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Heterocyclic Synthesis with Ethyl α-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylhydrazono)acetates: An Expeditious Synthetic Approach to Polyfunctionally Substituted Pyran, Pyridine, and Pyridazine Derivatives

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ABSTRACT: *Ethyl α-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylhydrazono)acetates* **1** *were prepared and established as previously described by our research group. Their reactivity toward a variety of active methylene reagents was studied to give pyran, pyridine, and pyridazine derivatives.* © 2004 Wiley Periodicals, Inc. Heteroatom Chem 15:300–306, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20019

INTRODUCTION

Our long-term continuing interest in the chemistry of tetrahydrobenzo[*b*]thiophenes [1–7] forms a part of our systematic efforts to obtain pyridines, pyrimidines, pyridazines, thiophenes, and their analogs. The importance of such compounds is due to their diverse pharmaceutical activities including antibacterial [8,9], antidiabetic [10], anti-HIV [11], antiviral [12,13], and analgesic [14] activities. We have recently reported on the synthesis of the title precursors thiophenylhydrazonoesters **1** [15]. Such synthetic route proved to be an easy, facile, and sole approach for the synthesis of unique derivatives of pyrazoles, isoxazoles, pyrimidines, triazines, and their analogs including the tetrahydrobenzo[*b*]thiophene moiety. In this article, we have turned our attention to investigating the scope and applicability of those key precursors **1** for their heterocyclization with various active methylene compounds, with the aim of obtaining some hitherto unreported polyfunctionally substituted heterocycles with potential biological properties.

RESULTS AND DISCUSSION

The starting materials ethyl α-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylhydrazono)acetate derivatives **1a,b** were prepared as previously described in our earlier publication [15]. The reactivity of **1a,b** toward some active methylene reagents is studied. Thus, the behaviour of **1a,b** toward some

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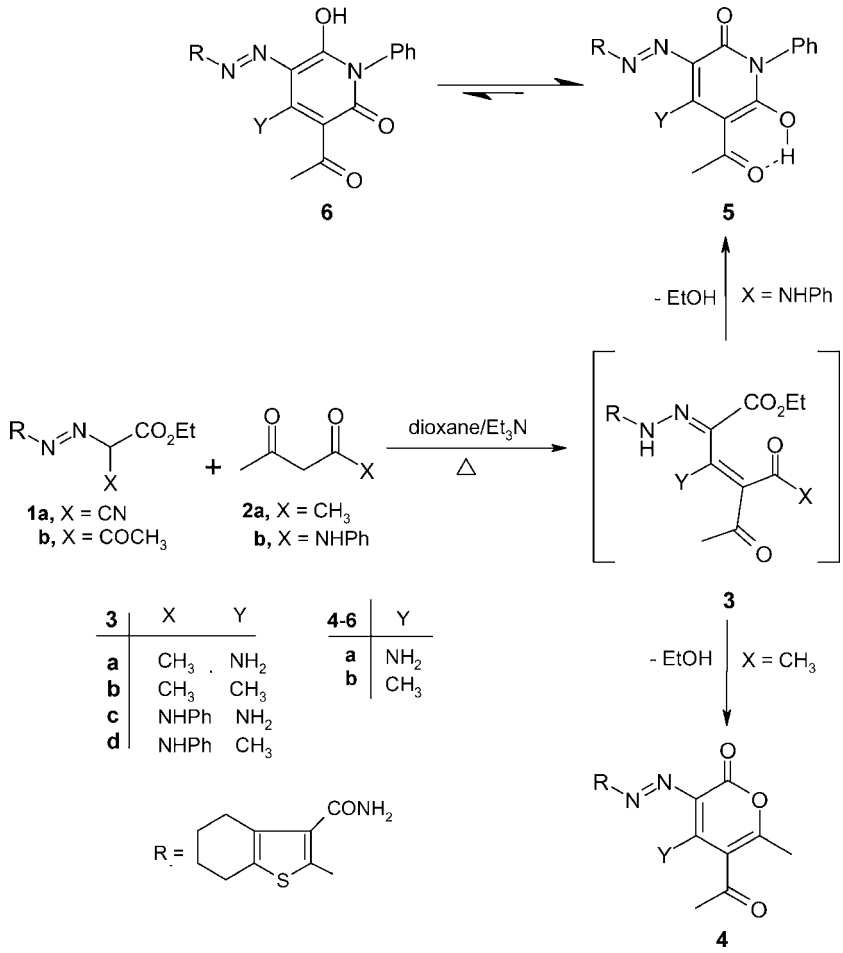
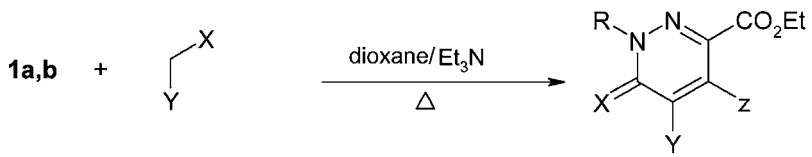
1,3-dicarbonyl compounds (**2a,b**; Scheme 1) was investigated with respect to the synthesis of highly substituted pyrans and pyridines. It was found that hydrazones**1a,b** reacted with equimolar amounts of acetylacetone (**2a**), upon boiling under reflux in 1,4-dioxane in the presence of triethylamine, to afford the corresponding 2*H*-pyran-2-one derivatives **4a,b**, respectively. Formation of the latter products is believed to be formed through the intermediacy of **3a,b** followed by intramolecular cyclization via loss of ethanol. Assignment of structures **4a,b** was confirmed on the basis of analytical and spectral data. Thus, e.g. the IR spectrum of **4a** showed the presence of two NH_2 groups stretching at 3410–3222 cm^{-1} as well as three CO groups stretching at 1702, 1687, and 1663 cm^{-1}. The ^1H NMR spectrum was also in accordance with the proposed structure. Similarly, the reaction of **1a,b** with acetoacetanilide (**2b**), under the same experimental conditions, yielded the corresponding 2-oxopyridine derivatives **5a,b**, respectively, via the intermediacy of **3c,d** followed by loss of ethanol (Scheme 1). The latter products were recommended to exist predominantly in the β-hydroxyketone form **5** rather than the β-diketone form **6** due to the existence of intramolecular H-bonding which has a stabilizing influence on these tautomers. Assignment of structures **5a,b** were based on analytical and spectral data (see Experimental section).

As an extension of such synthetic route, the behaviour of **1a,b** toward some other active methylene compounds (**7a–e**; Scheme 2) was also studied with the aim of synthesizing highly substituted pyridazines. Interestingly, the work has resulted in the development of convenient approaches for the synthesis of various polyfunctionally substituted ethyl 1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-1,6-dihydropyridazine-3-carboxylate derivatives **8a–j**, respectively, in reasonable yields. The importance of such pyridazine derivatives is due to their expected diverse pharmacological activities [16]. The identity of the product, in each case,

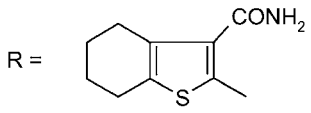


SCHEME 1



7	X	Y
a	CO_2Et	CN
b	CO_2Et	$COCH_3$
c	CO_2Et	COPh
d	CN	CN
e	$CSNH_2$	CN

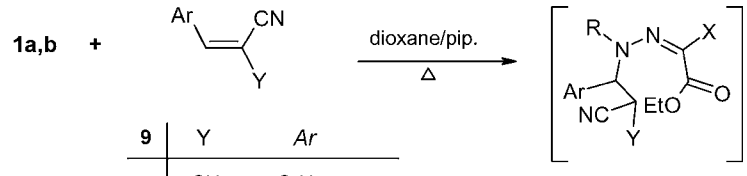
8	X	Y	Z
a	O	CN	NH_2
b	O	CN	CH_3
c	O	$COCH_3$	NH_2
d	O	$COCH_3$	CH_3
e	O	COPh	NH_2
f	O	COPh	CH_3
g	NH	CN	NH_2
h	NH	CN	CH_3
i	S	CN	NH_2
j	S	CN	CH_3



SCHEME 2

was established on the basis of its satisfactory elemental analyses and compatible spectral data (see Experimental section).

As a continuation of our study aimed at the synthesis of pyridazine derivatives with potential pharmacological activity [17], the behaviour of hydrazonoesters **1a,b** toward some α-substituted cinnamonitriles **9a–d** was examined. Thus, each of **1a,b** reacted with **9a–d**, in 1,4-dioxane-piperidine solutions, to give the corresponding oxopyridazine derivatives **11a–h**, respectively (Scheme 3). Formation of **11** is assumed to proceed via Michael-type addition of the NH of the hydrazone moiety in **1** to the activated α,β-unsaturated center in **9**, affording the acyclic Michael adducts **10** which spontaneously cyclize and aromatize to the final products **11** via elimination of an ethanol molecule and subsequent dehydrocyanation. A similar reaction has been reported previously [18–20]. Confirmation of the proposed structures **11a–h** was based on analytical and spectral data. As an example, the IR spectrum of **11a** (X = Y = CN; Ar = C_6H_5) revealed bands at 3350, 3209 (NH_2), 2216, 2210 (2CN), 1705, and 1666 cm^{-1} (2CO). Additionally, its ^1H NMR spectrum showed a singlet

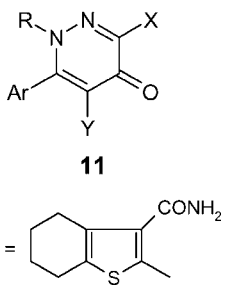


9	Y	*Ar*
a	CN	C_6H_5
b	CN	$C_6H_4OCH_3$-*p*
c	CO_2Et	C_6H_5
d	CO_2Et	$C_6H_4OCH_3$-*p*

10

- EtOH
- HCN

10,11	X	Y	*Ar*
a	CN	CN	C_6H_5
b	$COCH_3$	CN	C_6H_5
c	CN	CN	$C_6H_4OCH_3$-*p*
d	$COCH_3$	CN	$C_6H_4OCH_3$-*p*
e	CN	CO_2Et	C_6H_5
f	$COCH_3$	CO_2Et	C_6H_5
g	CN	CO_2Et	$C_6H_4OCH_3$-*p*
h	$COCH_3$	CO_2Et	$C_6H_4OCH_3$-*p*



11

SCHEME 3

at $\delta = 6.31$ ppm (D_2O exchangeable) for NH_2 protons and a multiplet at $\delta = 7.22$–7.41 ppm for phenyl protons.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal reference. Chemical shifts are expressed in δ ppm. Compounds **1a,b** were prepared according to the literature procedure [15].

Preparation of **4a,b** *and* **5a,b** *(General Procedure)*

Equimolar amounts (0.005 mol) of either **1a** or **1b** and either acetylacetone (**2a**) or acetoacetanilide (**2b**), in 1,4-dioxane (30 ml) containing a catalytic amount of Et_3N (0.5 ml), were heated under reflux for 7 h. The reaction mixture was concentrated in vacuo, whereupon the resulting solid product, in each case, was collected by filtration and crystallized from the proper solvent.

*5-Acetyl-4-amino-3-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)azo]-6-methyl-2H-pyran-2-ones (***4a***).* Pale orange crystals (from AcOH-H_2O), yield 71% (1.33 g), m.p. 197–200°C. IR (ν/cm^{-1}) = 3410–3222 ($2NH_2$), 2970–2862 (CH_3, CH_2), 1702, 1687, 1663 (3CO). ^{1}H NMR $\delta = 1.54$–1.81 (m, 4H, $2CH_2$), 2.05–2.50 (m, 7H, CH_3, $2CH_2$), 2.65 (s, 3H, CH_3CO), 5.12 (s, 2H, NH_2, exchangeable), 6.99 (s, 2H, NH_2, exchangeable). $C_{17}H_{18}N_4O_4S$ (374.40): Calcd: C, 54.53; H, 4.84; N, 14.96; S, 8.56; Found: C, 54.46; H, 4.77; N, 14.72; S, 8.41.

*5-Acetyl-3-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo-[b]thiophen-2-yl)azo]-4,6-dimethyl-2H-pyran-2-one (***4b***).* Yellowish brown crystals (form EtOH-H_2O), yield 60% (1.08 g), m.p. 192–195°C. IR (ν/cm^{-1}) = 3400, 3230 (NH_2), 2972–2860 (CH_3, CH_2), 1708, 1692, 1664 (3CO). ^{1}H NMR $\delta = 1.57$–1.88 (m, 4H, $2CH_2$), 2.00–2.55 (m, 10H, $2CH_3$, $2CH_2$), 2.66 (s, 3H, CH_3CO), 6.55 (s, 2H, NH_2, exchangeable). $C_{18}H_{19}N_3O_4S$ (373.41): Calcd: C, 57.89; H, 5.12; N, 11.25; S, 8.58; Found: C, 57.66; H, 5.07; N, 11.13; S, 8.57.

*5-Acetyl-4-amino-3-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)azo]-6-hydroxy-2-oxo-1-phenyl-1,2-dihydropyridine (***5a***).* Yellow crystals (from 1,4-dioxane-H_2O), yield 70% (1.58 g), m.p. 63–65°C. IR (ν/cm^{-1}) = 3530–3281 (OH, $2NH_2$), 3030 (CH aromatic), 2975–2868 (CH_3, CH_2), 1706, 1690, 1662 (3CO). ^{1}H NMR $\delta = 1.57$–1.89 (m, 4H, $2CH_2$), 2.00–2.32 (m, 4H, $2CH_2$), 2.60 (s, 3H, CH_3CO), 5.10 (s, 2H, NH_2, exchangeable), 6.13 (s, 2H, NH_2, exchangeable), 7.16–7.35 (m, 5H, C_6H_5), 10.12 (s, 1H, OH, exchangeable). $C_{22}H_{21}N_5O_4S$ (451.48): Calcd: C, 58.52; H, 4.68; N, 15.51; S, 7.10; Found: C, 58.38; H, 4.69; N, 15.52; S, 6.88.

*5-Acetyl-3-[(3-carbamoyl-4,5,6,7-tetrahydrobenzo-[b]thiophen-2-yl)azo]-6-hydroxy-4-methyl-2-oxo-1-phenyl-1,2-dihydropyridine (***5b***).* Pale brown crystals (from 1,4-dioxane-H_2O), yield 61% (1.37 g), m.p. 130–132°C. IR (ν/cm^{-1}) = 3520–3261 (OH, NH_2), 3022 (CH aromatic), 2970–2862 (CH_3, CH_2), 1704, 1687, 1664 (3CO). ^{1}H NMR $\delta = 1.60$–1.83 (m, 4H, $2CH_2$), 2.00–2.40 (m, 7H, CH_3, $2CH_2$), 2.65 (s, 3H, CH_3CO), 6.31 (s, 2H, NH_2, exchangeable), 7.14–7.36 (m, 5H,C_6H_5), 9.73 (s, 1H, OH, exchangeable). $C_{23}H_{22}N_4O_4S$ (450.49): Calcd: C, 61.32; H, 4.91; N, 12.43; S, 7.11; Found: C, 61.08; H, 4.88; N, 12.29; S, 7.12.

Preparation of **8a–j** *(General Procedure)*

A solution of each of **1a** or **1b** (0.005 mol), in 1,4-dioxane (30 ml) containing a catalytic amount of Et_3N (0.5 ml), was treated with the appropriate active methylene reagents **7a–e** (0.005 mol). The reaction mixture was boiled under reflux for 8 h, cooled at room temperature, poured over cold water and neutralized with dilute HCl. The obtained solid products were filtered off and crystallized from the proper solvents.

*Ethyl 4-amino-1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-cyano-6-oxo-1,6-dihydropyridazine-3-carboxylate (***8a***).* Pale yellow crystals (from 1,4-dioxane-H_2O), yield 57% (1.10 g), m.p. 144–148°C. IR (ν/cm^{-1}) = 3370–3200 ($2NH_2$), 2976–2865 (CH_3, CH_2), 2213 (CN), 1722, 1703, 1665 (3CO), 1627 (C=N). ^{1}H NMR $\delta = 1.38$ (t, 3H, CH_3), 1.58–2.05 (m, 4H, $2CH_2$), 2.27–2.53 (m, 4H, $2CH_2$), 4.30 (q, 2H, CH_2), 5.90 (s, 2H, NH_2, exchangeable), 6.41 (s, 2H, NH_2, exchangeable). $C_{17}H_{17}N_5O_4S$ (387.40): Calcd: C, 52.70; H, 4.41; N, 18.07; S, 8.27; Found: C, 52.73; H, 4.24; N, 17.94; S, 8.12.

*Ethyl 1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)-5-cyano-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (***8b***).* Yellow crystals (from EtOH), yield 69% (1.33 g), m.p. 154–155°C. IR (ν/cm^{-1}) = 3370, 3210 (NH_2), 2968–2859 (CH_3, CH_2), 2220 (CN), 1725, 1708, 1668 (3CO), 1635 (C=N). ^{1}H NMR $\delta = 1.35$ (t, 3H, CH_3), 1.61–2.06 (m, 4H, $2CH_2$),

2.22–2.79 (m, 7H, CH_3, $2CH_2$), 4.19 (q, 2H, CH_2), 6.81 (s, 2H, NH_2, exchangeable). $C_{18}H_{18}N_4O_4S$ (386.41): Calcd: C, 55.95; H, 4.69; N,14.49; S, 8.29; Found: C, 56.04; H, 4.47; N, 14.39; S, 8.14.

*Ethyl 5-acetyl-4-amino-1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (***8c***).* Pale brown crystals (from 1,4-dioxane-H_2O), yield 77% (1.51 g), m.p. 136–140°C. IR (ν/cm^{-1}) = 3390–3220 ($2NH_2$), 2969–2858 (CH_3, CH_2), 1730, 1709, 1685, 1665 (4CO), 1625 (C=N). ^{1}H NMR δ = 1.29 (t, 3H, CH_3), 1.65–2.01 (m, 4H, $2CH_2$), 2.27–2.42 (m, 4H, $2CH_2$), 2.63 (s, 3H, CH_3CO), 4.17 (q, 2H, CH_2), 5.99 (s, 2H, NH_2, exchangeable), 7.05 (s, 2H, NH_2, exchangeable). $C_{18}H_{20}N_4O_5S$ (404.42): Calcd: C, 53.45; H, 4.97; N,13.85; S, 7.92; Found: C, 53.17; H, 4.67; N, 13.69; S, 7.89.

*Ethyl 5-acetyl-1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (***8d***).* Pale yellow crystals (from AcOH-H_2O), yield 65% (1.31 g), m.p. 116–118°C. IR (ν/cm^{-1}) = 3366, 3215 (NH_2), 2970–2862 (CH_3, CH_2), 1725, 1705, 1683, 1665 (4CO), 1625 (C=N). ^{1}H NMR δ = 1.31 (t, 3H, CH_3), 1.62–2.01 (m, 4H, $2CH_2$), 2.20–2.52 (m, 7H, CH_3, $2CH_2$), 2.63 (s, 3H, CH_3CO), 4.17 (q, 2H, CH_2), 7.05 (s, 2H, NH_2, exchangeable). $C_{19}H_{21}N_3O_5S$ (403.43): Calcd: C, 56.56; H, 5.24; N, 10.41; S, 7.94; Found: C, 56.44; H, 5.04; N, 10.38; S, 7.69.

*Ethyl 4-amino-5-benzoyl-1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (***8e***).* Yellowish brown crystals (from DMF), yield 55% (1.28 g), m.p. 127–130°C. IR (ν/cm^{-1}) = 3405–3230 ($2NH_2$), 3030 (CH aromatic), 2970–2862 (CH_3, CH_2), 1735, 1710, 1695, 1662 (4CO), 1620 (C=N). ^{1}H NMR δ = 1.40 (t, 3H, CH_3), 1.60–2.05 (m, 4H, $2CH_2$), 2.22–2.64 (m, 4H, $2CH_2$), 4.27 (q, 2H, CH_2), 5.15 (s, 2H, NH_2, exchangeable), 6.27 (s, 2H, NH_2, exchangeable), 7.49–7.71 (m, 5H, C_6H_5). $C_{23}H_{22}N_4O_5S$ (466.49): Calcd: C, 59.21; H, 4.74; N, 12.00; S, 6.87; Found: C, 58.88; H, 4.57; N, 11.93; S, 6.67.

*Ethyl 5-benzoyl-1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (***8f***).* Yellowish brown crystals (from 1,4-dioxane-H_2O), yield 61% (1.42 g), m.p. 99–102°C. IR (ν/cm^{-1}) = 3380, 3225 (NH_2), 3030 (CH aromatic), 2972–2860 (CH_3, CH_2), 1733, 1707, 1690, 1666 (4CO), 1625 (C=N). ^{1}H NMR δ = 1.25 (t, 3H, CH_3), 1.62–2.00 (m, 4H, $2CH_2$), 2.25–2.85 (m, 7H, CH_3, $2CH_2$), 4.15 (q, 2H, CH_2), 6.21 (s, 2H, NH_2, exchangeable), 7.57–7.89 (m, 5H, C_6H_5). $C_{24}H_{23}N_3O_5S$ (465.50): Calcd: C, 61.92; H, 4.97; N, 9.02; S, 6.88; Found: C, 61.77; H, 4.79; N, 8.82; S, 6.79.

*Ethyl 4-amino-1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-cyano-6-imino-1,6-dihydropyridazine-3-carboxylate (***8g***).* Pale brown crystals (from EtOH), yield 68% (1.31 g), m.p. 169–171°C. IR (ν/cm^{-1}) = 3340–3178 ($2NH_2$, NH), 2975–2863 (CH_3, CH_2), 2212 (CN), 1717, 1664 (2CO), 1630 (C=N). ^{1}H NMR δ = 1.28 (t, 3H, CH_3), 1.63–1.82 (m, 4H, $2CH_2$), 2.01–2.44 (m, 4H, $2CH_2$), 4.18 (q, 2H, CH_2), 5.79 (s, 2H, NH_2, exchangeable), 7.01 (s, 2H, NH_2, exchangeable), 8.31 (br s, 1H, NH, exchangeable). $C_{17}H_{18}N_6O_3S$ (386.41): Calcd: C, 52.84; H, 4.69; N, 21.74; S, 8.29; Found: C, 52.44; H, 4.58; N, 21.47; S, 8.32.

*Ethyl 1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-cyano-6-imino-4-methyl-1,6-dihydropyridazine-3-carboxylate (***8h***).* Brown crystals (from EtOH), yield 62% (1.19 g), m.p. 140–143°C. IR (ν/cm^{-1}) = 3350–3183 (NH_2, NH), 2970–2861 (CH_3, CH_2), 2210 (CN), 1730, 1665 (2CO), 1624 (C=N). ^{1}H NMR δ = 1.41 (t, 3H, CH_3), 1.63–2.02 (m, 4H, $2CH_2$), 2.25–2.81 (m, 7H, CH_3, $2CH_2$), 4.27 (q, 2H, CH_2), 6.67 (s, 2H, NH_2, exchangeable), 8.76 (br s, 1H, NH, exchangeable). $C_{18}H_{19}N_5O_3S$ (385.42): Calcd: C, 56.09; H, 4.96; N, 18.16; S, 8.31; Found: C, 55.76; H, 5.03; N, 18.08; S, 8.16.

*Ethyl 4-amino-1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-cyano-6-thioxo-1,6-dihydropyridazine-3-carboxylate (***8i***).* Orange red crystals (from DMF-H_2O), yield 63% (1.27 g), m.p. 174–178°C. IR (ν/cm^{-1}) = 3380–3212 ($2NH_2$), 2970–2865 (CH_3, CH_2), 2212 (CN), 1715, 1665 (2CO), 1630 (C=N), 1190 (C=S). ^{1}H NMR δ = 1.31 (t, 3H, CH_3), 1.63–2.04 (m, 4H, $2CH_2$), 2.29–2.83 (m, 4H, $2CH_2$), 4.11 (q, 2H, CH_2), 5.99 (s, 2H, NH_2, exchangeable), 7.12 (s, 2H, NH_2, exchangeable). $C_{17}H_{17}N_5O_3S_2$ (403.46): Calcd: C, 50.60; H, 4.24; N, 17.35; S, 15.89; Found: C, 50.55; H, 3.99; N, 17.17; S, 15.56.

*Ethyl 1-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-cyano-4-methyl-6-thioxo-1,6-dihydropyridazine-3-carboxylate (***8j***).* Pale brown crystals (from DMF-H_2O), yield 71% (1.43 g), m.p. 120–123°C. IR (ν/cm^{-1}) = 3365, 3215 (NH_2), 2970–2865 (CH_3, CH_2), 2212 (CN), 1717, 1666 (2CO), 1630 (C=N), 1191 (C=S). ^{1}H NMR δ = 1.39 (t, 3H, CH_3), 1.64–2.01 (m, 4H, $2CH_2$), 2.25–2.83 (m, 7H, CH_3, $2CH_2$), 4.15 (q, 2H, CH_2), 7.10 (s, 2H, NH_2, exchangeable). $C_{18}H_{18}N_4O_3S_2$ (402.47): Calcd: C,

53.71; H, 4.50; N, 13.91; S, 15.93; Found: C, 53.36; H, 4.55; N, 14.04; S, 15.76.

Preparation of **11a–h** *(General Procedure)*

A mixture of equivalent amounts (0.005 mol) of either **1a** or **1b** and either the benzylidenemalononitrile (**9a**), *p*-methoxybenzylidene-malononitrile (**9b**) or the ethyl α-cyanocinnamate **9c,d**, was heated, under reflux, in 1,4-dioxane (30 ml) containing a catalytic amount of piperidine (0.5 ml) for 8 h. The solutions were cooled at room temperature, poured onto iced water, and neutralized with dilute HCl to isolate the products, which were filtered off and crystallized from the proper solvents.

*2-(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-oxo-3-phenyl-2,5-dihydropyridazine-4,6-dicarbonitrile (***11a***).* Yellowish brown crystals (from 1,4-dioxane), yield 65% (1.30 g), m.p. 162–166°C. IR (ν/cm^{-1}) = 3350, 3209 (NH_2), 3033 (CH aromatic), 2935, 2858 (CH_2), 2216, 2210 (2CN), 1705, 1666 (2CO), 1632 (C=N). ^{1}H NMR δ = 1.60–2.08 (m, 4H, $2CH_2$), 2.25–2.66 (m, 4H, $2CH_2$), 6.31 (s, 2H, NH_2, exchangeable), 7.22–7.41 (m, 5H, C_6H_5). $C_{21}H_{15}N_5O_2S$ (401.43): Calcd: C, 62.83; H, 3.76; N, 17.44; S, 7.98; Found: C, 62.48; H, 3.67; N, 17.28; S, 7.99.

*6-Acetyl-2-(3-carbamoyl-4,5,6,7-tetrahydrobenzo-[b]thiophen-2-yl)-5-oxo-3-phenyl-2,5-dihydropyridazine-4-carbonitrile (***11b***).* Pale yellow crystals (from DMF), yield 70% (1.46 g), m.p. 107–109°C. IR (ν/cm^{-1}) = 3367, 3210 (NH_2), 3024 (CH aromatic), 2967–2859 (CH_3, CH_2), 2220 (CN), 1707, 1690, 1665 (3CO), 1630 (C=N). ^{1}H NMR δ = 1.55–1.82 (m, 4H, $2CH_2$), 2.03–2.38 (m, 4H, $2CH_2$), 2.60 (s, 3H, CH_3CO), 6.69 (s, 2H, NH_2, exchangeable), 7.17–7.40 (m, 5H, C_6H_5). $C_{22}H_{18}N_4O_3S$ (418.45): Calcd: C, 63.14; H, 4.33; N, 13.38; S, 7.66; Found: C, 62.88; H, 4.27; N, 13.39; S, 7.39.

*2-(3-Carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-3-(p-methoxyphenyl)-5-oxo-2,5-dihydropyridazine-4,6-dicarbonitrile (***11c***).* Yellowish brown crystals (from 1,4-dioxane), yield 67% (1.44 g), m.p. 132–135°C. IR (ν/cm^{-1}) = 3355, 3209 (NH_2), 3030 (CH aromatic), 2971–2860 (CH_3, CH_2), 2221, 2215 (2CN), 1708, 1664 (2CO), 1630 (C=N). ^{1}H NMR δ = 1.62–2.03 (m, 4H, $2CH_2$), 2.26–2.71 (m, 4H, $2CH_2$), 3.80 (s, 3H, OCH_3), 5.97 (s, 2H, NH_2, exchangeable), 7.07–7.27 (m, 4H, C_6H_4). $C_{22}H_{17}N_5O_3S$ (431.45): Calcd: C, 61.24; H, 3.96; N, 16.23; S, 7.43; Found: C, 61.00; H, 4.03; N, 16.08; S, 7.36.

*6-Acetyl-2-(3-carbamoyl-4,5,6,7-tetrahydrobenzo-[b]thiophen-2-yl)-3-(p-methoxyphenyl)-5-oxo-2,5-dihydropyridazine-4-carbonitrile (***11d***).* Grey crystals (from 1,4-dioxane), yield 67% (1.50 g), m.p. 146–149°C. IR (ν/cm^{-1}) = 3355, 3203 (NH_2), 3030 (CH aromatic), 2965–2859 (CH_3, CH_2), 2212 (CN), 1706, 1695, 1663 (3CO), 1625 (C=N). ^{1}H NMR δ = 1.53–1.78 (m, 4H, $2CH_2$), 2.00–2.33 (m, 4H, $2CH_2$), 2.61 (s, 3H, CH_3CO), 3.85 (s, 3H, OCH_3), 6.56 (s, 2H, NH_2, exchangeable), 7.09–7.28 (m, 4H, C_6H_4). $C_{23}H_{20}N_4O_4S$ (448.48): Calcd: C, 61.59; H, 4.49; N, 12.49; S, 7.14; Found: C, 61.62; H, 4.26; N, 12.37; S, 6.78.

*Ethyl 2-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)-6-cyano-5-oxo-3-phenyl-2,5-dihydropyridazine-4-carboxylate (***11e***).* Brown crystals (from EtOH), yield 52% (1.16 g), m.p. 84–85°C. IR (ν/cm^{-1}) = 3368, 3215 (NH_2), 3030 (CH aromatic), 2965–2858 (CH_3, CH_2), 2223 (CN), 1726, 1707, 1663 (3CO), 1630 (C=N). ^{1}H NMR δ = 1.33 (t, 3H, CH_3), 1.61–2.00 (m, 4H, $2CH_2$), 2.26–2.70 (m, 4H, $2CH_2$), 4.24 (q, 2H, CH_2), 6.49 (s, 2H, NH_2, exchangeable), 7.13–7.35 (m, 5H, C_6H_5). $C_{23}H_{20}N_4O_4S$ (448.48): Calcd: C, 61.59; H, 4.49; N, 12.49; S, 7.14; Found: C, 61.56; H, 4.17; N, 12.43; S, 6.88.

*Ethyl 6-acetyl-2-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-5-oxo-3-phenyl-2,5-dihydropyridazine-4-carboxylate (***11f***).* Brown crystals (from EtOH), yield 62% (1.44 g), m.p. 74–77°C. IR (ν/cm^{-1}) = 3352, 3192 (NH_2), 3030 (CH aromatic), 2966–2858 (CH_3, CH_2), 1726, 1707, 1693, 1664 (4CO), 1625 (C=N). ^{1}H NMR δ = 1.25 (t, 3H, CH_3), 1.57–1.89 (m, 4H, $2CH_2$), 2.00–2.30 (m, 4H, $2CH_2$), 2.58 (s, 3H, CH_3CO), 4.15 (q, 2H, CH_2), 6.49 (s, 2H, NH_2, exchangeable), 7.15–7.40 (m, 5H, C_6H_5). $C_{24}H_{23}N_3O_5S$ (465.50): Calcd: C, 61.92; H, 4.97; N, 9.02; S, 6.88; Found: C, 62.04; H, 4.88; N, 8.76; S, 6.69.

*Ethyl 2-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)-6-cyano-3-(p-methoxyphenyl)-5-oxo-2,5-dihydropyridazine-4-carboxylate (***11g***).* Brown crystals (from DMF-H_2O), yield 59% (1.41 g), m.p. 74–75°C. IR (ν/cm^{-1}) = 3375, 3212 (NH_2), 3020 (CH aromatic), 2970–2862 (CH_3, CH_2), 2216 (CN), 1716, 1705, 1664 (3CO), 1630 (C=N). ^{1}H NMR δ = 1.35 (t, 3H, CH_3), 1.63–2.02 (m, 4H, $2CH_2$), 2.26–2.80 (m, 4H, $2CH_2$), 3.74 (s, 3H, OCH_3), 4.17 (q, 2H, CH_2), 6.62 (s, 2H, NH_2, exchangeable), 7.08–7.27 (m, 4H, C_6H_4). $C_{24}H_{22}N_4O_5S$ (478.50): Calcd: C, 60.24; H, 4.62; N, 11.70; S, 6.70; Found: C, 59.89; H, 4.45; N, 11.55; S, 6.47.

*Ethyl 6-acetyl-2-(3-carbamoyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-3-(p-methoxyphenyl)-5-oxo-2,5-dihydropyridazine-4-carboxylate (***11h***).* Brown crystals (from EtOH), yield 79% (1.96 g), m.p. 63°C. IR (ν/cm^{-1}) = 3364, 3205 (NH_2), 3031 (CH aromatic), 2962–2856 (CH_3, CH_2), 1716, 1700, 1692, 1666 (4CO), 1628 (C=N). ^{1}H NMR δ = 1.31 (t, 3H, CH_3), 1.61–2.02 (m, 4H, $2CH_2$), 2.10–2.37 (m, 4H, $2CH_2$), 2.59 (s, 3H, CH_3CO), 3.84 (s, 3H, OCH_3), 4.19 (q, 2H, CH_2), 6.59 (s, 2H, NH_2, exchangeable), 7.09–7.27 (m, 4H, C_6H_4). $C_{25}H_{25}N_3O_6S$ (495.53): Calcd: C, 60.59; H, 5.08; N, 8.47; S, 6.47; Found: C, 60.45; H, 4.87; N, 8.34; S, 6.47.

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