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The Uses of 3-α-Bromoacetylcoumarin in a Novel Syntheses of 3-(Coumarin-3-yl) pyridazine and 3-(Coumarin-3-yl) ketoximothiophene Derivatives

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ABSTRACT

Novel syntheses of bromohydrazones and ketoximes could be realized by reactions of 3-α-bromoacetylcoumarin with a variety of reagents. Such compounds reacted readily with nucleophiles to give unique heterocyclic systems. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

3-Acetylcoumarins and their analogs reversibly arrest the mitosis of cells in the metaphase and are useful in treatment of diseases caused by uncontrolled rapidly proliferating cells [1–3].

Extensive work has been carried out on the syntheses and chemistry of coumarins and their condensed systems [1–5]. However, little has been reported on the utility of bromination for the preparation of condensed coumarins. This report is on the reaction of oximes and phenylhydrazones of 3-α-bromoacetylcoumarin with a variety of reagents in novel syntheses of pyridazines and thiophenes. It has been found that 3-(α-bromoacetyl)coumarin **1** reacts with benzenediazonium chloride to afford the phenylhydrazone derivative **2**. Compound **2** reacts with cyanomethylene reagents to afford the corresponding substituted alkyl derivatives. Thus, with malononitrile **3a** and ethyl cyanoacetate **3b**, the alkylated derivatives **4a** and **4b** were formed. The structures of **4a** and **4b** were established based on analytical and spectral data (see Experimental section) (Scheme 1).

Similar to the reaction of **1** with nucleophilic reagents (**4**), compound **2** reacted with potassium cyanide and potassium thiocyanate to afford the cyano and thiocyano derivatives **5a** and **5b**. The structures of **5a** and **5b** were confirmed on the basis of analytical and spectral data (Table 1).

The reaction of **1** with phenylhydrazine in ethanol containing sodium acetate afforded the phenylhydrazone derivative **6**. The structure of **6** was established on the basis of analytical and spectral data. Thus, the IR spectrum of the product revealed the presence of an NH stretching absorbance at 3420 cm^{-1} and a C=O stretching absorbance at 1685 cm^{-1}. The ^1H NMR spectrum exhibited a singlet at δ = 4.23 corresponding to a CH_2 group, a singlet at δ = 6.98 for coumarin H-4, a multiplet at δ = 7.32–7.46 for C_6H_5 and C_6H_4 moieties, and a singlet at δ = 9.23 for an NH group. Further confirmation for the structure of **6** was obtained through studying its reactivity toward chemical reagents. Thus, **6** reacted with diethyl 3-aminocrotononitrile-1,4 dicarboxylate [6] **7** to afford products that were separated based on the higher solubility of one of them in ethanol. The ethanol insoluble product was found to have a molecular formula of $C_{25}H_{18}N_4O_5$. Two possible formulas for isomeric structures were considered, **8** and **9**. The structure **9** was established for the reaction product based on the ^1H NMR spectrum that revealed the presence of a triplet at δ = 1.38 for

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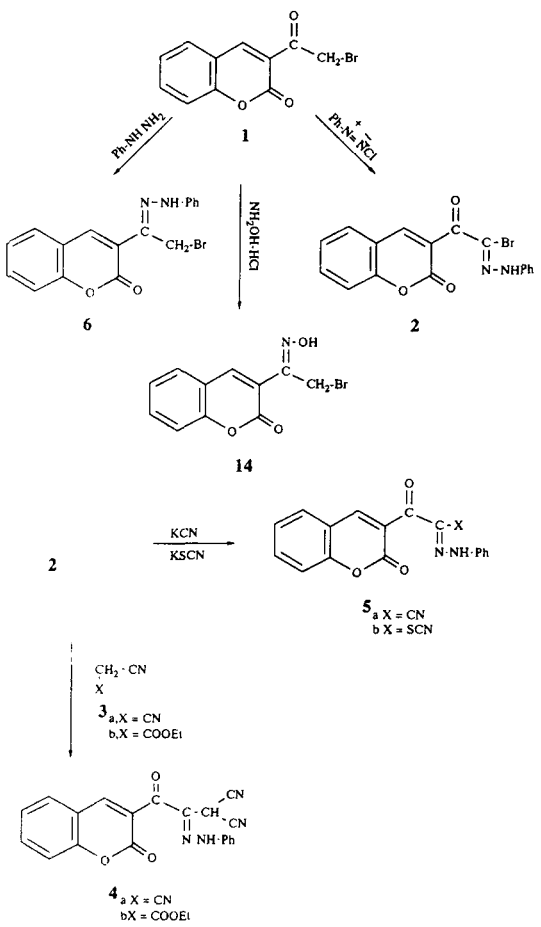
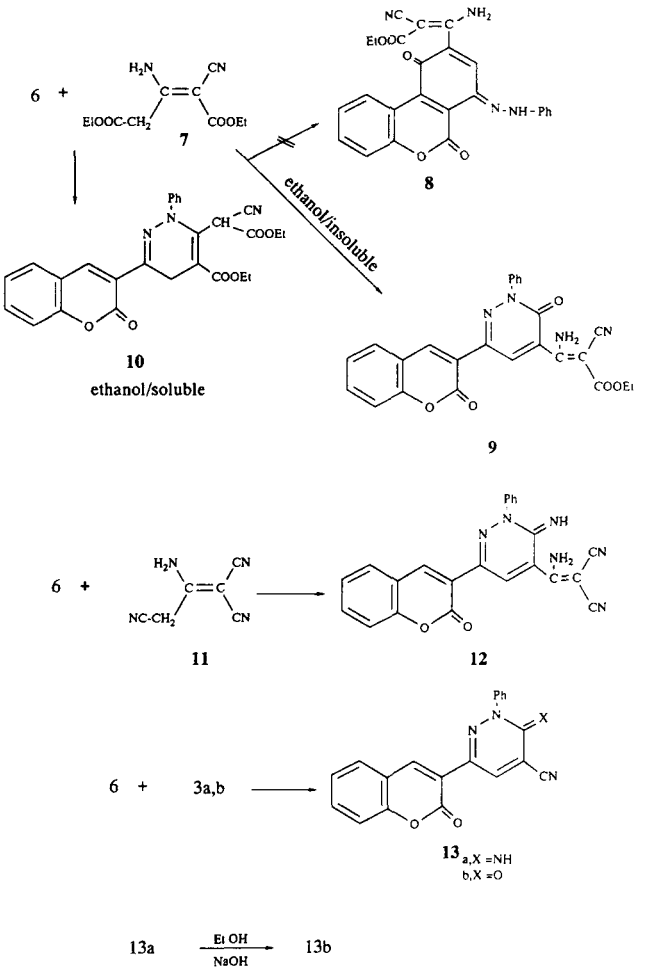
TABLE 1 IR and ^{1}H NMR Spectra of the New Compounds

Compounds	*IR* (ν, cm^{-1})	*^{1}H NMR* (δ)
2	3420 (NH), 3050 (CH), 1690, 1685 (2CO), 1640 (CN)	6.98 (s, 1H, coumarin H-4), 7.32–7.47 (m, 9H, C_6H_5, C_6H_4), 8.23 (s, 1H, NH)
4a	3420 (NH), 3045 (CM), 2220, 2225 (2CAN), 1685 (2CO), 1640 (CN)	4.21 (s, 1H, CH), 6.99 (s, 1H, coumarin H-4), 7.32–7.46 (m, 9H, C_6H_5, C_6H_4), 9.21 (s, 1H, NH)
4b	3410 (NH), 3050 (CH), 2980, 2875 (CH_3, CH_2), 2220 (CN), 1700, 1690, 1690, 1670 (3CO), 1640 (CN)	1.32 (t, 3H, J = 8.01 Hz, CH_3), 4.21 (9.2H, J = 8.01 Hz, CH_2), 4.25 (s, 1H, CH), 6.92 (s, 1H, coumarin H_4), 7.32–7.48 (m, 9H, C_6H_5, C_6H_4), 9.31 (s, 1H, NH)
5a	3425 (NH), 3050 (CH), 2220 (CN), 1690, 1690 (2 C=O), 1635 (CN)	6.98 (s, 1H, coumarin H-4), 7.34–7.46 (m, 9H, C_6H_5, C_6H_4), 9.22 (s, 1H, NH)
5b	3410 (NH), 3045 (CH), 2215 (CN), 1695, 1680	6.92 (S, 1H, coumarin H-4), 7.32–7.48 (m, 9H, C_6H_5, C_6H_4), 9.23 (s, 1H, NH)
6	3420 (NH), 3050 (CH), 2895 (CH_2), 1685 (C=O), 1640 (CN)	4.23 (s, 2H, cH_2), 6.98 (s, 1H, coumarin H-4), 7.32–7.64 (m, 9H, C_6H_5, C_6H_4), 9.23 (s, 1H, NH)
9	3450, 3420 (NH_2), 3050 (CH), 2975, 2890 (CH_3CH_2), 1695, 1680 (2C=O), 1640 (CN)	1.38 (t, 3H, J = 7.89 Hz, CH_3), 4.23 (q, 2H, J = 7.89 Hz, CH_2), 5.23 (s, 2H, NH_2), 6.99 (s, 1H, coumarin H-4), 7.23–7.47 (m, 10H, C_6H_5, C_6H_4, pyridazine H_4)
10	3045 (CH), 2990, 2895 (CH_3, CH_2), 2220 (CN), 1690, 1680 (3CO), 1640 (CN)	1.38 (t, 3H, J = 7.98 Hz, CH_3), 1.38 (t, 3H, J = 8.02 Hz, CH_3), 3.38 (s, 1H, CH), 4.21 (q, 2H, J = 8.02 Hz, CH_2), 4.25 (9.2H, J = 8.02 Hz, CHz), 6.11 (s, 2H, pyridazine CH_2), 6.99 (s, 1H, coumarin H-4), 7.33–7.48 (m, 9H, C_6H_5, C_6H_4)
12	3450–3420 (NH_2, NH), 3050 (CH) 2225, 2220 (2CN), 1685 (CO), 1675 exocyclic (CN), 1635 (CN)	4.58 (s, 2H, NH_2), 6.98 (S, 1H, coumarin H-4), 7.31–7.48 (m, 10H, C_6H_5, C_6H_4 pyridazine H-4), 9.56 (s, 1H, NH)
13a	3420 (NH), 3045 (CH), 2220 (CN), 1680 (CO), 1675 exocyclic (CN)	6.97 (s, 1H, coumarin H-4), 7.32–7.46 (m, 10H, C_6H_5, C_6H_4, pyridazine H-4), 8.21 (s, 1H, NH)
13b	3050 (CH), 2220 (CN), 1685, 1680 (2CO)	6.97 (s, 1H, coumarin H-4), 7.31–7.48 (m, 10H, C_6H_5, C_6H_4, pyridazine H-4)
14	3570–3380 (OH), 3045 (CH), 1690 (CO), 1640 (CN)	4.48 (s, 2H, CH_2), 6.99 (s, 1H, coumarin H-4), 7.32–7.45 (m, 5H, C_6H_5), 10.3 (s, 1H, OH)
15a	3570–3410 (OH), 3050 (CH), 2910 (CH_2), 2220 (CN), 1685 (CO), 1645 (CN)	3.81 (s, 2H, CH_2), 6.91 (s, 1H, coumarin H-4), 7.32–7.44 (m, 4H, C_6H_4), 10.3 (s, 1H, OH)
15b	3560–3410 (OH), 3050 (CH), 2215 (CN), 1635 (C=N)	3.84 (s, 2H, CH_2), 6.94 (s, 1H, coumarin H-4), 7.31–7.45 (m, 4H, C_6H_4), 10.31 (s, 1H, OH)
16	3560–3410 (OH, NH), 3040 (CH arom)	6.96 (5, 1H, OH)
17a	3560–3430 (OH), 3050 (CH arom.), 2220 (CN), 1680 (CO), 1640 (CN)	3.91 (s, 2H, CH_2), 6.92 (s, 1H, coumarin H-4), 7.32–7.46 (m, 4H, C_6H_4), 10.31 (s, 1H, OH)
17b	3560–3420 (OH, NH), 3045 (CH arom.), 2220 (CN), 1980 (CO), 1640 (CN)	6.93 (s, 1H, coumarin H-4), 7.32–7.48 (m, 9H, C_6H_5, C_6H_4), 8.44 (s, 1H, NH), 10.33 (s, 1H, OH)
18	3580–3400 (OH, $2NH_2$), 3050 (CH arom.), 1685 (CO), 1640 (C=N)	2.89, 4.58 (25, 4H, $2NH_2$), 6.94 (s, 1H, coumarin H_4), 6.01 (s, 1H, thiophene H-3), 7.33–7.47 (m, 4H, C_6H_4), 10.32 (s, 1H, OH)
21a	3580–3420 (OH, NH_2NH), 3050 (CH arom.), 2220 (CN), 1690 (CO), 1640 (C=N)	5.21 (s, 2H, NH_2), 6.94 (s, 1H, coumarin H-4), 7.30–7.47 (m, 9H, C_6H_5, C_6H_4), 8.42 (s, 1H, NH), 10.32 (s, 2H, OM)
21b	3560–3415 (OH, NH_2, NH), 3050 (CH arom.), 2968–2893 (CH_3, CH_2), 1680 (CO)	1.31 (t, 3H, J = 8.02 H_2 (H_3), 4.19 (q, 2H, J = 8.02 H_2, (H_2), 5.31 (s, 2H, NH_2), 6.99 (s, 14, coumarin H-4), 7.31–7.48 (m, 9H, C_6H_5, C_6H_4), 8.91 (s, 1H, NH), 10.28 (s, 1H, OH)
21c	3560–3420 (OH, NH), 3050 (CH arom.), 2946 (CH_3), 1700, 1658 (2CO), 1645 (C=N)	1.62 (s, 3H, CH_3), 2.21 (s, 3H, CO–CH_3), 6.93 (s, 1H, coumarin H_4), 7.32–7.49 (m, 9H, C_6H_5, C_6H_4), 8.35 (s, 1H, NH), 10.29 (s, 1, OH)
21d	3560–3425 (OH, NH), 3050 (CH arom.), 2985, 2892 (CH_3, CHz), 1695, 1680	1.31 (t, 3H, J = 7.99 Hz, CH_3), 1.91 (s, 3H, CH_3), 4.21 (q, 2H, J = 7.99 Hz, CH_2), 6.92 (s, 1H, coumarin H-4), 7.30–7.48 (m, 9H, C_6H_5, C_6H_4), 8.39 (s, 1H, NH), 10.21 (s, 1H, OH)



SCHEME 1



SCHEME 2

the CH_3 group; a quartet at δ = 4.23 for the CH_2 group; a singlet at δ = 5.23 for the NH_2 group; a singlet at δ = 6.99 for coumarin H-4; and a multiplet at δ = 7.23–7.47 for C_6H_5, C_6H_4, and pyridazine H-4.

The ethanol soluble product was found to have a molecular formula of $C_{27}H_{23}N_3O_6$ for which the pyridazine structure **10** was established on the basis of ^{1}H NMR spectrum that revealed the presence of two triplets at δ = 1.36 and δ = 1.38 for the two CH_3 groups, a singlet at δ = 3.38 for the CH group, two quartets at δ = 4.21 and 4.25 for the two CH_2 groups, a singlet at δ = 6.11 for the pyridazine CH_2 group, a singlet at δ = 6.99 for coumarin H-4, and a multiplet at δ = 7.33–7.48 for C_6H_5 and C_6H_4 (Scheme 2).

Similarly, the reaction of **6** with 3-amino-2,4 dicyanocrotononitrile **11** [7] afforded the 3-(coumarin-3-yl)pyridazine derivative **12**, the same arguments which were used to confirm the structure of **10** being applied to establish the structure of **12** (Scheme 2) (see Experimental section).

The reactions of **6** with cyanomethylene reagents were also studied. Thus, with each of the malononitrile **3a** and ethyl cyanoacetate **3b** in refluxing dimethylformamide containing a catalytic amount of piperidine the 3-(coumarin-3-yl)pyridazine, derivatives **13a** and **13b**, respectively, were obtained. However, **13a** was converted to **13b** when heated with ethanolic sodium hydroxide. Such a conversion of an imino function into a C=O group has been reported [7–11] (Scheme 2).

The reaction of **1** with hydroxylamine hydrochloride afforded the bromoketoxime derivative **14**. The structure of **14** was confirmed on the basis of analytical and spectral data. Thus, the IR spectrum revealed the presence of an OH group stretching absorbance at 2570–3380 cm^{-1} (Table 1).

Further confirmation for the structure of **14** was obtained through studying its reactivity toward various chemical reagents. Thus, the reaction of **14** with nucleophilic reagents, such as potassium cyanide and potassium thiocyanate, afforded the corresponding cyano and thiocyano derivatives **15a** and **15b**, respectively. On the other hand, **14** coupled with benzenediazonium chloride to afford the phenylhy-

TABLE 2 Physical and Analytical Data of Prepared Compounds

Compound No.	Mp (°C)	Yield (%)	Crystal Solvent	Formula (MW)	Found Analysis (%) (calcd) C	H	N
2	175	71	ethanol	$C_{17}H_{11}N_2O_3Br$	55.3	2.7	7.4
				(371.19)	54.9	2.9	7.5
4a	215	81	dioxane	$C_{20}H_{12}N_4O_3$	67.2	3.5	15.9
				(356.24)	67.4	3.4	15.7
4b	135	72	dioxane	$C_{22}H_{17}N_3O_5$	65.9	4.1	10.6
				(403.25)	65.5	4.2	10.6
5a	170	73	ethanol	$C_{18}H_{11}N_3O_3$	68.4	3.7	13.5
				(317.20)	68.1	3.5	13.1
5b	195	67	ethanol	$C_{18}H_{11}N_3O_3S$	61.5	3.4	12.3
				(349.31)	61.9	3.1	12.0
6	120	84	DMF	$C_{17}H_{13}N_2O_2Br$	57.4	3.8	7.5
				(357.09)	57.1	3.6	7.8
9	160	54	DMF	$C_{25}H_{18}N_4O_5$	66.4	4.1	12.4
				(454.29)	66.1	3.9	12.3
10	156	38	ethanol	$C_{27}H_{23}N_3O_6$	66.8	4.5	8.9
				(485.30)	66.8	4.7	8.6
12	251	90	DMF	$C_{23}H_{14}N_6O_2$	67.9	3.6	20.8
				(406.29)	67.9	3.4	20.7
13a	210	72	DMF	$C_{20}H_{12}N_4O_2$	70.4	3.3	16.5
				(340.24)	70.6	3.5	16.5
13b	197	68	ethanol	$C_{20}H_{11}N_3O_3$	70.2	3.3	12.5
				(341.23)	70.4	3.2	12.3
14	162	90	ethanol	$C_{11}H_8NO_3Br$	46.8	2.9	5.1
				(282.02)	46.8	2.8	4.9
15a	180	72	ethanol	$C_{12}H_8N_2O_3$	63.2	3.3	12.4
				(228.14)	631.1	3.5	12.3
15b	155	64	dioxane	$C_{12}H_8N_2O_3S$	55.3	3.3	10.5
				(260.24)	55.4	3.1	10.8
16	150	68	ethanol	$C_{17}H_{12}N_3O_3Br$	52.5	3.5	10.6
				(386.10)	52.8	3.1	10.8
17a	228	71	ethanol	$C_{18}H_{12}N_4O_3$	65.1	3.7	16.5
				(332.22)	65.0	3.6	16.8
17b	183	59	ethanol	$C_{18}H_{12}N_4O_3S$	59.6	3.5	15.5
				(364.32)	59.3	3.3	15.4
18	223	90	dioxane	$C_{14}H_{11}N_3O_3S$	56.2	3.3	14.0
				(298.27)	55.8	3.6	13.9
21a	130	71	DMF	$C_{21}H_{14}N_4O_3S$	62.9	3.2	13.6
				(402.35)	62.7	3.5	13.9
21b	100	67	dioxane	$C_{23}H_{19}N_3O_5S$	61.7	4.0	9.0
				(449.36)	61.4	4.2	9.3
21c	130	63	dioxane	$C_{23}H_{18}N_2O_4S$	66.1	4.5	6.9
				(418.35)	66.0	4.3	6.7
21d	85	78	DMF	$C_{24}H_{20}N_2O_5S$	64.5	4.7	6.5
				(448.36)	64.3	4.4	6.2

drazone derivative **16**. Similarly, **16** reacted with potassium cyanide and potassium thiocyanate to afford **17a** and **17b**, respectively (identical melting point and mixture melting point).

The reaction of **14** with cyanothioacetamide afforded the coumarin-3-yl ketoximo-2-thiophene derivative **18** [12] (Scheme 3).

The active methylene reagents **19a–b** reacted with phenyl isothiocyanate in basic dimethylformamide to afford the intermediate salts **20a–d**. The reaction of the latter intermediates with **14** afforded the thiophene derivatives **21a–d**. The structures of **21a–d** were established on the basis of analytical and spectral data. Thus, as an example, the structure of **21a** was based on its IR spectrum, which revealed the presence of OH, NH_2, and NH stretching absorbances at 3580–3420 cm^{-1} and a CN group stretching absorbance at 2220 (cm^{-1}). The ^1H NMR spectrum revealed the presence of a singlet at $\delta = 5.21$ for the NH_2 group (D_2O exchangeable), a singlet at $\delta = 6.94$

for coumarin H-4, a multiplet at δ = 7.30–7.47 for C_6H_5 and C_6H_4, a singlet at δ = 8.42 for the NH group, and a singlet at δ = 10.32 for the OH group (Table 1).

EXPERIMENTAL

All melting points were uncorrected. The IR spectra were taken as KBr disks on a Pye unicam SP-100 spectrometer. ^{1}H NMR spectra (DMSO-d6 as solvent) were obtained on a varian A-90 spectrometer using TMS as an internal standard. Analytical data were obtained from the Microanalytical Data Unit at Cairo University of Egypt.

3-(α-Bromo-α-phenylhydrazonoacetyl)coumarin **2** *and 3-(α-bromo-α-phenylhydrazonoacetyloximino)coumarin* **16**

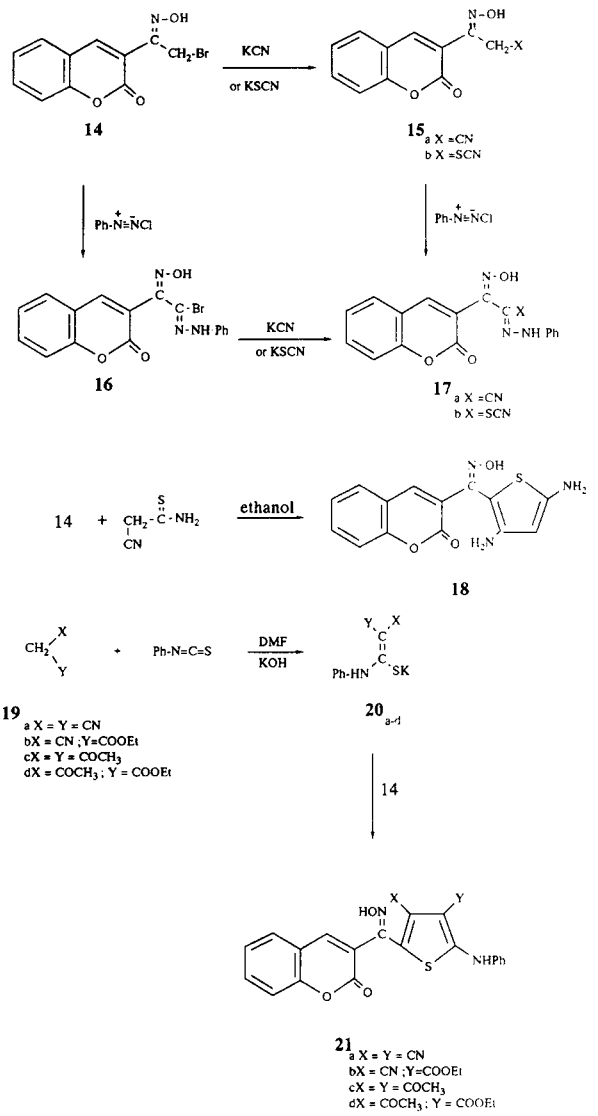
To a cold solution (0–5°C) of **1** or **14** (0.01 mole) in ethanol (30 mL) containing sodium acetate (5 g), benzenediazonuim chloride (0.01 mole) [prepared by the addition of sodium nitrite solution (0.01 mole) to a cold suspension of aniline (0.01 mole) containing the appropriate amount of hydrochloric acid] was added with stirring. The reaction mixture was left for 2 hours with stirring and the resulting solid product was collected by filtration compound **2**, orange crystals, yield 71%, mp 175°C from ethanol; compound **16** (see Table 2).

4-(Coumarin-3-yl)-2-cyano-3-(phenylhydrazono)-4-oxobutyronitrile **4a**. *4-(Coumarin-3-yl)-2-ethoxycarbonyl-3-(phenylhydrazono)-4-oxobutyronitrile* **4b**

General Procedure for Preparation of Compounds **4a** *and* **4b**. To a solution of **2** (0.01 mole) in dimethylformamide (20 mL) containing triethylamine (0.5 mL), malononitrile **3a** (0.01 mole) or ethyl cyanoacetate **3b** (0.01 mole) was added. The reaction mixture was heated under reflux for 3 hours. The solid product formed upon dilution with water containing a few drops of hydrochloric acid was collected by filtration and recrystallized from dioxane (Table 2).

3-(Coumarin-3-yl)3-oxo-2-(phenylhydrazono)propiononitrile **5a**. *3-(Coumarin-3-yl)ketoximopropiononitrile* **15b**, *3-(Coumarin-3-yl)-3-ketoximopropionitrile* **15a**, *3-(Coumarin-3-yl)-3-ketoximopropionothionitrile* **15b**, *3-(Coumarin-3-yl)-3-ketoximo-2-(phenylhydrazono)propiononitrile* **17a**, *3-(Coumarin-3-yl)-3-ketoximo-2-(phenylhydrazono)propionothionitrile*, **17b**.

5a, **5b**, **15a**, **15b**, **17a**, *and* **17b**. General Procedure. To a solution of **2**, **14**, or **16** (0.01 mole) in ethanol (30 mL), a solution of potassium cyanide or potassium thiocyanate (0.01 mole) was added. The reaction mixture was heated in a boiling water bath for 10 minutes. The solid product formed upon dilution with water containing a few drops of hydrochloric acid was collected by filtration and crystallized from ethanol (Table 2).



SCHEME 3

3-(α-Bromacetyl-α-phenylhydrazono)coumarin **6**. To a solution of **1** (0.01 mole), phenylhydrazine (0.01 mole) was added. The reaction mixture was heated under reflux for 3 hours, then evaporated *in vacuo*. The residual product was triturated with diethyl ether and collected by filtration (Table 2).

3-(Coumarin-3-yl)-1-phenyl-5-(3-amino-1-ethoxycarbonylcrotononitrile-3-yl)pyridazine-6-one **9** *(Eth-*

anol Insoluble), 3-(Coumarin-3-yl)-(4H)-1-phenyl-5-ethoxycarbonyl-6-(ethoxycarbonyl-cyanomethyl) pyridazine **10** *(Ethanol Soluble).* To a solution of **6** (0.01 mole) in ethanol (50 mL) containing triethylamine (0.5 mole), diethyl 3-aminocrotononitrile-1.4-dicarboxylate **7** (0.01 mole) was added. The reaction mixture was heated under reflux for 5 hours, solid that had formed was collected by filtration to yield **9**, and the filtrate was diluted with water to yield **10** (Table 2).

3-(Coumarin-3-yl)-6-imino-5-(2-cyano-3-amino-crotononitrile-3-yl)-1-phenylpyridazine **12**, *3-(coumarin-3-yl)-6-imino-1-phenylpyridazine-5-carbonitrile* **13a**, *3-(coumarin-3-yl)-6-oxo-1-phenylpyridazine-5-carbonitrile* **13b**. *General Procedure.* To a solution of **6** (0.01 mole) in dimethylformamide (30 mL) containing triethylamine or piperidine (0.5 mole), either 3-amino-2,4,dicyanocrotononitrile **11**, malononitrile **3a**, or ethyl cyanoacetate **3b** (0.01 mole) was added. The reaction mixture was heated under reflux for 8 hours. The solid product that formed upon dilution with water was collected by filtration and crystallized from the proper solvent (Table 2) to give **12**, **13a**, and **13b**, respectively.

3-(α-Bromoacetyloximo)coumarin **14**. To a solution of **1** (0.01 mole) in methanol (50 mL), a solution of hydroxylamine hydrochloride (0.01 mole) in water (5 mL) was added. The reaction mixture was stirred at 25°C for 24 hours, then poured into water. The solid product that formed was collected by filtration and crystallized from ethanol (Table 2).

Coumarin-3-yl 4,5-Diaminothiophene-2-yl Ketoxime **18**. To a solution of *14* (0.01 mole) in ethanol (50 mL), cyanothioacetamide (0.01 mole) was added. The mixture was heated under reflux for 4 hours. The solid product that formed was collected by filtration and crystallized from dioxane (Table 2).

3,4-Dicyano-5-(phenylamino)thiophene-2-yl Coumarin-3-yl Ketoxime (**21a**), *3-Cyano-4-ethoxycarbonyl-5-(phenylamino)thiophene-2-yl Coumarin-3-yl Ketoxime* (**21b**), *3,4-Diacetyl(phenylamino)thiophene-2-yl Coumarin-3-yl Ketoxime* (**21e**), *4-Ethoxycarbonyl-3-acetyl-5-(phenylamino)thiophene-2-yl Coumarin-3-yl Ketoxime* (**21d**). General Procedure. To a solution of each compound (malononitrile **3a**, ethyl cyanoacetate **3b**, acetylacetone, or ethyl acetoacetate) (0.025 mole) in dimethylformamide (30 mL), potassium hydroxide (0.025 mole) in dimethylformamide (30 mL) was added followed by phenyl isothiocyanate (0.25 mole). The reaction mixture was stirred at room temperature overnight, then treated with **14** (0.05 mole) and left at room temperature (25°C) for 24 hours. The solid product that was formed upon addition of water containing a few drops of hydrochloric acid (to pH = 6) was collected by filtration and crystallized from the proper solvent to give **21a**, **21b**, **21c**, and **21d**, respectively.

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