold water (50 ml) were filtered off, washed with water several times, dried, and crystallized from the proper solvents.

4a: Yellow crystals (from 1,4-dioxane–H_2O), yield 69% (11.04 g), m.p. 115°C. IR ν (cm^{-1}) = 3419–3197 (NH_2, NH), 2970–2862 (CH_3, CH_2), 2220 (CN), 1718, 1664 (2C=O), 1630 (C=N). ^1H NMR δ = 1.32 (t, 3H, CH_3), 1.64–2.04 (m, 4H, 2H-5, 2H-6), 2.25–2.82 (m, 4H, 2H-4, 2H-7), 4.13 (q, 2H, CH_2), 6.53 (s, 2H, NH_2, D_2O-exchangeable), 8.29 (s, 1H, NH, D_2O-exchangeable). $C_{14}H_{16}N_4O_3S$ (320.35): Calcd: C, 52.49; H, 5.02; N, 17.48; S, 10.00; Found: C, 52.3; H, 4.9; N, 17.5; S, 9.9.

4b: Reddish brown crystals (from EtOH), yield 64% (10.78 g), m.p. 86°C. IR ν (cm^{-1}) = 3421–3191 (NH_2, NH), 2965–2859 (CH_3, CH_2), 1719, 1680, 1663 (3C=O), 1628 (C=N). ^1H NMR δ = 1.29 (t, 3H, CH_3), 1.55–1.81 (m, 4H, 2H-5, 2H-6), 2.01–2.32 (m, 4H, 2H-4, 2H-7), 2.57 (s, 3H, CH_3CO), 4.20 (q, 2H, CH_2), 6.75 (s, 2H, NH_2, D_2O-exchangeable), 8.55 (s, 1H, NH, D_2O-exchangeable). $C_{15}H_{19}N_3O_4S$ (337.38): Calcd: C, 53.40; H, 5.67; N, 12.45; S, 9.50; Found: C, 53.4; H, 5.4; N, 12.1; S, 9.4.

*5-Amino-3-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)azo]-2,7-dihydroxypyrazolo[1,5-a]pyrimidine (***8a***) and 5-Amino-3-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)azo]-2,7-dihydroxypyrazolo-[1,5-a]pyridine (***8b***)*

A mixture of equivalent amounts (0.005 mol) of **4a** or **4b** and **5**, in 1,4-dioxane (30 ml) containing a catalytic amount of Et_3N (0.5 ml), was heated under reflux for 8 h. The reaction mixture was cooled at room temperature, diluted with water, and acidified with dilute HCl (pH 6.5), whereby the resulting solid products were filtered off, dried, and crystallized from the proper solvents.

8a: Yellow crystals (from 1,4-dioxane), yield 59% (1.10 g), m.p. 189°C. IR ν (cm^{-1}) = 3530–3195 (2OH, $2NH_2$), 2933, 2856 (CH_2), 1666 (C=O), 1635 (C=N). ^{1}H NMR δ = 1.63–2.10 (m, 4H, $2CH_2$), 2.21–2.44 (m, 4H, $2CH_2$), 5.55 (s, 2H, NH_2, D_2O-exchangeable), 6.22 (s, 2H, NH_2, D_2O-exchangeable), 7.41 (s, 1H, CH), 8.99 (s, 1H, OH, D_2O-exchangeable), 10.98 (s, 1H, OH, D_2O-exchangeable). $C_{15}H_{15}N_7O_3S$ (373.37): Calcd: C, 48.25; H, 4.04; N, 26.25; S, 8.58; Found: C, 48.2; H, 3.9; N, 26.3; S, 8.4.

8b: Pale brown crystals (from DMF–H_2O), yield 54% (1.00 g), m.p. > 300°C. IR ν (cm^{-1}) = 3520–3205 (2OH, $2NH_2$), 2933, 2856 (CH_2), 1663 (C=O), 1630 (C=N). ^{1}H NMR δ = 1.52–2.00 (m, 4H, $2CH_2$), 2.21–2.45 (m, 4H, $2CH_2$), 5.12 (s, 2H, NH_2, D_2O-exchangeable), 6.41 (s, 2H, NH_2, D_2O-exchangeable), 7.12, 7.25 (2s, 2H, 2CH), 9.10 (s, 1H, OH, D_2O-exchangeable), 11.09 (s, 1H, OH, D_2O-exchangeable). $C_{16}H_{16}N_6O_3S$ (372.38): Calcd: C, 51.60; H, 4.32; N, 22.56; S, 8.61; Found: C, 51.5; H, 4.3; N, 22.3; S, 8.5.

*2-(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)-6-cyano–5-oxo-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine (***10a***) and 6-Acetyl-2-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-oxo-4-phenyl-3-thioxo-2,3,4,5-tetrahydro-1,2,4-triazine (***10b***)*

To a solution of equimolar amounts (0.005 mol) of **4a,b** and phenyl isothiocyanate, in 1,4-dioxane (30 ml), a catalytic amount of triethylamine (0.5 ml) was added. The reaction mixture was heated under reflux for 5 h, cooled at room temperature, poured onto cold water (50 ml), and neutralized with dilute HCl. The solid product that formed, in each case, was collected by filtration and crystallized from the proper solvent.

10a: Pale yellow crystals (from DMF–H_2O), yield 72% (1.47 g), m.p. 95°C. IR ν (cm^{-1}) = 3370, 3200 (NH_2), 3035 (CH aromatic), 2933, 2855 (CH_2), 2218 (CN), 1708, 1664 (2C=O), 1630 (C=N), 1195 (C=S). ^{1}H NMR δ = 1.65–2.03 (m, 4H, 2H-5, 2H-6), 2.23–2.70 (m, 4H, 2H-4, 2H-7), 6.51 (s, 2H, NH_2, D_2O-exchangeable), 7.21–7.42 (m, 5H, C_6H_5). $C_{19}H_{15}N_5O_2S_2$ (409.47): Calcd: C, 55.73; H, 3.68; N, 17.10; S, 15.66; Found: C, 55.5; H, 3.7; N, 16.9; S, 15.6.

10b: Pale yellow crystals (from 1,4-dioxane), yield 68% (1.45 g), m.p. 180°C. IR ν (cm^{-1}) = 3375, 3212 (NH_2), 3038 (CH aromatic), 2970–2864 (CH_3, CH_2), 1710, 1695, 1665 (3C=O), 1625 (C=N), 1195 (C=S). ^{1}H NMR δ = 1.61–1.85 (m, 4H, $2CH_2$), 2.00–2.34 (m, 4H, $2CH_2$), 2.59 (s, 3H, CH_3CO), 6.23 (s, 2H, NH_2, D_2O-exchangeable), 7.17–7.40 (m, 5H, C_6H_5). $C_{20}H_{18}N_4O_3S_2$ (426.49): Calcd: C, 56.32; H, 4.24; N, 13.13; S, 15.03; Found: C, 56.3; H, 4.0; N, 13.0; S, 14.9.

*6-Amino-5-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)azo]-2,4-dihydroxypyrimidine (***11a***) and 6-Amino-5-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)azo]-4-hydroxy-2-mercaptopyrimidine (***11b***)*

To a solution of **4a** (0.005 mol), in ethanolic sodium ethoxide solution (0.005 mol) [prepared by dissolving sodium metal (0.005 mol) in absolute ethanol (40 ml)], urea or thiourea (0.005 mol) was added. The reaction mixture was boiled, under reflux, for 7 h. The solvent was evaporated in vacuo, and the residue was triturated with cold water whereupon the solid that formed, in each case, was collected by filtration and crystallized from the proper solvent.

11a: Brown crystals (from DMF–H_2O), yield 60% (1.00 g), m.p. 185°C. IR ν (cm^{-1}) = 3510–3295 (2OH, $2NH_2$), 2933, 2856 (CH_2), 1665 (C=O), 1632 (C=N). ^{1}H NMR δ = 1.59–2.06 (m, 4H, $2CH_2$), 2.26–2.57 (m, 4H, $2CH_2$), 5.53 (s, 2H, NH_2, D_2O-exchangeable), 6.21 (s, 2H, NH_2, D_2O-exchangeable), 9.41 (s, 1H, OH, D_2O-exchangeable), 10.94 (s, 1H, OH, D_2O-exchangeable). $C_{13}H_{14}N_6O_3S$ (334.34): Calcd: C, 46.70; H, 4.21; N, 25.13; S, 9.59; Found: C, 46.5; H, 4.2; N, 24.8; S, 9.6.

11b: Pale brown crystals (from EtOH), yield 65% (1.14 g), m.p. 222°C. IR ν (cm^{-1}) = 3515–3302 (OH, $2NH_2$), 2933, 2858 (CH_2), 2555 (SH), 1663 (C=O), 1632 (C=N). ^{1}H NMR δ = 1.62–2.05 (m, 4H, $2CH_2$), 2.20–2.62 (m, 4H, $2CH_2$), 3.54 (s, 1H, SH, D_2O-exchangeable), 5.31 (s, 2H, NH_2, D_2O-exchangeable), 6.35 (s, 2H, NH_2, D_2O-exchangeable), 9.70 (s, 1H, OH, D_2O-exchangeable). $C_{13}H_{14}N_6O_2S_2$ (350.40): Calcd: C, 44.56; H, 4.02; N, 23.98; S, 18.30; Found: C, 44.5; H, 3.9; N, 23.8; S, 18.3.

*5-[(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)azo]-2,4-dihydroxy-6-methyl-pyrimidine (***11c***) and 5-[(3-Carbamoyl-4,5,6, 7-tetrahydrobenzo[b]thiophen-2-yl)azo]-4-hydroxy-2-mercapto-6-methylpyrimidine (***11d***)*

A solution of **4b** (0.005 mol), in ethanolic sodium ethoxide solution (0.005 mol) [prepared by dissolving sodium metal (0.005 mol) in absolute ethanol (40 ml)], was treated with urea or thiourea (0.005 mol). The reaction mixture was heated, under reflux, for 7 h and then left to cool. The solid products formed upon pouring onto ice/water containing few drops of hydrochloric acid were collected by filtration and crystallized from the appropriate solvents.

11c: Buff crystals (from 1,4-dioxane–H_2O), yield 61% (1.02 g), m.p. 230°C. IR ν (cm^{-1}) = 3520–3305 (2OH, NH_2), 2963, 2857 (CH_3, CH_2), 1666 (C=O), 1628 (C=N). ^{1}H NMR δ = 1.60–2.04 (m, 4H, $2CH_2$), 2.22–2.83 (m, 7H, CH_3, $2CH_2$), 7.12 (s, 2H, NH_2, D_2O-exchangeable), 9.10 (s, 1H, OH, D_2O-exchangeable), 10.51 (s, 1H, OH, D_2O-exchangeable). $C_{14}H_{15}N_5O_3S$ (333.35): Calcd: C, 50.44; H, 4.53; N, 21.00; S, 9.61; Found: C, 50.3; H, 4.5; N, 20.9; S, 9.5.

11d: Yellowish brown crystals (from DMF), yield 59% (1.03 g), m.p. 249°C. IR ν (cm^{-1}) = 3512–3294 (OH, NH_2), 2965–2859 (CH_3, CH_2), 2550 (SH), 1667 (C=O), 1625 (C=N). $C_{14}H_{15}N_5O_2S_2$ (349.41): Calcd: C, 48.12; H, 4.32; N, 20.04; S, 18.35; Found: C, 48.2; H, 4.3; N, 19.7; S, 18.1.

*3-Amino-4-[(3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)azo]-5-hydroxy-1H-pyrazole (***12a***) and 3-Amino-4-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)azo]-5-hydroxy-1-phenylpyrazole (***12b***)*

Equimolar amounts (0.005 mol) of **4a** and hydrazine hydrate or phenylhydrazine in 1,4-dioxane (30 ml) were heated, under reflux, for 6 h. The reaction mixture was concentrated in vacuo and then triturated with ethanol whereby the resulting solid products were collected by filtration and crystallized from DMF–H_2O.

12a: Yellow crystals (from DMF–H_2O), yield 73% (1.12 g), m.p. 160°C. IR ν (cm^{-1}) = 3520–3189 (OH, $2NH_2$, NH), 2933, 2856 (CH_2), 1665 (C=O), 1630 (C=N). ^{1}H NMR δ = 1.58–2.12 (m, 4H, $2CH_2$), 2.23–2.57 (m, 4H, $2CH_2$), 4.96 (s, 2H, NH_2, D_2O-exchangeable), 5.92 (s, 2H, NH_2, D_2O-exchangeable), 8.19 (s, 1H, NH, D_2O-exchangeable), 9.81 (s, 1H, OH, D_2O-exchangeable). $C_{12}H_{14}N_6O_2S$ (306.33): Calcd: C, 47.05; H, 4.60; N, 27.43; S, 10.46; Found: C, 46.8; H, 4.5; N, 27.4; S, 10.3.

12b: Orange crystals (from DMF–H_2O), yield 65% (1.24 g), m.p. 90°C. IR ν (cm^{-1}) = 3525–3207 (OH, $2NH_2$), 3030 (CH aromatic), 2933, 2857 (CH_2), 1664 (C=O), 1630 (C=N). $C_{18}H_{18}N_6O_2S$ (382.42): Calcd: C, 56.53; H, 4.73; N, 21.97; S, 8.38; Found: C, 56.5; H, 4.7; N, 21.8; S, 8.1.

*4-[(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)azo]-5-hydroxy-3-methyl-1H-pyrazole (***12c***) and 4-[(3-Carbamoyl-4,5,6, 7-tetrahydrobenzo[b]thiophen-2-yl)azo]-5-hydroxy-3-methyl-1-phenylpyrazole (***12d***)*

A solution of **4b** (0.005 mol), in 1,4-dioxane (30 ml), was treated with hydrazine hydrate or phenylhydrazine (0.005 mol). The reaction mixture was heated, under reflux, for 6 h and then poured onto ice-cold water. The solid products, formed upon standing at room temperature for 24 h, were isolated by filtration and crystallized from the proper solvents.

12c: Buff crystals (from DMF–H_2O), yield 67% (1.02 g), m.p. 138°C. IR ν (cm^{-1}) = 3526–3185 (OH, NH_2, NH), 2960–2859 (CH_3, CH_2), 1664 (C=O), 1628 (C=N). ^{1}H NMR δ = 1.61–2.05 (m, 4H, $2CH_2$), 2.24–2.82 (m, 7H, CH_3, $2CH_2$), 6.15 (s, 2H, NH_2, D_2O-exchangeable), 8.11 (s, 1H, NH, D_2O-exchangeable), 10.50 (s, 1H, OH, D_2O-exchangeable). $C_{13}H_{15}N_5O_2S$ (305.34): Calcd: C, 51.13; H, 4.94; N, 22.93; S, 10.50; Found: C, 51.0; H, 5.0; N, 22.7; S, 10.5.

12d: Orange red crystals (from 1,4-dioxane–H_2O), yield 58% (1.10 g), m.p. 170°C. IR ν (cm^{-1}) = 3518–3202 (OH, NH_2), 3022 (CH aromatic), 2965–2859 (CH_3, CH_2), 1663 (C=O), 1625 (C=N). ^{1}H NMR δ = 1.58–2.00 (m, 4H, $2CH_2$), 2.23–2.84 (m, 7H, CH_3, $2CH_2$), 6.49 (s, 2H, NH_2, D_2O-exchangeable), 7.21–7.47 (m, 5H, C_6H_5), 10.11 (s, 1H, OH, D_2O-exchangeable). $C_{19}H_{19}N_5O_2S$ (381.43): Calcd: C, 59.82; H, 5.01; N, 18.35; S, 8.40; Found: C, 59.8; H, 4.8; N, 18.2; S, 8.3.

*3-Amino-4-[(3-carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)azo]-5-hydroxyisoxazole (***13a***) and 4-[(3-Carbamoyl-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)azo]-5-hydroxy-3-methylisoxazole (***13b***)*

Equimolar amounts (0.005 mol) of **4a** or **4b** and hydroxylamine hydrochloride, in 1,4-dioxane (30 ml) containing sodium acetate (0.006 mol), were refluxed for 6 h. The reaction mixture was then cooled, poured onto cold water, and the precipitated solid, in each case, was filtered off, dried, and crystallized from the proper solvent.

13a: Pale yellow crystals (from AcOH–H_2O), yield 71% (1.09 g), m.p. 152°C. IR ν (cm^{-1}) = 3535–3222 (OH, $2NH_2$), 2933, 2856 (CH_2), 1668 (C=O), 1632 (C=N). ^1H NMR δ = 1.60–2.06 (m, 4H, $2CH_2$), 2.24–2.69 (m, 4H, $2CH_2$), 5.19 (s, 2H, NH_2, D_2O-exchangeable), 6.87 (s, 2H, NH_2, D_2O-exchangeable), 10.18 (s, 1H, OH, D_2O-exchangeable). $C_{12}H_{13}N_5O_3S$ (307.31): Calcd: C, 46.90; H, 4.25; N, 22.78; S, 10.43; Found: C, 46.6; H, 4.3; N, 22.5; S, 10.3.

13b: Orange red crystals (from DMF–H_2O), yield 75% (1.15 g), m.p. 240°C. IR ν (cm^{-1}) = 3510–3204 (OH, NH_2), 2970–2861 (CH_3, CH_2), 1667 (C=O), 1630 (C=N). ^1H NMR δ = 1.58–2.07 (m, 4H, $2CH_2$), 2.25–2.79 (m, 7H, CH_3, $2CH_2$), 7.17 (s, 2H, NH_2, D_2O-exchangeable), 9.87 (s, 1H, OH, D_2O-exchangeable). $C_{13}H_{14}N_4O_3S$ (306.33): Calcd: C, 50.97; H, 4.60; N, 18.28; S, 10.46; Found: C, 50.8; H, 4.5; N, 18.3; S, 10.4.

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