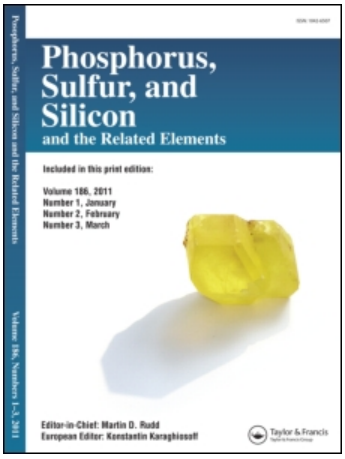

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Reaction of Ethyl 2-Diazo-4,5,6,7-Tetrahydrobenzo[B] Thiophene 3-Carboxylate with Benzoyl Acetonitrile: Synthesis of Pyrazoles, Pyridazines, Pyrimidines and Their Fused Derivatives

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REACTION OF ETHYL 2-DIAZO-4,5,6,7-TETRAHYDROBENZO[b] THIOPHENE 3-CARBOXYLATE WITH BENZOYL ACETONITRILE: SYNTHESIS OF PYRAZOLES, PYRIDAZINES, PYRIMIDINES AND THEIR FUSED DERIVATIVES

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The reaction of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene 3-carboxylate **1** with benzoylacetonitrile (**2**) gave compound **3**. The reactivity of the latter product towards variety of chemical reagents was studied to give fused thiophene derivatives of high potential pharmaceutical uses.

Keywords: Thiophene; benzoylacetonitrile; pyrazole; pyrimidine

INTRODUCTION

Over recent years we have been involved in a comprehensive program aimed at investigating the reaction of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene 3-carboxylate with a variety of active methylene reagents followed by heterocyclization of the resulting products to form pyridines, pyrimidines and pyridazines.[1] The importance of such compounds is due to their diverse pharmaceutical activities including antithrombotic[2] anticonvulsive[3], antiflammatory[4] and antiviral activities[5–8] and as protein kinase inhibitors[9].

* Corresponding Author.

RESULTS AND DISCUSION

In this work we report the reaction of ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene (**1**)[10] with benzoyl acetonitrile (**2**) to form α-hydrazo-β-oxonitrile derivative that showed interesting reactivity towards chemical reagents to form heterocyclic and fused heterocyclic derivatives that showed wide spectrum of biological activities.[11,12] Thus the reaction of **1** with benzoyl-acetonitrile (**2**) in ethanolic sodium acetate solution formed a single product with molecular formula $C_{20}H_{19}N_3SO_3$ for which two isomeric structures were proposed **3** and **4**. The hydrazo derivative **3** was assigned for the reaction product on the basis of spectral data. Thus, the IR spectrum showed NH stretching at 3465–3435 cm^{-1}, one CN group stretching at 2220 cm^{-1}. Moreover, the ^1H NMR spectrum showed beside the usual signal due to cyclohexane ring, a triplet at δ 1.65 ppm due to CH_3 group, a quartet at δ 4.28 ppm due to CH_2 group, a multiplet at δ 7.32–7.39 ppm due to phenyl group and a singlet (D_2O exchangeable) at δ 8.89 ppm due to NH group. Further confirmation for structure **3** was obtained through studying its reactivity towards chemical reagents. Thus, the reaction of **3** with either hydrazine hydrate **5a** or phenyl hydrazine **5b** gave the corresponding pyrazole derivatives **6a** and **6b** respectively. Moreover, the reaction of **3** with hydroxylamine hydrochloride gave the isoxazole derivative **7**. Structures of compounds **6a,b** and **7** were established on the basis of analytical and spectral data. The reaction of compound **3** with either urea **8a** or thiourea **8b** in sodium ethoxide solution gave the pyrimidine derivatives **9a** and **9b** respectively. Structures of the latter products were established on the basis of analytical and spectral data. The reaction of either of compounds **9a** or **9b** with formaldehyde in presence of triethylamine gave the pyrimidino[5,4-e]-1,2,4-triazine derivative **10a** and **10b** respectively.

The reaction of **3** with either malononitrile **11a** or ethyl cyanoacetate **11b** in ethanolic triethylamine solution gave the Knoevenagel condensation products **12a** and **12b** respectively. Structures of **12a** and **12b** were based on analytical and spectral data. Thus the IR spectrum of **12a**, as an example, showed three cyano group stretchings at 2222, 2220 and 2215 cm^{-1}. Moreover, the ^{13}C NMR spectrum showed δppm 27.2 (CH_3), 29.3, 30.1 (cyclohexane C-1, C-4), 23.3, 23.9 (cyclohexane C-2, C-3), 56.5 (CH_2), 64.2 (CH), 117.4, 118.3, 120.0 (3 CN), 121.0, 122.6 (C=C), 123.6, 123.9, 124.9, 126.7, 132.2, 133.0, 139.8 (phenyl-C, thiophene-C).

Compound **12a** underwent ready cyclisation when heated in sodium ethoxide solution to form the tetrahydrobenzo[b]thieno[2,3:6,5]pyridazo[6,1:a]pyrimidine derivative **14**, the reaction took place through the intermediate formation of the 2-iminopyridazine derivative **13**. Structure of compound **14** was based on analytical and spectral data. Thus, the IR spectrum showed two CN group stretchings at 2225, 2220 cm^{-1} and ^1H NMR spectrum showed beside the cyclohexyl ring expected peaks, only a mutiplet at δ 7.29–7.35 ppm due to the phenyl group. In a similar manner, compound **12b** was cyclized to give a single product with molecular formula $C_{23}H_{18}N_4SO_3$. Two possible isomeric structures were considered, the tetrahydrobenzo[b]thieno[2,3:6,5]pyridazino[6,1-a]-pyrimidine derivative **15** and the 2-oxopyridazine derivative **16**. The possiblity of structure **15** was ruled out based on IR spectrum of the reaction product which showed the presence of two CN groups stretching at 2225, 2220 cm^{-1} and the ^{13}C NMR spectrum which showed beside the usual signals, two CN group signals at 118.8 and 120.4.

The reactivity of **3** towards dimer adducts was studied in the aim to form annulated products with potential biological activities. Thus, the reaction of **3** with β-amino-α-cyanocrononitrile (**17**)[13] gave the tetrahydrobenzo[b]thieno-[2,3:6,5]pyridazino[6,1-a]pyrimidine derivative **19** which is formed via the intermediate formation of **18** followed by addition of NH to CN group and ethanol elimination. Structure of compound **19** is based on analytical and spectral data, thus, ^1H NMR spectrum showed beside the cyclohexyl protons, a singlet (D_2O exchangeable) at δ 4.86 ppm due to NH_2 group, a mutiplet at δ 7.23–7.32 ppm due to phenyl protons. Further confirmation for the structure of **19** was obtained through its synthesis via another reaction route. Thus, the reaction of malononitrile (**5a**) with **14** in ethanolic piperidine solution gave the same product **19** (mixed. p., finger print IR spectrum).

In a similar way, the reaction of **3** with ethyl α-cyano-β-cyano-γ-ethoxy-carbonylcrononoate (**20**)[14] to give the tetrahydrobenzo[b]thiophene-2-pyridazin-1-yl **21**. Structure of compound **21** was confirmed on the basis of analytical and spectral data (see experimental section). Further confirmation for this structure were obtained through the synthesis of **21** via another reaction route. Thus the reaction of **16** with ethyl cyanoacetate **5a** in ethanolic triethyl amine solution gave the same product **21** (same m.p. and mixed m.p.). Moreover, the reaction of **3** with β-iminobutyronitrile (**22**)[15] gave the 2-iminopyridazine derivative **23**. The

latter product underwent ready cyclization in sodium ethoxide solution to give the tetrahydrobenzo[b]thieno[2,3:6,5]pyridazo[6,1-b]pyrimidine derivative **24**. The structures of compounds **23** and **24** were established on the basis of analytical and spectral data.

Reaction of compound **3** with either phenyl isothiocyanate **25a** or benzoyl isothiocyanate **25b** gave the triazine derivatives **27a** and **27b** respectively. The latter products were formed via the intermediate formation of **26a** and **26b** respectively. Structures of the latter products were established on the basis of analytical and spectral data.

The reaction of **3** with cinnamonitrile derivatives were studied, thus, with either α-cyanocinnamonirile (**28a**) or α-ethoxycarbonylcinnamonitrile (**28b**) gave the 4-oxopyridazine derivatives **31a** and **31b** respectively. Formation of **31a,b** is explained in terms of the intermediate formation of **29a,b** and **30a,b** followed by loss of hydrogen cyanide and hydrolysis of the imino group of. On the other hand, the reaction of **3** with 4-phenyl-3-thiosemicarbazide (**32**) gave the corresponding thiosemicarbazone derivative **33**. The latter product was cyclized in sodium ethoxide solution to give the pyrazole derivative **34**. Structure **34** was established for the reaction product on the basis of ^{1}H NMR spectrum which showed the presence of a singlet at δ 5.34 (D_2O exchangeable) due to NH_2 group and only one singelet at δ 9.11 ppm due to NH group.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded for KBr discs on a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR & ^{13}C NMR spectra were measured on a Varian EM390–200 MHZ in CD_3SOCD_3 as solvent using TMS as internal standard, and chemical shifts are expressed as δ ppm. Analytical data were obtained from the Microanalytical Data Unite at Cairo University, Giza, Egypt.

Ethyl 2-(α-hydrazono-α-phenylmethanoylacetonitrilo)-4,5,6,7-tetrahydrobenzo-[b]thiophene (3)

To a cold solution of **2** (1.4 g, 0.01 mol) in ethanol (50 mL) containing sodium acetate (10.0 g), a cold solution of diazonium salt of **1** (0.01 mol)

[prepared by adding sodium nitrite solution (0.7 g, 0.1 mol) to a cold solution of ethyl 2-amino4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (3.81 g, 0.01 mol) in acetic acid (20 ml), hydrochloric acid (5 mL) dropwise with stirring] was added with stirring for 1 h at 0–5°C. The formed solid product was collected by filtration.

Compound **3**: Reddish brown crystals, from acetic acid, yield 79 % (3.01 g), m.p. 127–9 °C. Analysis for $C_{20}H_{19}N_3O_3S$ (381.50): Calcd: C, 62.96; H, 5.02; N, 11.01; S, 8.42 %. Found: C, 62.65; H, 4.89; N. 10.78; S, 8.21 %. IR (υ/cm^{-1}): 3465–3435 (NH), 3065 (CH aromatic), 2980, 2865 (CH_3, CH_2), 2220 (CN), 1720, 1685 (2 C=O), 1655 (C=N), 1645 (C=C). ^1H NMR (δ ppm): 1.65 (t, 3H, CH_3), 2.21 (m, 4H, 2 CH_2), 2.31 (m, 4H, $2CH_2$), 4.28 (q, 2H, CH_2), 7.32–7.39 (m, 5H, C_6H_5), 8.89 (s, 1H, NH).

Ethyl 2-azo-(3-phenyl-5-amino-1H-pyrazol-4-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (6a), Ethyl 2-azo-(1,3-diphenyl-5-amino-1H-pyrazol-4-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (6b)

General procedure

To a solution of **3** (3.8 g, 0.01 mol) in ethanol (40 ml) either hydrazine hydrate (0.5 g, 0.01 mol) or phenyl hydrazine (1.1 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h then poured into ice/water mixture containing few drops of hydrochloric acid. The formed solid product, in each case, was collected by filtration.

Compound **6a**: Orange crystals, from acetic acid, yield 70 % (2.98 g), m.p. 275–8°C. Analysis for $C_{20}H_{21}N_5O_2S$ (395.42): Calcd: C, 60.69; H, 5.31; N, 17.70; S, 8.09 %. Found: C, 60.34; H, 5.69; N. 17.52; S, 8.31 %. IR (υ/cm^{-1}): 3475–3350 (NH_2, NH), 3065 (CH aromatic), 2983, 2870 (CH_3, CH_2), 1695 (C=O), 1655 (C=N), 1628 (C=C). ^1H NMR (δ ppm): 1.65 (t, 3H, CH_3), 2.21 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2 CH_2), 4.25 (q, 2H, CH_2), 4.89 (s, 2H, NH_2), 7.29–7.34 (m, 5H, C_6H_5), 9.21 (s, 1H, NH).

Compound **6b**: Orange crystals, from acetic acid, yield 67 % (3.37 g), m.p. 240–4 °C. Analysis for $C_{26}H_{25}N_5O_2S$ (471.59): Calcd: C, 66.13; H, 5.30; N, 14.83; S, 6.74 %. Found: C, 66.34; H, 5.69; N. 14.52; S, 6.31 %. IR (υ/cm^{-1}): 3475–3350 (NH_2, NH), 3065 (CH aromatic), 2983, 2870 (CH_3, CH_2), 1695 (C=O), 1666(C=N), 1639 (C=C). ^1H NMR (δ ppm):

1.65 (t, 3H, CH3), 2.21 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2 CH_2), 4.25 (q, 2H, CH_2), 4.99 (s, 2H, NH_2), 7.30–7.38 (m, 10H, 2 C_6H_5).

Ethyl 2-azo-(3-phenyl-5-amino-isoxazolo-4-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (7)

To a solution of **3** (3.8 g, 0.01 mol) in absolute ethanol (50 ml) containing sodium acetate (0.8 g, 0.01 mol), hydroxylamine hydrochloride (0.67 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3h then poured into ice water. The formed solid product was collected by filtration.

Compound **7**: Orange crystals, from 1,4-dioxane, yield 55% (2.27 g), m.p. °C. Analysis for $C_{20}H_{20}N_4O_3S$ (396.47): Calcd: C, 60.58; H, 5.08; N, 14.13; S, 8.10 %. Found: C, 60.39; H, 5.06; N, 14.08; S, 8.31 %. IR (υ/cm^{-1}): 3460–3335 (NH_2, NH), 3055 (CH aromatic), 2980, 2860 (CH_3, CH_2), 1690 (C=O), 1662 (C=N), 1643 (C=C). ^1H NMR (δ ppm): 1.63 (t, 3H, CH_3), 2.20 (m, 4H, 2 CH_2), 2.33 (m, 4H, 2 CH_2), 4.20 (q, 2H, CH_2), 5.31 (s, 2H, NH_2), 7.31–7.37 (m, 5H, C_6H_5).

Ethyl 2-(3-amino-6-phenyl-2-oxopyrimidine-5-hydrazono-N-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (9a) and Ethyl 2-(3-amino-6-phenyl-2-thioxoprimidine-5-hydrazono-N-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (9b)

General method

A suspension of **3** (3.8 g, 0.01 mol) in sodium ethoxide (0.01 mol) [prepared by dissolving sodium metal (0.23 g, 0.01 mol) in absolute ethanol (40 ml)] either urea (0.6 g, 0.01 mol) or thiourea (0.7 g, 0.01 mol) was added. The reaction mixture, in each case, was heated in a boiling water bath for 2 h then poured into ice/water containing dilute hydrochloric acid (till pH 6) and the formed solid product was collected by filtration.

Compound (**9a**): Buff crystals, from acetic acid, yield 71 % (3.01 g), m.p. 230–3 °C. Analysis for $C_{21}H_{21}N_5O_3S$ (423.41): Calcd: C, 59.57; H, 4.96; N, 16.55; S, 7.56 %. Found: C, 59.86; H, 4.44; N, 16.43; S,7.52 %. IR (υ/cm^{-1}): 3460–3325 (NH_2, NH), 3060 (CH aromatic), 2979, 2870 (CH_3, CH_2), 1700, 1685 (2 C=O), 1666 (C=N), 1640 (C=C). ^1H NMR (δ ppm): 1.64 (t, 3H, CH_3), 2.23 (m, 4H, 2 CH_2), 2.35 (m, 4H, 2 CH_2),

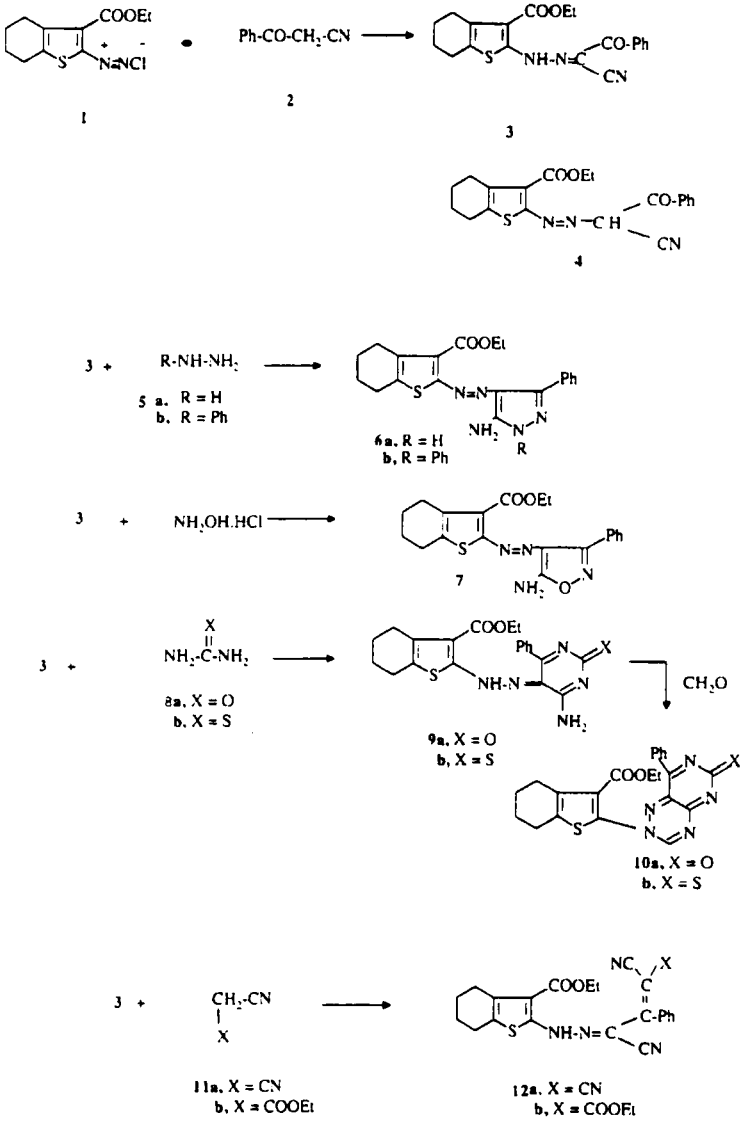

CHART 1

4.25(q, 2H, CH_2), 4.99 (s, 2H, NH_2), 7.29–7.40 (m, 5H, C_6H_5), 8.88 (s, 1H, NH).

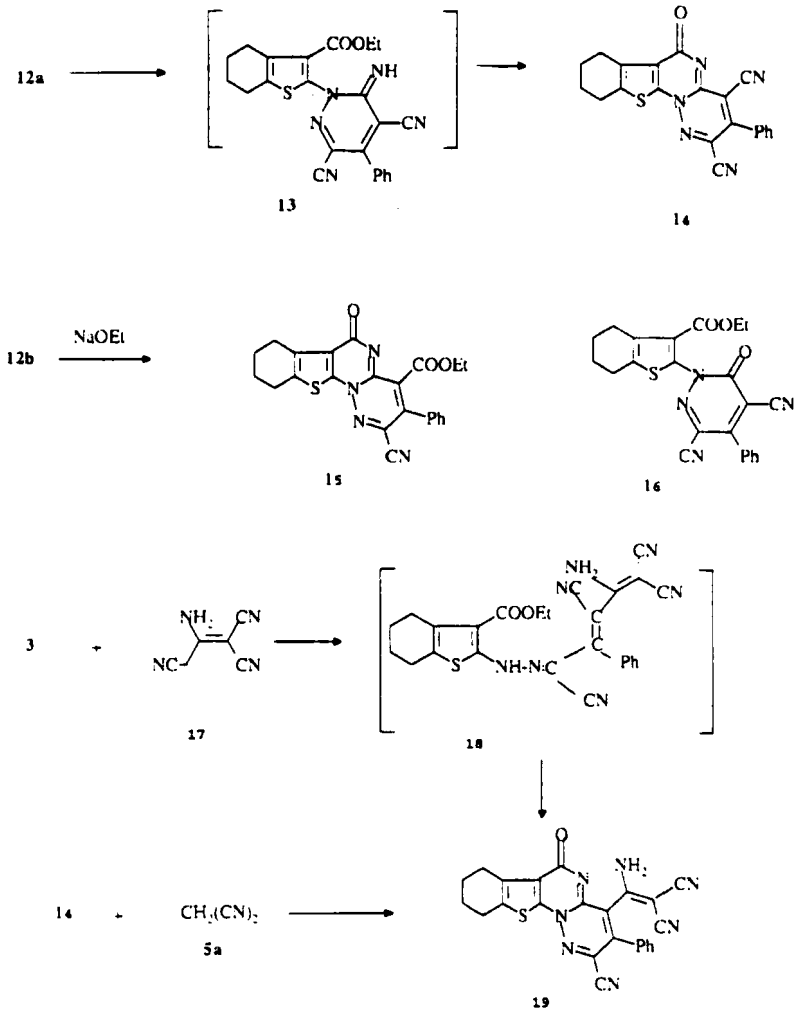

CHART 2

Compound (**9b**): Buff crystals, from acetic acid, yield 79 % (3.47 g), m.p. 267–9 °C. Analysis for $C_{21}H_{21}N_5O_2S_2$ (439.51): Calcd: C, 57.40; H, 4.78; N, 15.95; S, 14.58 %. Found: C, 57.57; H, 4.47; N, 16.09; S, 14.42 %. IR (υ/cm^{-1}): 3466–3337 (NH_2, NH), 3050 (CH aromatic), 2980, 2881 (CH_3, CH_2), 1685 (C=O), 1663 (C=N), 1638 (C=C). ^{1}H NMR (δ

ppm): 1.66 (t, 3H, CH_3), 2.22 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2 CH_2), 4.24 (q, 2H, CH_2), 4.87 (s, 2H, NH_2), 7.30–7.38 (m, 5H, C_6H_5), 8.91 (s, 1H, NH).

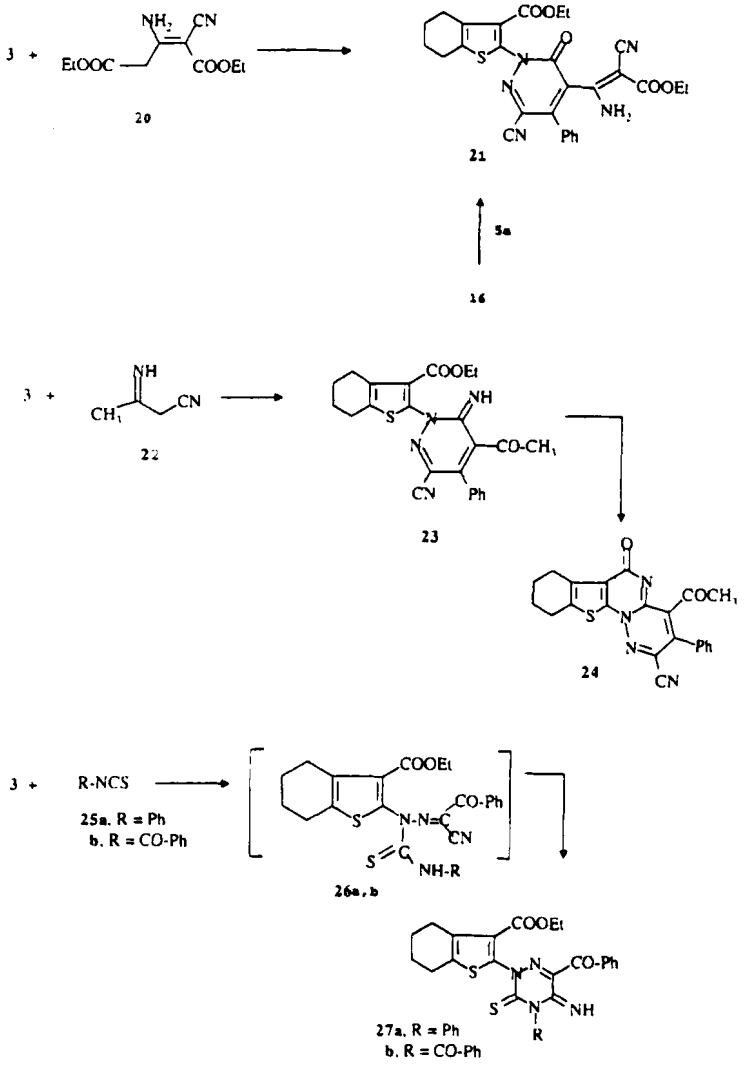

CHART 3

Ethyl 2-(6-oxo-8-phenylpyrimidino[4,5-e]-1,2,4-triazin-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxlate (10a) and Ethyl 2-(8-phenyl-6-thioxopyrimidino[4,5-e]-1,2,4-triazin-2-yl)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxlate (10b)

General procedure

Either compound **9a** (4.2 g, 0.01 mol) or **9b** (4.4 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.5 mL), formaldehyde (0.3 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6 h then evapourated in vaccu. The remaining product was triturated with diethyl ether and the formed solid product, in each case was collected by filtration.

Compound (**10a**): Red crystals, from acetic acid, yield 65 % (2.79 g), m.p. > 300 °C. Analysis for $C_{22}H_{19}N_5O_3S$ (433.23): Calcd: C, 60.47; H, 4.39; N, 16.17; S, 7.39 %. Found: C, 60.22; H, 4.34; N, 16.37; S, 7.51 %. IR (υ/cm^{-1}): 3060 (CH aromatic), 2988, 2874 (CH_3, CH_2), 1690 (C=O), 1660 (C=N), 1635 (C=C). ^{1}H NMR (δ ppm): 1.65 (t, 3H, CH_3), 2.20 (m, 4H, 2 CH_2), 2.32 (m, 4H, 2 CH_2), 4.26 (q, 2H, CH_2), 7.29–7.40 (m, 6H, triazine H-3, C_6H_5).

Compound (**10b**): Red crystals, from acetic acid, yield 75 % (3.37 g), m.p. 288–91 °C. Analysis for $C_{22}H_{19}N_5O_2S_2$ (449.41): Calcd: C, 58.79; H, 4.23; N, 15.57; S, 7.39 %. Found: C, 85.74; H, 4.34; N, 15.37; S, 7.51 %. IR (υ/cm^{-1}): 3060 (CH aromatic), 2988, 2874 (CH_3, CH_2), 1690 (C=O), 1660 (C=N), 1635 (C=C). ^{1}H NMR (δ ppm): 1.67 (t, 3H, CH_3), 2.21 (m, 4H, 2 CH_2), 2.32 (m, 4H, 2 CH_2), 4.26 (q, 2H, CH_2), 7.27–7.36 (m, 6H, triazine H-3,C_6H_5).

Ethyl 2-hydrazono(4,4-dicyano-3-phenyl-3-ene-butyronitrile-2-ylidene)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (12a) and Ethyl 2-hydrazono(4-cyano-4-ethoxycarbonyl-3-phenyl-3-ene-butyronitrile-2-ylidene)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (12b)

General procedure

Either malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) was added to a solution of **3** (3.8 g, 0.01 mol) in 1,4-dioxane (30 mL) containing triethylamine (0.5 mL). The reaction mixture in each case was heated under reflux for 3 h then evapourated in vaccu. The remaining

product was triturated with ethanol and the formed solid product was collected by filtration.

Compound **12a**: Orange crystals, from 1,4-dioxane, yield 60% (2.57 g), m.p. 270–4 °C. Analysis for $C_{23}H_{19}N_5O_2S$ (429.55): Calcd: C, 64.31; H, 4.45; N, 16.30; S, 7.47 %. Found: C, 64.09; H, 4.65; N, 16.29; S, 7.18 %. IR (υ/cm^{-1}): 3450–3380 (NH), 3065 (CH aromatic), 2985, 2875 (CH_3, CH_2), 2222, 2215 (2 CN) 1695 (C=O), 1634 (C=C). ^1H NMR (δ ppm): 1.60 (t, 3H, CH_3), 2.21 (m, 4H, 2 CH_2), 2.30 (m, 4H, 2 CH_2), 4.25 (q, 2H, CH_2), 7.30–7.39 (m, 5H, C_6H_5), 8.99 (s, 1H, NH). ^{13}C NMR (DMSO, δppm): 27.2 (CH_3), 29.3, 30.1 (cyclohexan C-1, C-4), 23.3, 23.9 (cyclohexan C-2, C-3), 56.5 (CH_2), 64.2 (CH), 117.4, 118.3, 120.0 (3 CN), 121.0, 122.6 (C=C), 123.6, 123.9, 124.9, 126.7, 132.2, 133.0, 139.8 (phenyl-C, thiophene-C).

Compound **12b**: Orange crystals, from 1,4-dioxane, yield 58 % (3.80 g), m.p. 262–6 °C. Analysis for $C_{25}H_{24}N_4O_4S$ (476.61): Calcd: C, 63.00; H, 5.07; N, 11.75; S, 6.73 %. Found: C, 63.09; H, 4.95; N, 11.94; S, 7.09 %. IR (υ/cm^{-1}): 3455–3375 (NH), 3060 (CH aromatic), 2985, 2875 (CH_3, CH_2), 2220 (CN), 1690 (C=O), 1635 (C=C). ^1H NMR (δ ppm): 1.62, 1.64 (2t, 6H, $2CH_3$), 2.23 (m, 4H, 2 CH_2), 2.33 (m, 4H, 2 CH_2), 4.25, 4.29 (2q, 4H, $2CH_2$), 7.28–7.37 (m, 5H, C_6H_5), 8.75 (s, 1H, NH).

2,4-Dicyano-3-pheny-6-oxo-7,8,9,10-tetrahydrobenzo[b]thieno [1,2:6,5]pyridazino[6,1-a]pyridazine (14), ethyl 2-(3,5-dicyano-4-phenyl-6-oxopyridazin-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene -3-carboxylate (16)

General procedure

A suspended solution of either **12a** (4.3 g, 0.01 mol), **12b** (4.3 g, 0.01 mol), in sodium ethoxide (0.01 mol) [prepared by dissolving sodium metal (0.23 g, 0.01 mol) in absolute ethanol (30 ml)] was heated in a boiling water bath for 2h. The solid product formed, in each case, upon pouring into ice/water containing dilute hydrochloric acid (till pH 6) was collected by filtration.

Compound **14**: Yellow crystals, from 1,4-dioxane, yield 50 % (1.91 g), m.p. 177–80 °C. Analysis for $C_{21}H_{13}N_5OS$ (383.47): Calcd: C, 65.71; H, 3.39; N, 18.25; S, 8.34 %. Found: C, 66.09; H, 3.11; N, 18.09; S, 8.35 %. IR (υ/cm^{-1}): 3050 (CH aromatic), 2870 (CH_2), 2225, 2220 (2 CN), 1685

(C=O), 1635 (C=C). ^{1}H NMR (δ ppm): 2.23 (m, 4H, 2 CH_2), 2.33 (m, 4H, 2 CH_2), 7.29–7.35 (m, 5H, C_6H_5).

Compound **16**: Orange crystals, from 1,4-dioxane, yield 71 % (3.05 g), m.p. 188–90 °C. Analysis for $C_{23}H_{18}N_4O_3S$ (430.34): Calcd: C, 64.13; H, 4.18; N, 13.01; S, 7.43 %. Found: C, 64.32; H, 4.27; N, 13.31; S, 7.35 %. IR (υ/cm^{-1}) 3055 (CH aromatic), 2980, 2880 (CH_3, CH_2), 2225, 2220 (2 CN), 1695 (C=O), 1640 (C=C). ^{1}H NMR (δ ppm): 1.60 (t, 3H, CH_3), 2.25 (m, 4H, 2 CH_2), 2.36 (m, 4H, 2 CH_2), 4.27 (q, 2H, CH_2), 7.29–7.40 (m, 5H, C_6H_5). ^{13}C NMR (DMSO, δ ppm): 27.6 (CH_3), 29.4, 30.5 (cyclohexan C-1, C-4), 23.7, 23.6 (cyclohexan C-2, C-3), 59.5 (CH_2), 118.8, 120.4 (2 CN), 123.6, 123.9, 123.7, 128.7, 132.6, 134.0, 139.8 (phenyl-C, thiophene-C), 178.3, 180.6 (2 C=O).

2-Cyano-3-phenyl-4-(3-amino-2-cyanoacrylonitril-3-yl)-6-oxo-7,8,9,10-tetrahydrobenzo[b]thieno[2,3:6,5]pyridazino[6,1-a] pyrimidine (19), ethyl 2-[3-cyano-4-phenyl-5-(3-amino-2-ethoxycarbonylacrylonitril-3-yl)-6-oxopyridazin-1- yl]-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (21) and ethyl 2-(5-acetyl-3-cyano-6-imino-4-phenylpyridazin-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (23)

General procedure

To a solution of **3** (3.8 g, 0.01 mol) in 1,4-dioxane (40 ml) containing triethylamine (0.5 mL) either **17** (1.3 g, 0.01 mol), **20** (2.26 g, 0.01 mol) or **22** (0.82 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 6 h then poured into ice/water containing few drops of hydrochloric acid. The solid product, formed in each case, was collected by filtration.

Another method for synthesis of 19 and 21

To a solution of each of compounds **11** (0.66 g, 0.01 mol) and **16** (4.3 g, 0.01 mol) in dimethylformamide (40 mL) containing triethylamine (0.05 mL), malononitrile (**11**) (0.66 g, 0.01 mol) was added. The reaction mixture, in each case, was heated under reflux for 5 h then evapourated in vaccu. The remaining product was triturated with ethanol, then collected by filtration.

Compound (**19**): Yellow crystals, from 1,4-dioxane, yield 82 % (3.61 g), m.p. 233–35 °C. Analysis for $C_{24}H_{15}N_7OS$ (449.41): Calcd: C, 64.42; H, 3.44; N, 21.76; S, 7.12 %. Found: C, 64.75; H, 3.34; N, 21.40; S,7.08 %. IR (υ/cm^{-1}): 3486–3365 (NH_2), 3050 (CH aromatic), 2988, 2870 (CH_3, CH_2), 2225, 2220, 2217 (3 CN), 1695 (C=O), 1665 (C=N), 1643 (C=C). ^1H NMR (δ ppm): 2.23 (s, 4H, 2 CH_2), 2.34 (s, 4H, 2 CH_2), 4.88 (s, 2H, NH_2), 7.23–7.32 (m, 5H, C_6H_5). ^{13}C NMR (DMSO, δppm): 29.3, 30.1 (cyclohexan C-1, C-4), 23.3, 23.9 (cyclohexan C-2, C-3), 116.8, 118.0, 120.4 (3 CN), 121.0, 122.6 (C=C), 123.6, 124.2, 124.9, 126.7, 132.2, 133.0, 136.2, 139.0, 139.9, 141.7 (phenyl-C & heterocyclic ring C), 179.8 (C=O).

Compound (**21**): Yellow crystals, from 1,4-dioxane, yield 66 % (3.37 g), m.p. 222–5 °C. Analysis for $C_{28}H_{25}N_5O_3S$ (511.61): Calcd: C, 65.73; H, 4.92; N, 13.69; S, 6.26 %. Found: C, 65.64; H, 4.68; N, 13.68; S, 5.9 %. IR (υ/cm^{-1}): 3470–3350 (NH_2), 3055 (CH aromatic), 2979, 2883 (CH_3, CH_2), 2226, 2220 (2 CN), 1678 (C=O), 1663 (C=N), 1634 (C=C). ^1H NMR (δ ppm): 1.61, 1.66 (2t, 6H, 2 CH_3), 2.23 (s, 4H, 2 CH_2), 2.34 (s, 4H, 2 CH_2), 4.20, 4.24 (2q, 4H, 2 CH_2), 4.72 (s, 2H, NH_2), 7.31–7.37 (m, 5H, C_6H_5).

Compound (**23**): Pall yellow crystals, from acetic acid, yield 60 % (2.52 g), m.p. 186–9 °C. Analysis for $C_{24}H_{22}N_4O_3S$ (446.52): Calcd: C, 64.45; H, 4.96; N, 12.54; S, 7.19 %. Found: C, 64.44; H, 4.92; N, 12.34; S,7.38 %. IR (υ/cm^{-1}): 3460–3332 (NH), 3063 (CH aromatic), 2976, 2876 (CH_3, CH_2), 2225 (CN), 1698, 1685 (2 C=O), 1670 (exocyclic C=N), 1638 (C=C). ^1H NMR (δ ppm): 1.61 (t, 3H, CH_3), 2.20 (m, 4H, 2 CH_2), 2.27 (s, 3H, CH_3), 2.32 (m, 4H, 2 CH_2), 4.25 (q, 2H, CH_2), 7.30–7.39 (m, 5H, C_6H_5), 9.38 (s, 1H, NH).

Ethyl 2-(4-phenyl-5-imino-6-phenylmethanoyl-3-thioxo-1,2,4-triazin-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (27a) and ethyl 2-(4,6-diphenylmethanoyl-5-imino-3-thioxo-1,2,4-triazin-2-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (27b)

General procedure

To a solution of **3** (3.8 g, 0.01 mol) in 1,4-dioxane (40 mL) containing triethylamine (0.5 mL), either phenyl isothiocyanate (1.3 g, 0.01 mol) or benzoyl isothiocyanate (1.4 g, 0.01 mol) was added. The reaction mixture

was heated under reflux for 5 h then evapourated in vacuum. The remaining product was triturated with ethanol and the formed solid product, in each case, was collected by filtration.

Compound (**27a**): Yellow crystals, from acetic acid, yield 66 % (3.40 g), m.p. 110 °C. Analysis for $C_{27}H_{24}N_4O_3S_2$ (516.46): Calcd: C, 62.79; H, 4.65; N, 10.84; S, 12.42 %. Found: C, 62.64; H, 4.90; N, 10.76; S, 12.19 %. IR (υ/cm^{-1}): 3460–3340 (NH), 3050 (CH aromatic), 2970, 2876 (CH_3, CH_2), 1695, 1688 (2 C=O), 1670 (exocyclic C=N), 1660 (C=N), 1632 (C=C), 1220 (C=S). ^{1}H NMR (δ ppm): 1.65, (t, 3H, CH_3), 2.23 (m, 4H, 2 CH_2), 2.34 (m, 4H, 2 CH_2), 4.25 (q, 2H, CH_2), 7.30–7.36 (m, 10H, 2 C_6H_5), 9.37 (s, 1H, NH).

Compound (**27b**): Yellow crystals, from acetic acid, yield 70 % (3.80 g), m.p. 213–5 °C. Analysis for $C_{28}H_{24}N_4O_4S_2$ (544.47): Calcd: C, 61.76; H, 4.41; N, 10.29; S, 11.77 %. Found: C, 61.64; H, 4.35; N, 10.08; S, 12.08 %. IR (υ/cm^{-1}): 3465–3360 (NH), 3065 (CH aromatic), 2978, 2887 (CH_3, CH_2), 1705, 1690, 1680 (3 C=O), 1673 (exocyclic C=N), 1667 (C=N), 1641 (C=C), 1210–1195 (C=S). ^{1}H NMR (δ ppm): 1.60 (t, 3H, CH_3), 2.24 (s, 4H, 2 CH_2), 2.33 (s, 4H, 2 CH_2), 4.27 (q, 2H, CH_2), 7.32–7.45 (m, 10H, 2 C_6H_5), 9.29 (s, 1H, NH).

Ethyl 2-(5-cyano-6-phenyl-3-phenylmethanoyl-4-oxopyridazine-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (31a) and Ethyl 2-(5-ethoxy-carbonyl-6-phenyl-3-phenylmethanoyl-4-oxopyridazine-1-yl)-4,5,6.7-tetrahydrobenzo[b]thiophene-3-carboxylate (31b)

General procedure

To a solution of **3** (3.8 g, 0.01 mol) in 1,4-dioxane (60 mL) containing triethylamine (0.5 mL) either of **28a** (1.5 g, 0.01 mol) or **28b** (2.3 g, 0.01) was added. The reaction mixture was heated under reflux for 6 h then evapourated under vacuum. The remaining product was triturated with ethanol and the formed solid product, in each case was collected by filtration.

Compound (**31a**): Orange crystals, from ethanol, yield 70 % (3.50 g), m.p. 182 °C. Analysis for $C_{29}H_{23}N_3O_4S$ (509.59): Calcd: C, 68.33; H, 4.59; N, 8.24; S, 6.30 %. Found: C, 68.64; H, 4.43; N, 8.44; S, 6.29 %. IR (υ/cm^{-1}): 3058 (CH aromatic), 2987, 2888 (CH_3, CH_2), 2220 (CN), 1706,

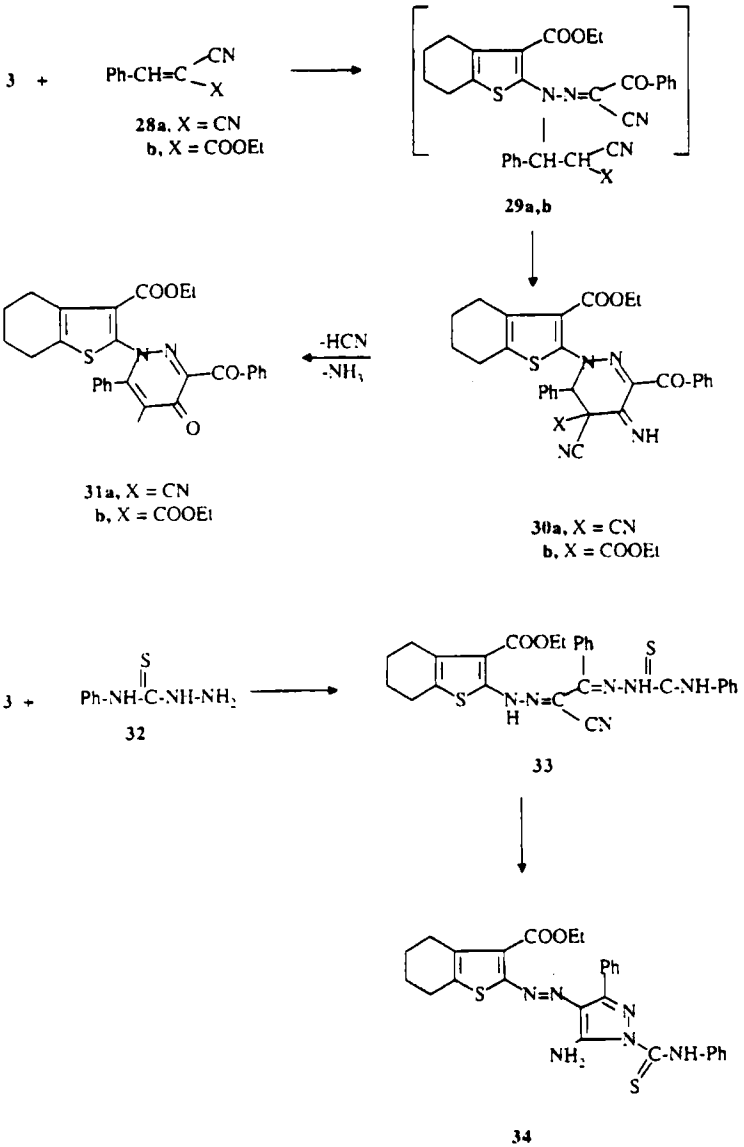

CHART 4

1690, 1680 (3 C=O), 1660 (C=N), 1650 (C=C). ^{1}H NMR (δ ppm): 1.63 (t, 3H, CH_3), 2.24 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2 CH_2), 4.23 (q, 2H, CH_2), 7.28–7.39 (m, 10H, 2 C_6H_5).

Compound (**31b**): Orange crystals, from ethanol, yield 55 % (3.06 g), m.p. 180.3 °C. Analysis for $C_{31}H_{28}N_2O_6S$ (556.57): Calcd: C, 66.88; H, 5.06; N, 5.03; S, 5.77 %. Found: C, 66.58; H, 4.96; N, 5.44; S, 5.69 %. IR (υ/cm^{-1}): 3065 (CH aromatic), 2990, 2875 (CH_3, CH_2), 1703, 1690–1685 (4 C=O), 1655 (C=N), 1645 (C=C). ^{1}H NMR (δ ppm): 1.60, 1.62 (2t, 6H, 2 CH_3), 2.24 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2 CH_2), 4.21, 4.25 (2q, 4H, 2 CH_2), 7.31–7.37 (m, 10H, 2 C_6H_5).

Synthesis of the thiosemicarbazon derivative (33)

A solution of compound **3** (3.8 g, 0.01 mol) in sodium ethoxide [prepared by adding (0.64 g, 0.02 mol) sodium metal to absolute ethanol 50 mL] was heated under reflux for 3 h and the formed solid product was collected by filtration.

Compound (**33**): Orange crystals, from ethanol, yield 70 % (3.75 g), m.p. 220 °C. Analysis for $C_{27}H_{26}N_6O_2S_2$ (530.29): Calcd: C, 61.10; H, 4.90; N, 15.84; S, 6.03 %. Found: C, 60.99; H, 4.83; N, 16.01; S, 6.37 %. IR (υ/cm^{-1}): 3060 (CH aromatic), 2989, 2870 (CH_3, CH_2), 2220 (CN), 1680 (C=O), 1656 (C=N), 1645 (C=C), 1200-1195 (C=S). ^{1}H NMR (δ ppm): 1.62 (t, 3H, CH_3), 2.23 (m, 4H, 2 CH_2), 2.33 (m, 4H, 2 CH_2), 4.22 (q, 2H, CH_2), 7.22-7.39 (m, 10H, 2 C_6H_5), 9.44-9.67 (m, br, 3H, 3NH).

To a suspension of **33** (5.3 g, 0.01 mol) in sodium ethoxide solution [prepared by dissolving sodium metal (0.64 g, 0.02 mol) in absolute ethanol (50 ml)]. The reaction mixture was heated in a boiling water bath for 5 h then the solid product formed upon pouring into ice/water containing hydrochloric acid (to pH 6) was collected by filtration.

Ethyl 2-azo(5-amino-1-phenylaminothiomethanoyl-3-phenylpyrazole-4-yl)-4,5,6.7-tetrahydrobenzo[b]thiophene-3-carboxylate (34)

Compound (**34**): Yellow crystals, from ethanol, yield 55 % (3.06 g), m.p. 300 °C. Analysis for $C_{27}H_{26}N_6O_2S_2$ (530.29): Calcd: C, 61.10; H, 4.90; N, 15.84; S, 6.03 %. Found: C, 61.26; H, 4.96; N, 15.49; S, 6.39 %. IR (υ/cm^{-1}): 3065 (CH aromatic), 2990, 2875 (CH_3, CH_2), 1685 (C=O), 1650 (C=N), 1640 (C=C), 1200–1190 (C=S). ^{1}H NMR (δ ppm): 1.63 (t, 3H,

CH_3), 2.24 (m, 4H, 2 CH_2), 2.31 (m, 4H, 2 CH_2), 4.25 (q, 2H, CH_2), 5.34 (5.2H, NH_2) 7.28–7.40 (m, 10H, 2 C_6H_5), 9.11 (s, br, 1H, NH).

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