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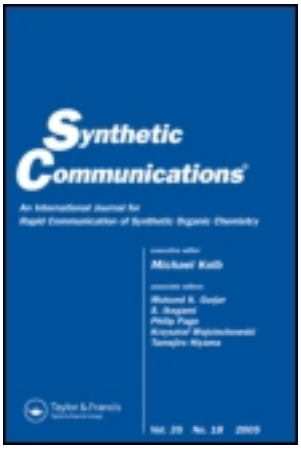

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Reactions With Hydrazonoyl Halides 45: Synthesis of Some New Triazolino [4,3-*a*]pyrimidines, Pyrazolo [3,4-*d*]pyridazines, Isoxazolo[3,4-*d*]pyridazines, and Thieno[2,3-*b*]pyridines

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Abstract: Triazolino[4,3-*a*]pyrimidines pyrazolo[3,4-*d*]pyridazines and isoxazolo[3,4-*d*] pyridazines were synthesized from hydrazonoyl halides. Also, 3-aminothieno[2,3-*b*] pyridines and pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridines were synthesized from cynothioacetamide. Structures of the newly synthesized compounds were established on the basis of elemental analyses and spectral data.

Keywords: Hydrazonoyl halides, isoxazolo[3,4-*d*]pyridazines, pyrazolo[3,4-*d*]pyridazines, triazolino[4,3-*a*]pyrimidines, thieno[2,3-*b*]pyrimidines

INTRODUCTION

1,2,4-Triazolo[4,3-*a*]pyrimidines have been found to exhibit antiviral, antifungal, antimicrobial, herbicidal, plant regulator, antitumor, antihypertensive, cardiovascular, and anxiolytic activities.[1,2] Pyrazoles and annelated pyrazoles have long been known to exhibit diverse biological activities. Among these activities include their use as antipyretic,[3,4]analgesic,[4,5] antitumor,[5] hypnotic,[6] fungicidal,[7] and herbicidal[8] agents. Oxazoles are widely investigated for therapentic uses, especially as tranquilizing agents

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and central nervous system (CNS) regulants and are reported to have bacteriostatic, bactericidal, and fungicidal activities.[9] Moreover thienopyridines are of special importance because of their reported biological activities.[10] Also, hydrazonoyl halides have been widely used for the synthesis of heterocyclic compounds.[11–16] We report herein the synthesis of some new triazolino[4,3-*a*]pyridazines pyrazolo[3,4-*d*]pyridazines, isoxazolo[3,4-*d*] pyridazines, and thieno[2,3-*b*]pyrimidines.

RESULTS AND DISCUSSION

Treatment of ethyl 4-methyl-6-[2-(thienyl)]-2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate (**1a**) with *C*-methoxy-*N*-phenylhydrazonoyl chloride (**2a**) and triethylamine in boiling chloroform under reflux gave the 1,2,4-triazolo[4,3-*a*]pyrimidine-5-carboxylates **5a**. ^{1}H NMR spectrum of **5a** showed signals at $\delta = 1.25$ (t, 3H, CH_2CH_3), 2.52 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.12 (q, 2H, CH_2CH_3), 6.83 (s, 1H, CH), and 7.07–8.21 (m, 8H, ArH). Its IR spectrum revealed bands at $\nu = 1735$ and $1689\,cm^{-1}$ (CO).

Thus, treatment of ethyl 6-methyl-4-(2-thienyl)-2-methylthio-3,4-dihydropyrimidine-5-carboxylate (**6a**) with **2a** in boiling ethanolic sodium ethoxide solution gave products identical with **5a**.

The formation of **5** can be explained by 1,3-dipolar cycloaddition of nitrile imide **6** (generated in situ from hydrazonoyl halides **2** with triethylamine or sodium ethoxide) to the C═S of **1a** to give intermediate **3**, with ring opening and ring closure to afford **5** by elimination of hydrogen sulfide (Scheme 1).

Similarly, treatment of the appropriate hydrazonoyl halides **2b–f** with **1a** (or treatment of **2a–g** with **1b**) in boiling chloroform containing triethylamine gave 1,2,4-triazolo[4,3-*a*]pyrimidine-5-carboxylate derivatives **5b–f** and **9a–g**, respectively.

By analogy, the appropriate hydrazonoyl halides **2a–g** (or **2a–e**) reacted with each of 2-methylthio-4-oxo-6-(2-thienyl)-3-hydropyrimidine-5-carbonitrile (**10**) or 2-methylthio-4-oxo-6-phenyl-3-hydropyrimidine-5-carbonitrile (**11**) in boiling ethanolic sodium ethoxide solution under reflux to give 1,2,4-triazolino[4,3-*a*]pyrimidine derivatives **12a–g** and **13a–f**, respectively (Scheme 2).

Treatment of *C*-methoxycarbonyl-*N*-phenylhydrazonoyl chloride (**2a**) with 3-(dimethylamino)-1-(2-thienyl)prop-2-en-1-one (**15**) and triethylamine in boiling tolune under reflux afforded methyl 1-phenyl-4-(2-thienylcarbonyl)pyrazole-3-carboxylate (**16a**) (Scheme 3). ^{1}H NMR spectrum of **16a** showed signals at $\delta = 3.69$ (s, 3H, OCH_3), 7.44–7.88 (m, 8H, ArHs), and 8.24 (s, 1H, pyrazole C-5). Similarly, the appropriate hydrazonoyl halides **2b–g** reacted with **15** to give 1-phenyl-3-substituted 4-(2-thienylcarbonyl)-pyrazoles **16b–g**, respectively.

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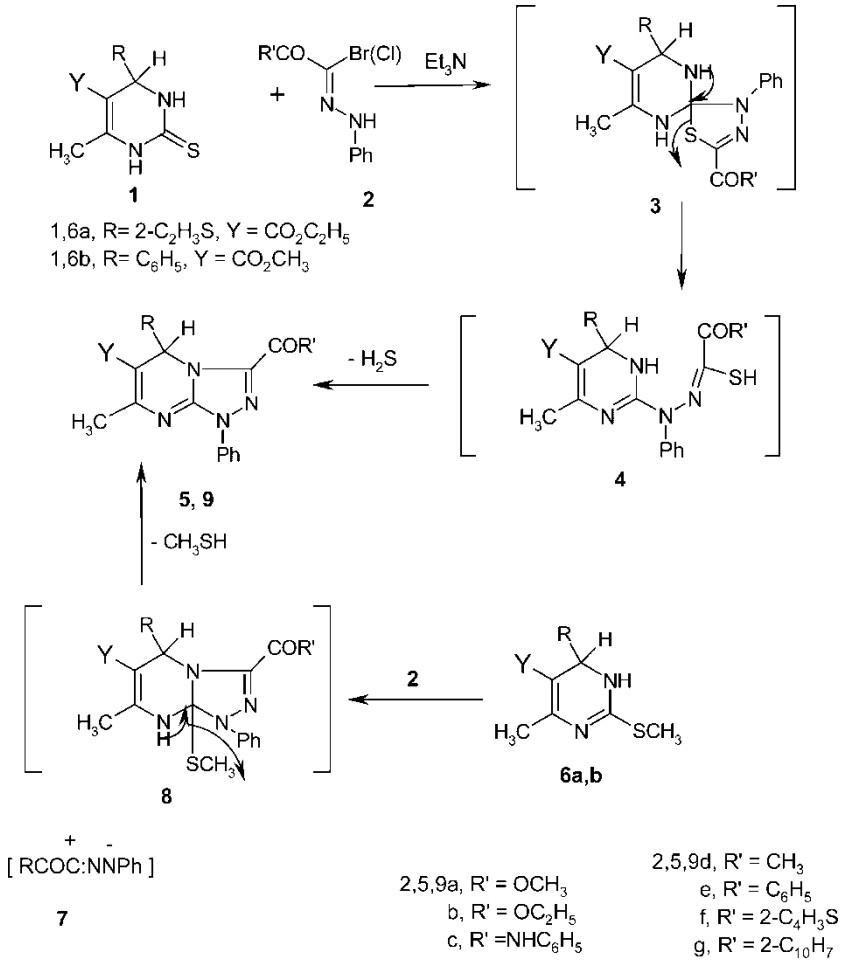

Scheme 1.

Treatment of **16a** with hydrazine hydrate in boiling ethanol afforded one isolable product according to TLC, formulated as 2-phenyl-4-(2-thienyl)-6-hydropyrazolo[3,4-*d*]pyridazin-7-one (**17a**). Structure of **17a** was elucidated by elemental analysis, spectral data, and alternative synthesis. ^{1}H NMR spectrum of **17a** showed signals at $\delta = 7.33-7.62$ (m, 8 H, ArHs), 8.23 (s, 1H, pyrazole C-5), and 11.12 (s, br., 1H, NH). Thus, treatment of either **16b** or **16c** with boiling ethanol gave a product identical in all respects (mp, mixed mp, and spectra) to **17a**. Also, pyrazolo[3,4-*d*]pyridazines **17b–e** were obtained from the appropriate pyrazoles **11d–g** with hydrazine hydrate in boiling ethanol under reflux (Scheme 3).

Treatment of the appropriate hydroximoyl chlorides **18a–f** with **15** in toluene at room temperature in presence of triethylamine gave 4,5-diacylisoxazoles

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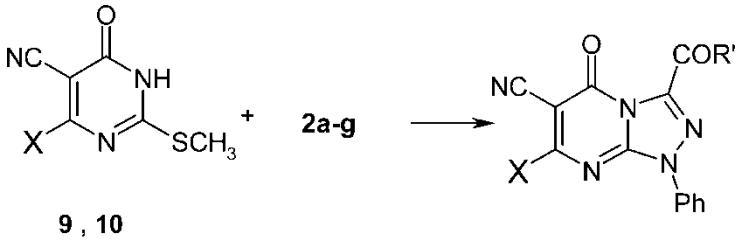

9 , 10

(12, 13)a-g

9, 12, X = 2-thienyl
10, 11, X = Phenyl

12,13a, R' = OCH_3
b, R' = OC_2H_5
c, R' = NHC_6H_5
d, R' = CH_3

12,13e, R' = C_6H_5
f, R' = 2-C_4H_3S
g, R' = 2-$C_{10}H_7$

Scheme 2.

19a–f, respectively. Compounds **19a–f** were converted to isoxazolo[3,4-*d*] pyridazines **20a–f**, respectively (Scheme 3).

Treatment of **15** with cyanothioacetamide in boiling pyridine (or in ethanol containing catalytic amount of piperidine) under reflux gave 2-sulfanyl-6-(2-thienyl)pyridine-3-carbonitrile (**21**) in a good yield. Structure **21** was elucidated by elemental analysis, spectra, and chemical transformation. Thus, **21** reacted with ethyl chloroacetate in *N*,*N*-dimethylformamide containing potassium hydroxide to afford the product corresponding to addition and dehydrochlorination reactions.

The IR spectrum of this product showed bands corresponding to CN and ester-CO groups. Its ^{1}H NMR spectrum revealed the signals at $\delta = 1.23$ (t, 3H, CH_2CH_3), 4.09 (s, 2H, SCH_2), 4.19 (q, 2H, CH_3CH_2), and 7.47–8.04 (m, 5H, ArHs). Based on the these data, these reaction products could be formulated as ethyl 2-(3-cyano-6-(2-thienyl)-2-pyridylthio) acetate (**22a**). Further confirmation of the structure of **22a** arose from their cyclization in boiling ethanol containing a catalytic amount of piperidine to give the corresponding ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxyylate **23a** (Scheme 1). The IR spectrum of **23a** showed no band of the CN function but the bands at 3420, 3301 (NH_2 group). ^{1}H NMR spectrum of **23a** revealed an absence of signals of the $-SCH_2-$ group and the presence of the NH_2 protons. These findings proved that the CN and the $-SCH_2-$ groups were both involved in the cyclization step leading to **23a**.

Also, **21** reacted with chloroacetone in *N*,*N*-dimethylformamide containing potassium hydroxide to afford 2-(2-oxopropylthio)-6-(2-thienyl)pyridine-3-carbonitrile (**22b**). The reaction seemed to proceed through dehydrochlorination to give the **22b**, which underwent cyclization via addition of the $-SCH_2-$

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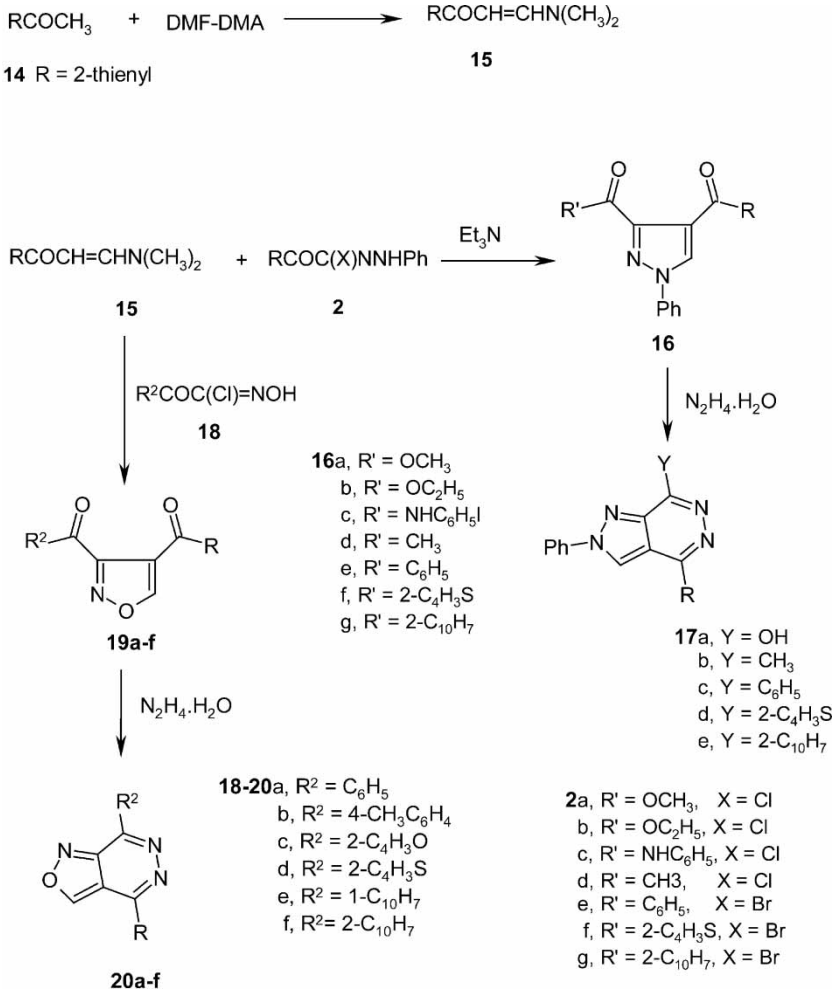

Scheme 3.

hydrogens to the nitrile function to give 1-(3-amino-6-(2-thienyl)thiopheno [2,3-*b*]pyridine-2-yl)ethan-1-one (**23b**). ^{1}H NMR of **23b** showed signals at $\delta = 2.39$ (s, 3H), 4.05 (s, 2H), and 7.14–7.78 (m, 5H).

Similarly, compound **21** reacted with each of chloroacetonitrile or iodomethane in *N*,*N*-dimethylformamide containing potassium hydroxide and afforded 2-(cyanomethylthio)-6-(2-thienyl)pyridine-3-carbonitrile (**22c**) and 2-methylthio-6-(2-thienyl)pyridine-3-carbonitrile (**22d**), respectively. Compound **22c** was converted to 3-amino-6-(2-thienyl)thieno[2,3-*b*] pyridine-2-carbonitrile (**23c**) by boiling in ethanol containing catalytic amounts of piperidine (Scheme 4).

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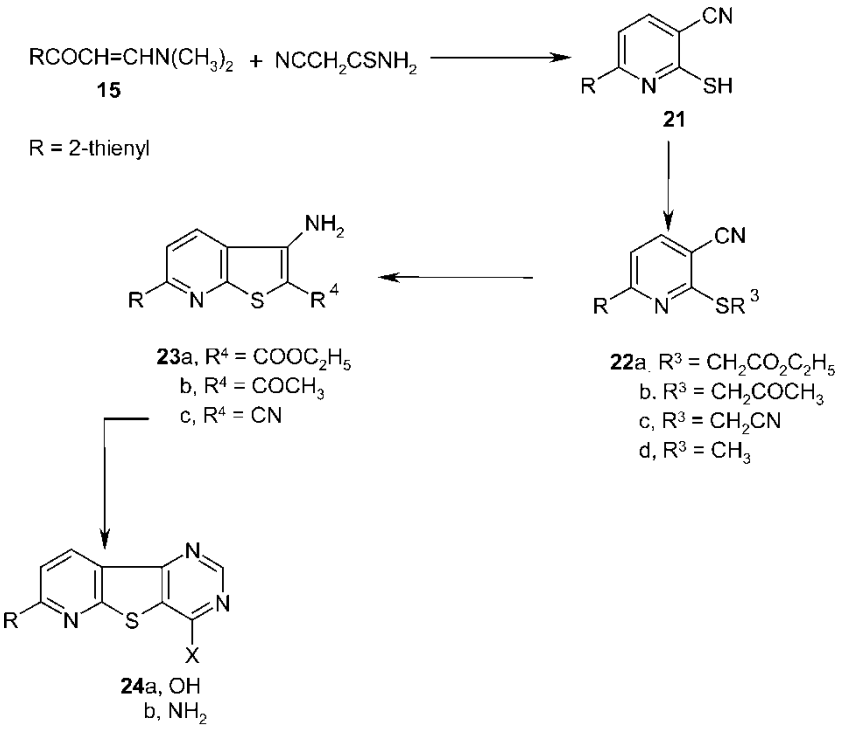

Scheme 4.

Compound **23c** reacted with each of formic acid or formamide to give the corresponding 7-(2-thienyl)-3-hydropyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine-4-one (**24a**) and 7-(2-thienyl)pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine-4-ylamine (**24b**), respectively (Scheme 4). Structures **24a** and **24b** were established on the basis of spectral data and elemental analysis. Thus, IR spectrum of **24a** revealed a band at 1654 (C═O). IR spectrum of **24b** revealed bands at 3471, 3317 (NH_2).

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300-MHz spectrometer, and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center of the Cairo University. 2-Bromoacetylthiopene,[17] hydrazonoyl halides[18–24] **2a–g**, and hydroximoyl chorides[25–28] **18a–e** were prepared as previously reported.

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1,2,4-Triazilino[4,3-*a*]pyrimidines 5a–f, 9a–g, 12b–g, and 13b–e

Method A: An equimolar amount of each of the appropriate hydrazonoyl halides **2a–g**, the appropriate **6a**, **6b**, **10**, or **11**, and sodium ethoxide (5 mmol) in ethanol (20 mL) was refluxed for 3 h. The reaction mixture was cooled, and the resulting solid was collected and crystallized from ethanol to give (**5a–f**, **9a–g**, **12b–g**, and **13a–e** (Tables 1 and 2).

Method B: A mixture of the appropriate hydrazonoyl halides **2a–g** (5 mmol) and the appropriate pyrimidin-2-thione **1a** or **1b** (1.38 g, 5 mmol) in chloroform (20 mL) containing triethylamine [0.5 g (0.75 mL), 5 mmol] was refluxed for 10 h. Chloroform was evaporated under reduced pressure, and the residue solid was crystallized from ethanol to give products identical in all respects (mp, mixed mp, and spectra) with corresponding products obtained by method A.

Ethyl 6-Methyl-4-(2-thienyl)-2-methylthio-3,4-dihydropyrimidine-5-carboxylate (6a) and Ethyl 6-Methyl-2-methylthio-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (6b)

Equimolar amounts of the appropriate pyrimidine-2-thione derivatives **1a** and **1b** and sodium methoxide (5 mmol) in methanol (20 mL) were stirred for 3 h. Iodomethane (0.72 g, 5 mmol) was added with stirring; after 2 h the resulting solid was collected and recrystallized from the proper solvent to give **6a** and **6b**, respectively (Tables 1 and 2).

3-(Dimethylamino)-1-(2-thienyl)prop-2-en-1-one (15)

Equimolar amounts of 2-acetylthiophene (**14**) and dimethylformamide-dimethylacetal (50 mmol each) were refluxed in dry xylene (40 mL) for 4 h. The hot solution was evaporated to its half volume and then cooled. The resulting solid was collected and crystallized to give **15** (Tables 1 and 2).

3-Acyl-1-phenyl-4-(2-thienoyl)pyrazoles 16a–g

Equimolar amounts of each of 3-(dimethylamino)-1-(2-thienyl)prop-2-en-1-one (**15**) and the appropriate hydrazonoyl halides **2a–g** (5 mmol) were refluxed in dry toluene containing triethylamine for 3 h. The hot solution was filtered off, and the filtrate was evaporated and triturated with petroleum ether (40–60°C). The resulting solid was collected and recrystallized from ethanol to give **16a–g**, respectively (Tables 1 and 2).

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Table 1. Characterization data of the newly synthesized compounds

Compd. no.	Mp (°C) solvent	Yield (%), color	Mol. Formula, Mol. wt	% Analyses calcd., found			
				C	H	N	S
5a	125–27	55	$C_{21}H_{20}N_4O_4S$	59.42	4.75	13.20	7.55
	EtOH	Brown	424.48	59.58	4.63	13.36	7.39
5b	160–61	65	$C_{22}H_{22}N_4O_4S$	60.26	5.06	12.78	7.31
	EtOH	Brown	438.51	60.00	4.92	12.65	7.43
5c	109–10	55	$C_{26}H_{23}N_5O_3S$	64.31	4.77	14.42	6.60
	EtOH	Deep brown	485.57	64.48	4.88	14.51	6.71
5d	194–96	75	$C_{21}H_{20}N_4O_3S$	61.75	4.94	13.72	7.85
	EtOH	Pale olive	408.48	61.84	5.03	13.83	7.94
5e	145–46	50	$C_{26}H_{22}N_4O_3S$	66.37	4.71	11.91	6.81
	EtOH	Deep brown	470.55	66.22	4.85	12.00	6.73
5f	176–78	62	$C_{24}H_{20}N_4O_3S_2$	60.49	4.23	11.76	13.46
	EtOH	Brown	476.58	60.65	4.10	11.82	13.33
6a	125–26	67	$C_{13}H_{16}N_2O_2S_2$	52.68	5.44	9.45	21.63
	Pet.ether	Pale olive	296.41	52.78	5.31	9.56	21.69
6b	159–60	72	$C_{14}H_{16}N_2O_2S$	60.85	5.84	10.14	11.60
	EtOH	Colorless	276.36	61.04	5.72	10.26	11.43
9a	160–61	68	$C_{22}H_{20}N_4O_4$	65.34	4.98	13.85	
	EtOH	Yellow	404.43	65.50	5.00	14.02	
9b	161–62	70	$C_{23}H_{22}N_4O_4$	66.02	5.30	13.39	
	EtOH	Yellow	418.46	66.19	5.47	13.22	
9c	212–13	81	$C_{27}H_{23}N_5O_3$	69.66	4.98	15.04	
	EtOH	Yellow	465.52	69.60	4.82	14.91	
9d	204–205	72	$C_{22}H_{20}N_4O_3$	68.03	5.19	14.42	
	EtOH	Yellow	388.43	67.90	4.98	14.63	
9e	148–49	75	$C_{27}H_{22}N_4O_3$	71.99	4.92	12.44	
	EtOH	Pale brown	450.51	72.00	5.00	12.27	
9f	190–92	78	$C_{25}H_{20}N_4O_3S$	65.77	4.42	12.27	7.02
	EtOH	Brown	456.53	65.69	4.40	12.34	6.90
9g	153–54	73	$C_{31}H_{24}N_4O_3$	74.38	4.83	11.19	
	EtOH	Red	500.56	74.30	4.66	10.95	
12b	213–15	80	$C_{19}H_{13}N_5O_3S$	58.30	3.35	17.89	8.19
	AcOH	Pale brown	391.41	58.51	3.41	17.97	8.36
12c	322–24	70	$C_{23}H_{14}N_6O_2S$	63.00	3.22	19.17	7.31
	DMF	Pale orange	438.47	62.91	3.40	19.00	7.39
12d	237–39	74	$C_{18}H_{11}N_5O_2S$	59.82	3.07	19.38	8.78
	AcOH	Pale brown	361.38	60.00	3.25	19.49	8.67
12e	219–21	82	$C_{23}H_{13}N_5O_2S$	65.24	3.09	16.54	7.57
	AcOH	Pale brown	423.46	65.06	3.22	16.64	7.38
12f	174–77	55	$C_{21}H_{11}N_5O_2S_2$	58.73	2.58	16.31	14.93
	DMF	Yellow	429.48	58.91	2.73	16.23	15.08
12g	249–50	60	$C_{27}H_{15}N_5O_2S$	68.49	3.19	14.79	6.77

(*continued*)

Table 1. Continued

Compd. no.	Mp (°C) solvent	Yield (%), color	Mol. Formula, Mol. wt	% Analyses calcd., found			
				C	H	N	S
	AcOH	Perpel	473.52	68.35	3.34	14.87	6.66
13b	234–35	76	$C_{21}H_{15}N_5O_3$	65.45	3.92	18.17	
	AcOH	Yellow	385.39	65.23	4.00	18.02	
13c	228–30	70	$C_{25}H_{16}N_6O_2$	69.44	3.73	19.43	
	AcOH	Pale yellow	432.45	69.58	3.87	19.31	
13d	205–207	60	$C_{20}H_{13}N_5O_2$	67.60	3.69	19.71	
	AcOH	Yellow	355.36	67.71	3.78	19.57	
13e	202–204	72	$C_{25}H_{15}N_5O_2$	71.93	3.62	16.78	
	EtOH	Yellow	417.43	72.04	3.80	16.85	
15	147–49	70	$C_9H_{11}NOS$	59.64	6.12	7.73	17.69
	EtOH	Pale yellow	181.25	59.80	6.00	7.90	17.52
16a	123–24	52	$C_{16}H_{12}N_2O_3S$	61.53	3.87	8.97	10.36
	EtOH	Colorless	312.35	61.67	3.89	9.13	10.20
16b	105–106	65	$C_{17}H_{14}N_2O_3S$	62.56	4.32	8.58	9.82
	EtOH	Pale yellow	326.38	62.66	4.15	8.39	9.66
16c	187–89	70	$C_{21}H_{15}N_3O_2S$	67.54	4.05	11.25	8.59
	EtOH	Yellow	373.44	67.55	4.20	11.40	8.77
16d	153–56	75	$C_{16}H_{12}N_2O_2S$	64.85	4.08	9.45	10.82
	EtOH	Yellow	296.35	64.70	3.90	9.32	11.00
16e	174–75	66	$C_{21}H_{14}N_2O_2S$	70.37	3.94	7.82	8.95
	EtOH	Orange	358.40	70.54	3.79	7.68	8.81
16f	190–92	72	$C_{19}H_{12}N_2O_2S_2$	62.62	3.32	7.69	17.60
	AcOH	Pale orange	364.45	62.53	3.18	7.55	17.48
16g	170–72	63	$C_{25}H_{16}N_2O_2S$	73.51	3.95	6.86	7.85
	AcOH	Pale orange	408.48	73.30	4.11	7.03	7.72
17a	286–87	78	$C_{15}H_{10}N_4OS$	61.21	3.42	19.04	10.89
	EtOH	Yellow	294.34	61.00	3.60	18.89	10.75
17b	233–35	60	$C_{16}H_{12}N_4S$	65.73	4.14	19.17	10.97
	EtOH	Yellow	292.36	65.90	3.98	19.35	11.13
17c	300–303	55	$C_{21}H_{14}N_4S$	71.17	3.98	15.80	9.04
	AcOH	Yellow	354.53	71.26	4.08	15.63	8.84
17d	318–20	70	$C_{19}H_{12}N_4S_2$	63.31	3.36	15.54	17.79
	AcOH	Yellow	360.46	63.17	3.25	15.68	17.84
17e	263–64	63	$C_{25}H_{16}N_4S$	74.23	4.00	13.85	7.92
	AcOH	Yellow	404.50	73.99	3.86	13.96	8.07
19a	74.76	70	$C_{15}H_9NO_3S$	63.59	3.02	4.94	11.32
	EtOH	Colorless	283.31	63.42	3.36	4.79	11.23
19b	89–91	68	$C_{16}H_{11}NO_3S$	64.65	3.73	4.71	10.79
	EtOH	Colorless	297.27	64.53	3.62	4.58	10.68
19c	80–82	50	$C_{13}H_7NO_4S$	57.14	2.58	5.13	11.73
	EtOH	Pale brown	273.27	56.97	2.47	5.28	11.83

(*continued*)

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Table 1. Continued

Compd. no.	Mp (°C) solvent	Yield (%), color	Mol. Formula, Mol. wt	% Analyses calcd., found			
				C	H	N	S
19d	103–105	80	$C_{13}H_7NO_3S_2$	53.97	2.44	4.84	22.16
	EtOH	Yellow	289.33	54.14	2.31	4.67	22.00
19e	133–35	60	$C_{19}H_{11}NO_3S$	68.46	3.33	4.20	9.62
	EtOH	Brown	333.37	68.35	3.50	4.37	9.77
19f	105–107	70	$C_{19}H_{11}NO_3S$	68.46	3.33	4.20	9.62
	EtOH	Yellow	333.37	68.26	3.17	4.11	9.51
20a	150–52	85	$C_{15}H_9N_3OS$	64.50	3.25	15.04	11.48
	EtOH	Yellowish brown	279.32	64.37	3.12	15.20	11.62
20b	85–87	71	$C_{16}H_{11}N_3OS$	65.51	3.78	14.32	10.93
	EtOH	Yellow	293.35	65.38	3.61	14.25	11.05
20c	110–12	55	$C_{13}H_7N_3O_2S$	57.98	2.62	15.60	11.91
	EtOH	Brown	269.28	57.83	2.74	15.51	11.86
20d	228–30	85	$C_{13}H_7N_3OS_2$	54.72	2.47	14.73	22.47
	AcOH	Yellow	285.35	54.60	2.33	14.81	22.58
20e	59–61	55	$C_{19}H_{11}N_3OS$	69.28	3.37	12.76	9.73
	EtOH	Yellow	329.38	69.13	3.25	12.71	9.87
20f	188–90	63	$C_{19}H_{11}N_3OS$	69.28	3.37	12.76	9.73
	EtOH	Olive	329.38	69.33	3.43	12.65	9.78
21	233–35	75	$C_{10}H_6N_2S_2$	55.02	2.77	12.83	29.38
	AcOH	Pale brown	218.30	54.85	2.61	12.75	29.47
22a	134–36	65	$C_{14}H_{12}N_2O_2S_2$	55.25	3.97	9.20	21.07
	EtOH	Pale brown	304.39	55.36	4.14	8.99	20.84
22b	132–34	73	$C_{13}H_{10}N_2OS_2$	56.91	3.67	10.21	23.37
	EtOH	Pale brown	274.37	57.02	3.56	10.03	23.49
22c	184–85	60	$C_{12}H_7N_3S_2$	56.01	2.74	16.33	24.92
	EtOH	Brown	257.34	56.05	3.77	16.38	25.14
22d	119–20	70	$C_{11}H_8N_2S_2$	56.87	3.47	12.06	27.60
	EtOH	Pale orange	232.33	56.94	3.29	11.91	27.51
23a	254–56	55	$C_{14}H_{12}N_2O_2S_2$	55.25	3.97	9.20	21.07
	AcOH	Yellowish brown	304.39	55.36	4.14	8.99	20.84
23b	225–27	62	$C_{13}H_{10}N_2OS_2$	56.91	3.67	10.21	23.37
	EtOH	Orange	274.37	56.74	3.51	10.11	23.20
23c	275–76	70	$C_{12}H_7N_3S_2$	56.01	2.74	16.33	24.92
	AcOH	Yellowish brown	257.34	56.05	3.77	16.38	25.14
24a	<340	62	$C_{13}H_7N_3OS_2$	54.72	2.47	14.73	22.47
	DMF	Yellow	285.35	54.60	2.36	14.68	22.50
24b	<310	60	$C_{13}H_8N_4S_2$	54.91	2.84	19.70	22.55
	DMF	Brown	284.36	55.08	2.78	19.62	22.63

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Table 2. Spectra of some newly synthesized compounds

Comp. no.	Spectral data
5a	^{1}H NMR: 1.22 (t, 3H), 2.54 (s, 3H), 4.03 (s, 3H, OCH_3), 4.15(q, 2H), 6.87 (s, 1H) and 7.22–8.18 (m, 8H). IR: 3090 (CH), 1733, 1690 (CO), and 1606 (C═C).
5b	^{1}H NMR: 1.23 (t, 3H), 1.45 (t, 3H), 2.54 (s, 3H), 4.17 (q, 2H), 4.50 (q, 2H), and 6.84–8.19 (m, 9H). IR: 3093 (CH), 1729, 1691 (CO), and 1606 (C═C).
5c	^{1}H NMR: 1.20 (t, 3H), 2.57 (s, 3H), 4.14 (q, 2H), 6.86–8.16(m, 14H) and 8.63 (s, br., NH). IR: 3390, 3259 (NH), 3062 (CH), 1685 (CO), and 1600 (C═C).
5d	IR: 3107 (CH), 1730, 1696 (CO), and 1599 (C═C).
5e	IR: 3070 (CH), 1691, 1654 (CO), and 1606 (C═C).
5f	IR: 3070 (CH), 1689 (CO) and 1608 (C═C).
6a	^{1}H NMR: 1.26 (t, 3H), 2.29 (s, 3H, SCH_3), 2.46 (s, 3H), 4.16 (q, 2H), 5.95 (s, br., NH), and 6.88–7.15 (m, 4H). IR: 3313 (NH), 3074 (CH) and 1651 (CO).
6b	^{1}H NMR: 2.39 (s, 3H), 2.46 (s, 3H, SCH_3), 3.63 (s, 3H, OCH_3), 5.71 (s, br., NH), 6.58 (s, 1H), and 7.20–7.30 (m, 5H). IR: 3320 (NH), 3081 (CH) and 1653 (CO).
9a	^{1}H NMR: 2.51 (s, 3H), 3.64 (s, 3H, OCH_3), 3.93 s, 3H, OCH_3), 8.85 (s, 1H) and 7.22–8.20 (m, 10H). IR: 1712 (CO), and 1604 (C═C).
9b	^{1}H NMR: 1.36 (t, 3H), 2.51 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 4.39 (q,2H), 6.86 (s, 1H), 7.21–8.21 (m, 10H). IR: 1728 (CO) and 1604 (C═C).
9c	^{1}H NMR: 2.54 (s, 3H), 3.63 (s, 3H, OCH_3), 7.07 (s, 1H), 7.15–8.20 (m, 15H), and 8.36 (s, br., NH). IR: 3240 (NH), 1705, 1666 (CO), and 1612 (C═C).
9d	^{1}H NMR: 1.58 (s, 3H), 2.54 (s, 3H), 3.63 (s, 3H, OCH_3), 6.87 (s, 1H), and 7.21–8.23 (m, 10H). IR: 1697 (CO), and 1604 (C═C).
9e	^{1}H NMR: 2.57 (s, 3H), 3.64 (s, 3H, OCH_3), 7.02 (s, 1H), and 7.15–8.24 (m, 15H) IR: 1697, 1658 (CO), and 1612 (C═C).
9f	^{1}H NMR: 2.35 (s, 3H), 3.64 (s, 3H, OCH_3), 7.03 (s, 1H), and 7.13–8.29 (m, 13H). IR: 2923 (CH), 1697 (CO), and 1612 (C═C).
9g	^{1}H NMR: 2.58 (s, 3H), 3.64 (s, 3H, OCH_3), 7.04 (s, 1H) and 7.08–8.62 (m, 17 H). IR: 1697 (CO) and 1604 (C═C).
12b	^{1}H NMR: 1.49 (t, 3H), 4.59 (q, 2H), and 7.19–8.51 (m, 8H). IR: 3097 (CH), 2214 (CN), 1697 (CO) and 1604 (C═C).
13b	^{1}H NMR: 1.50 (t, 3H), 4.64 (q, 2H), and 7.26–8.15 (m, 10H). IR: 3068 (CH), 2225 (CN), 1713 (CO), and 1596 (C═C).
13c	IR: 3379 (NH), 2214 (CN), 1670 (CO), and 1562 (C═C).
13d	IR: 3062 (CH), 2218 (CN), 1692 (CO), and 1598 (C═C).
13e	IR: 2214 (CN), 1689 (CO), and 1604 (C═C).
16a	IR: 3082 (CH), 1720, 1635 (COs), and 1542 (C═C).

(*continued*)

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Table 2. Continued

Comp. no.	Spectral data
16b	^{1}H NMR: 1.16 (t, 3H), 4.24 (q, 2H), 7.10–7.77 (m, 8H), and 8.25 (s, 1H, C-3 pyrazole). IR: 3066 (CH), 1724 (CO), and 1596 (C=C).
16c	IR: 3394 (NH), 3112 (CH), 1689, 1635 (COs), and 1593 (C=C).
16d	IR: 3097 (CH), 1693 (CO), and 1596 (C=C).
16e	IR: 3074 (CH), 1662 (CO), and 1593 (C=C).
16f	IR: 3085 (CH), 1689, 1643 (CO), and 1608 (C=C).
16g	IR: 3051 (CH), 1662 (CO), and 1608 (C=C).
17a	IR: 3348 (NH), 1678 (CO), and 1593 (C=C).
19b	^{1}H NMR 2.42 (s, 3H), 7.10–7.98 (m, 7H), and 8.99 (s, 1H). IR: 3097 (CH), 1677 (CO), and 1612 (C=C).
21	IR: 3079 (CH), 2218 (CN), and 1585 (C=C).
22a	^{1}H NMR: 1.26 (t, 3H), 4.04 (s, 2H, SCH_2), 4.19 (q, 2H), and 7.11–7.76 (m, 5H). IR: 3078 (CH), 2214 (CN), 1735 (CO), and 1566 (C=C).
22b	^{1}H NMR: 2.38 (s, 3H), 4.10 (s, 2H, SCH_2), and 7.13–7.79 (m, 5H). IR: 3093 (CH), 2214 (CN), 1652 (CO), and 1566 (C=C).
22c	IR: 3105 (CH), 2217 (CN), and 1568 (C=C).
22d	^{1}H NMR: 2.70 (s, 3H), and 7.12–7.78 (m, 5H). IR: 3055 (CH), 2218 (CN), and 1573 (C=C).
23a	^{1}H NMR: 1.31 (t, 3H), 4.27 (q, 2H), and 7.20–8.58 (m, 7H). IR: 3420, 3301 (NH_2), 3097 (CH), and 1612 (C=C).
23b	^{1}H NMR: 2.52 (s, 3H), and 7.22–8.62 (m, 7H). IR: 3398, 3282 (NH_2), 3058 (CH), 1701 (CO), and 1612 (C=C).
23c	IR: 3453, 3349 (NH_2), 3077 (CH), 2194 (CN), and 1572 (C=C).

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2-Phenyl-4-(2-thienyl)-7-substituted 6-Hydropyrazolo[3,4-*d*] pyridazines 17a–e and 6-(2-Thienyl)-3-substituted Isoxazolo[4,3-*d*] pyridazins 20a–f

An appropriate amount of **16a–g** or **19a–f** (0.5 g) and hydrazine hydrate (1 mL) in ethanol (15 mL) were refluxed for 1 h. The resulting solid was collected and recrystallized from DMF (or EtOH) to give the corresponding pyrazolo[3,4-*d*]pyridazines **17a–e** and isoxazolo[3,4-*d*]pyridaziines **20a–f** (Tables 1 and 2).

3-Acyl-6-(2-thienyl)isoxazoles 19a–f

Triethylamine [0.5 g (0.75 mL), 5 mmol] was added dropwise to equimolar amounts of **15** and the appropriate hydroximoyl chloride **18a–f** (5 mmol each) in dry toluene (20 mL) with stirring. Stirred was continued for 10 h. The reaction mixture was filtered off, and the filtrate was evaporated and triturated

with petroleum ether (40–60°C). The resulting solid was collected and recrystallized from proper solvent to give **19a–f**, respectively (Tables 1 and 2).

6-(2-Thienyl)-2-thioxohydropyridine-3-carbonitrile (21)

Method A: A mixture of **15** (1.8 g, 10 mmol) and cyanothioacetamide (1 g, 10 mmol) was refluxed in pyridine (25 mL) for 5 h, and then poured onto ice-cold water and neutralized with 10% hydrochloric acid. The resulting solid was collected and recrystallized from ethanol to give **21** (Tables 1 and 2).

Method B: A mixture of **15** (1.8 g, 10 mmol), cyanothioacetamide (1 g, 10 mmol), and piperidine (0.5 mL) was refluxed in ethanol (20 mL) for 3 h, and then poured onto ice-cold water and neutralized with hydrochloric acid (3 drops). The resulting solid was collected and recrystallized from ethanol to product identical in all respects (mp, mixed mp, and spectra) with sample obtained in method A.

Thieno[2,3-*b*]pyridines 23a–c

A mixture of 6-(2-thienyl)-2-thioxohydropyridine-3-carbonitrile (**21**) (1.1 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (15 mL) was stirred at room temperature for 6 h. An appropriate amount of ethyl chloroacetate, chloroacetone, chloroacetonitrile, or iodomethane (5 mmol) was added to the solution with stirring. The resulting solid was collected and recrystallized from ethanol to afford **22a–d**, respectively (Tables 1 and 2). An appropriate amount of **22a–c** (0.5 g) was refluxed in ethanol (15 mL) containing piperidine (3 drops) for 2 h. The solid formed while boiling was collected and recrystallized from AcOH to give **23a–c**, respectively (Tables 1 and 2).

Hydropyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine-4-one (24a)

A mixture of **23c** (1.2 g, 5 mmol) and formic acid (5 mL) in *N*,*N*-dimethylformamide (10 mL) was refluxed for 5 h. The reaction mixture was poured onto crushed ice (20 g). The resulting solid was collected and recrystallized from DMF to give **24a** (Tables 1 and 2).

Pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine-4-ylamine (24b)

A mixture of **23c** (1 g) and formamide (5 mL) in *N*,*N*-dimethylformamide (10 mL) was refluxed for 5 h. The reaction mixture was poured onto crushed

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ice (20 g). The resulting solid was collected and recrystallized from DMF to give **24b** (Tables 1 and 2).

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