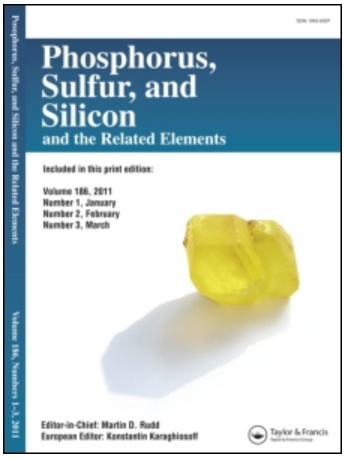

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of Some New Thieno[2,3-*b*]pyridines, Pyrimidino[4',5':4,5]thieno[2,3-*b*]-pyridines, and 2,3-Dihydro-1,3,4-thiadiazoles

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Synthesis of Some New Thieno[2,3-*b*]pyridines, Pyrimidino[4′,5′:4,5]thieno[2,3-*b*]-pyridines, and 2,3-Dihydro-1,3,4-thiadiazoles

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Thieno[2,3-b]pyridines were synthesized from 6-benzofuran-2-yl-4-phenyl-2-sulfanylpyridine-3-carbonitrile and each of chloro acetone, ethyl chloroacetate, ω-bromoacetophenone, and chloroacetonitrile. These compounds were conveniently converted into novel pyrido[4′,5′:4,5]thieno[3,2-d]pyrimidines. Also, 2,3-dihydro-1,3,4-thiadiazole was synthesized from hydrazonoyl halides and 2-benzofuran-2-yl-3-(phenylamino)-3-thioxopropanenitrile. The structures of the products have been elucidated by elemental analyses, spectral data studies, and alternative syntheses whenever possible. The newly synthesized compounds were tested towards microorganisms.

Keywords 2,3-Dihydro-1,3,4-thiadiazole; hydrazonoyl halides; pyrimidino[4′,5′:4,5]thieno[2,3-*b*]pyridine; thieno[2,3-*b*]pyrimidine

INTRODUCTION

Thienopyrimidine derivatives are characterized by a very broad spectrum of biological activities, such as antiallergic,[1] antiatherosclerotic,[2] antibacterial,[3–5] anticancer,[6] antiviral,[7,8] antihypertensive,[9,10] antidepressant,[11] antihistaminic,[12] antimicrobial,[13–16] and neurotropic[17] activities. We report herein the reaction of 6-benzofuran-2-yl-4-phenyl-2-sulfanylpyridine-3-carbonitrile with each of chloro acetone,

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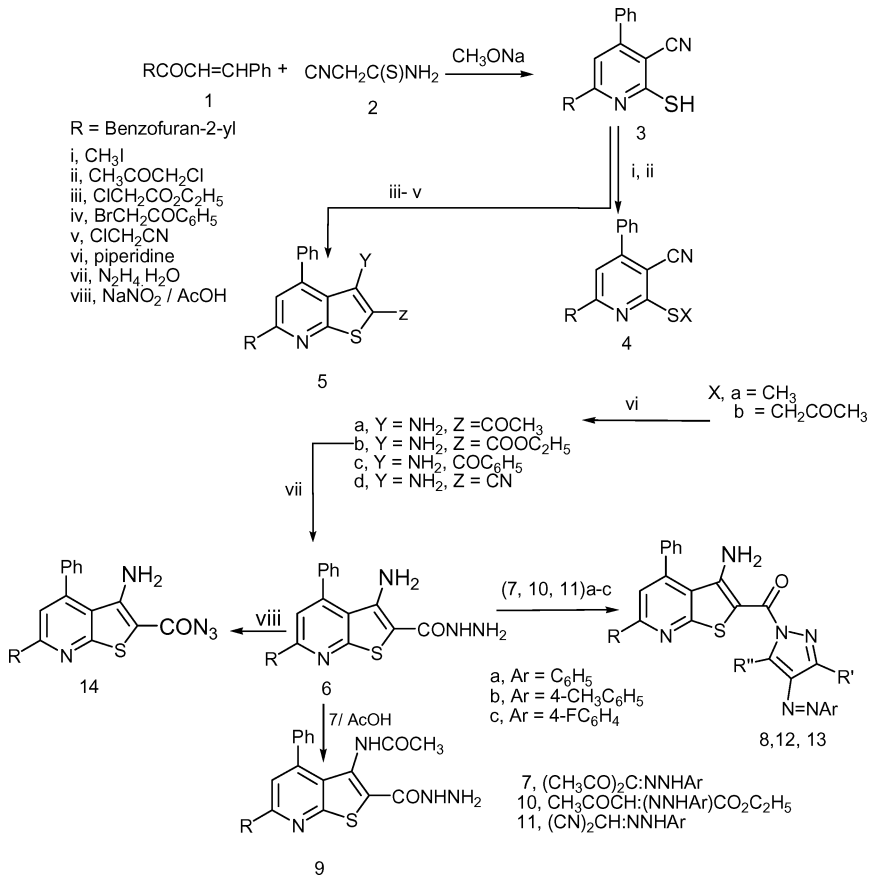
ethyl chloroacetate, ω-bromoacetophenone, and chloroacetonitrile. Also, the reaction of hydrazonoyl halides with 2-benzofuran-2-yl-3-(phenylamino)-3-thioxopropanenitrile was studied.

RESULTS AND DISCUSSION

Treatment of 1-benzofuran-2-yl-3-phenylprop-2-en-1-one[18] (**1**) with cyanothioacetamide (**2**) in sodium methoxide afforded 6-benzofuran-2-yl-4-phenyl-2-sulfanylpyridine-3-carbonitrile (**3**). Structure **3** was confirmed by elemental analysis, spectral data, and chemical transformation. Thus, compound **3** reacted with each of methyl iodide and chloroacetone in ethanoilc triethylamine (or ethanolic potassium hydroxide) to give **4a** and **4b**, respectively (Scheme 1), as evidenced from its elemental analysis and spectral data. The latter was cyclized in boiling ethanol containing few drops of piperidine to afford 1-(3-amino-6-benzofuran-2-yl-4-phenylthieno[2,3-*b*]pyridin-2-yl)ethan-1-one (**5a**). In contrast, compound **3** reacted with ethyl chloroacetate, ω-bromoacetophenone, or chloroacetonitrile to give ethyl 3-amino-6-benzofuran-2-yl-4-phenylthieno[2,3-*b*]pyridine-2-carboxylate (**5b**), (3-amino-6-benzofuran-2-yl-4-phenylthieno[2,3-*b*]pyridin-2-yl)phenylmethanone (**5c**), and 3-amino-6-benzofuran-2-yl-4-phenylthieno[2,3-*b*]pyridine-2-carbonitrile (**5d**), respectively. The IR spectra of compounds **5b–d** revealed amino groups with two bands appearing at 3496–3249 cm^{-1} in the form of two bands due to intramolecular association between the 3-NH_2 and 2-$COOC_2H_5$, CO or 2-C≡N group of compounds **5b–d**, as observed in other cyclo enamino esters.[19] ^{1}H NMR spectra of compounds **5b–d** showed a broad singlet at δ 6.21–6.57 (b, 2H) assigned for the NH_2 group and a singlet at δ 7.84–8.31 (s, 1H) assigned for the pyridine-5H of the thieno[2,3-*b*]pyridine ring. The ^{1}H NMR spectrum of **5b** showed signals at $\delta = 1.29$ (t, $J = 7$Hz, 3H, $CH_2\mathbf{CH}_3$), 4.24 (q, $J = 7$Hz, 2H, $\mathbf{CH}_2CH_3$), 6.21 (s, br., 2H, NH_2) and 7.12–7.87 (m, 10H, aromatic protons) and 7.99 (s, 1H, 5-H of the thienopyridine ring).

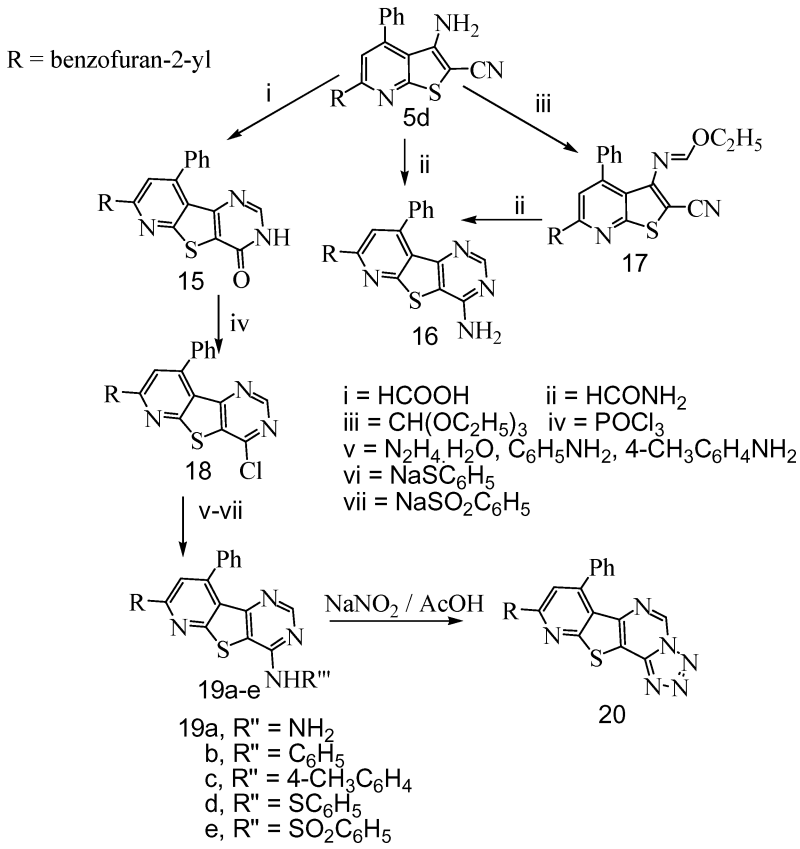
Compound **5b** reacted with hydrazine hydrate in refluxing ethanol to give *N*-amino-(3-amino-6-benzofuran-2-yl-4-phenylthieno[2,3-*b*]pyridine-2-yl)carboxamide (**6**) (Scheme 1). The structure of **6** was confirmed by spectral data and elemental analyses. Its ^{1}H NMR spectrum revealed the absence of ethyl ester protons signals, indicating the elimination of ethanol and all other spectral data (IR and mass spectra) are in agreement with the proposed structure. Compound **6**, reacted with the arylazoacetylacetone derivatives **7a–c** in ethanolic triethylamine, yielded **8a–c** (Scheme 1).



SCHEME 1 Synthesis of compounds **3–6**, **8**, **9**, **12**, **13**, and **14**.

Alternatively, compound **6** reacted with the appropriate **7a–c** in glacial acetic acid to give the *N*-acetyl derivative **9**. Structure **9** was confirmed by elemental analyses, spectral data, and alternate synthetic route. Thus, compound **6** reacted with acetyl chloride to give the *N*-acetyl derivative to afford the product identical in all aspects (mp., mixed mp., and spectra) with **9**.

Also, treatment of **6** with the appropriate arylazo of each of ethyl acetoacetate or malononitrile **10a, 10b, 11a–c** in ethanolic triethylamine gave pyrazoles **12a, 12b**, and **13a–c**, respectively. Compound **6d** reacted with nitrous acid to give **14**. The IR spectrum of **14** revealed a band at 2119 cm^{-1} representative of the azido group. Compound **5d** reacted with the appropriate formic acid, formamide, or triethyl orthoformate to give **15–17**, respectively (Scheme 2). Structures **15–17** were

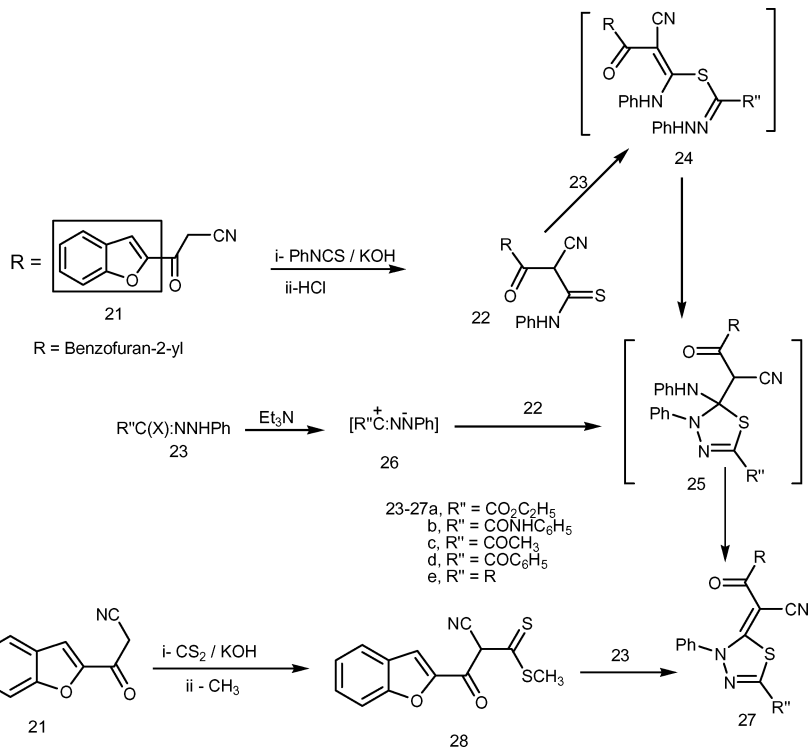


SCHEME 2 Synthesis of compounds **15–20**.

confirmed by elemental analysis, spectral data, and chemical transformation. Thus, compound **17** reacted with formamide to give product identical in all aspects (mp., mixed mp., and spectra) with **16**.

Treatment of **15** with phosphorus oxychloride afforded the chloroderivative **18**; the latter reacted with the appropriate hydrazine hydrate, aniline, 4-methylaniline, and sodium thiophenolate or sodium benzenesulfinate to give **19a–e**, respectively. Structures **19** were elucidated by elemental analysis, spectral data, and chemical reactions. Thus, treatment of **19d** with hydrogen peroxide in acetic acid at room temperature gave product identical in all aspects (mp., mixed mp., and spectra) with **19e**. Also, compound **19a** reacted with nitrous acid to give teterazole **20**.

3-Benzofuran-2-yl-3-oxopropanenitrile[20] (**21**) reacted with phenyl isothiocyanate in *N*,*N*-dimethylformamide containing potassium



SCHEME 3 Synthesis of compounds **22**, **27**, and **28**.

hydroxide to give non-isolable product, which was converted to **22** by hydrochloric acid. Structure **22** was elucidated by microanalytical, spectral data, and chemical transformation (Scheme 3). IR (cm^{-1}) spectrum of **22** revealed characteristic bands at 3386 (NH) and 2198 (CN). Its ^1H NMR showed signals at $\delta = 7.31$–8.10 (m, 11H, aromatic protons) and 12, 53 (s, br., 1H).

Treatment of the appropriate hydrazonoyl halides **23a–e** with **22** in ethanolic triethylamine at room temperature gave 2,3-dihydro-1,3,4-thiadiazole derivatives **27a–e**, respectively (Scheme 3). IR spectra of **27a–e** revealed bands near 2190 (CN) and 1720–1680 (CO). ^1H NMR spectrum of **27a** showed signals at $\delta = 1.36$ (t, 3H, $J = 7.5$ Hz, $CH_2\mathbf{CH}_3$), 4.2 (q, 2H, $J = 7.5$ Hz, $\mathbf{CH}_2CH_3$), 7.10–7.92 (m, 10H) ppm. Its ^{13}C NMR spectrum showed signals at $\delta = 13.8$ ($\mathbf{CH}_3$CH2O), 60.7 ($CH_3\mathbf{CH}_2$O), 87.2, 111.6, 115.9, 116.3, 116.7, 118.8, 121.0, 123.3, 124.7, 129.6, 131.4, 146.4, 154, 155.2, 195.2, 161.0, 161.7, 175 (CO) ppm. Also, treatment of *C*-ethoxycarbonyl-*N*-phenylhydrazonoyl chloride

23a with 2-(benzo[*d*]furan-2-ylcarbonyl)-3-methylthio-3-sulfanylprop-2-enenitrile (**28**), which was prepared from **21** and carbon disulfide in potassium hydroxide followed by iodomethane, in ethanolic triethylamine to give a product identical in all aspects (mp., mixed mp., and spectra) with **27a** .

In light of these results, the mechanism outlined in Scheme 3 seems to be the most plausible pathway for the formation of **27** from the reaction of the **22** with **23** (or nirile imine **26**), which was prepared in situ by treatment of **23** with triethylamine. The reaction involves the initial formation of thiohydrazonate **24**, which undergoes intermolecular cyclization as soon as it is formed to yield the intermediate **26** or via 1,3-dipolar cycloaddition of nitrilimine **26** to C=S double bond of **22** to give final product **27** via elimination of aniline.

Biological Activity

The tested microorganisms were Gram-positive bacteria [*Staphylococcus aureus* (ATCC25923) and *Streptococcus pyrogenes* (ATCC19615)], Gram-negative bacteria [*Pseudomonas Phaseolicola* (GSPB 2828) *and Pseudomonas fluorescens* (S 97)], and some fungal pathogens (*Fusarium oxysporum* and *Aspergillus funigatus*).

The tested compounds were dissolved in *N*,*N*-dimethylformamide, which has no inhibition activity, to obtained concentrations of 2 mg/mL and 1 mg/1 mL. The test was performed on medium potato dextrose agar (PDA), which contains infusion 200 g potato, 6g dextrose, and 15g agar. Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10 μL) from the specific concentration of dissolved tested compounds and carefully placed on inoculated agar surface. After incubation for 36 h at 27°C in the case of bacteria and 48 h at 24°C in the case of fungi, inhibition of the organisms, which is evidenced by a clear zone surround each disk, was measured and used to calculate mean inhibition zones.[21] See Table I.

In general (for high concentration), compounds **6e, 11**, and **31a** were capable of a high inhibition, compounds **6b,c, 12, 17b,d, 23b, 31b,e, 33b,c**, and **38a,b** were capable of intermediate to inhibition, and compounds **17e, 22, 26b, 31c**, and **33a** were capable of low to inhibition of the growth of Gram-positive and Gram-negative.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a

TABLE I Response of Various Microorganisms to Some Synthesized Compounds in Vitro (Culture)

	Mean * of zone diameter, nearest whole mm											
	Gram-positive				Gram-negative bacteria				Fungi**			
Organisms	*Staphylococcus aureus* (ATCC 25923)		*Streptococcus pyogenes* (ATCC 19615)		*Pseudomonas phaseolicola* (GSPB 2828)		*Pseudomonas fluorescens* (S 97)		*Fusarium oxysporum*		*Aspergillus fumigatus*	
Conc.	1	2	1	2	1	2	1	2	1	1	1	2
Sample	2mg/ml	1mg/ml	2mg/ml	1mg/ml	2mg/ml	1mg/ml	2mg/ml	1mg/ml	2mg/ml	1mg/ml	2mg/ml	1mg/ml
3	H	I	I	L	–	–	I	L	I	–	–	–
5a	I	L	I	L	L	–	I	L	–	L	–	–
5b	I	–	I	L	L	–	–	–	–	–	–	–
5d	H	L	–	–	L	–	I	L	–	–	I	–
6	L	L	–	–	H	I	–	–	I	L	–	–
7a	H	I	I	L	–	–	I	L	I	–	–	–
7b	I	L	I	L	I	–	I	L	L	L	–	–
10c	H	I	I	I	L	–	I	L	–	–	I	L
11a	I	L	–	–	L	–	–	–	–	–	–	–
11c	L	L	L	–	–	–	L	–	–	–	–	–
15	L	–	L	–	–	–	–	–	–	–	–	–
16	–	–	H	I	L	–	–	–	–	–	–	–
17	l	–	I	L	L	–	–	–	–	–	–	–
19a	I	L	I	L	L	L	I	L	–	–	L	–
19e	H	I	I	L	I	L	L	L	–	–	L	–
27b	l	L	I	L	L	–	L	–	I	L	–	–
27c	L	–	H	L	L	–	–	–	–	–	–	–
27d	I	L	L	L	L	–	H	I	I	L	–	–
27e	H	I	I	L	L	–	L	–	–	–	–	–
Control #	H	H	H	H	H	H	H	H	H	H	H	H

* = Calculate from 3 values.

** = Identified depending on morphological and microscopically characters = No effect.

L = Low activity = Mean of zone diameter ≤1/3 of mean zone diameter of control.

I = Intermediate activity = Mean of zone diameter ≤2/3 of mean zone diameter of control.

H = High activity = Mean of zone diameter ≥2/3 of mean zone diameter of control.

= Chloramphencol in the case of Gram-negative bacteria, Cephalothin in the case of Gram-positive bacteria and Cicloheximide in the case of fungi.

Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2$ SO solutions on a Varian Gemini 300 MHz spectrometer, and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses and

microorganism tests were carried out at the Microanalytical Center of Cairo University. Hydrazonoyl halides[22–26] **23a-e** were obtained as previously reported.

Synthesis of 6-Benzofuran-2-yl-4-phenyl-2-sulfanylpyridine-3-carbonitrile (3)

A mixture of **1** (3.61 g, 10 mmoles) and cyanothioacetamide **2** (1.0 g, 0.1 mol) was heated under reflux in methoxide solution [sodium metal (0.23g) in methanol (25 mL)] for 7 h. The reaction mixture was cooled and stirred at room temperature overnight. The precipitate was filtered, washed with water, and recrystallized from ethanol to give **3** (Tables II and III).

Synthesis of 6-Benzofuran-2-yl-2-methylthio-4-phenylpyridine-3-carbonitrile (4a) and 2-Acetyl-6-benzofuran-2-yl-4-phenylpyridine-3-carbonitrile (4b)

A mixture of **3** (1.6 g, 10 mmol) and potassium hydroxide (0.6 g, 10 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. Each of methyl iodide and chloroacetone (10 mmol each) was added, and stirring was continued for 2 h. The resulting solid was collected and recrystallized from the proper solvent to give **4a** and **4b**, respectively (Tables II and III).

Synthesis of 1-(3-Amino-6-benzofuran-2-yl-4-phenylthieno[2,3-b]pyridin-2-yl)ethan-1-one (5a)

A solution of **4b** (1.71 g, 5 mmol) in ethanol (20 mL) containing piperidine (0.3 mL) was heated under reflux for 2 h. After cooling, the resulting solid was collected by filtration and recrystallized from dioxin/ethanol to give **5a** (Tables II and III).

Synthesis of Ethyl 3-amino-6-benzofuran-2-yl-4-phenylthieno[2,3-b]pyridine-2-carboxylate (5b), (3-Amino-6-benzofuran-2-yl-4-phenylthieno[2,3-b]pyridin-2-yl)phenylmethanone (5c), and 3-Amino-6-benzofuran-2-yl-4-phenylthieno[2,3-b]pyridine-2-carbonitrile (5d)

A mixture of **3** (1.6 g, 10 mmol) and potassium hydroxide (0.6 g, 10 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. Each of ethyl chloroacetate, ω-bromoacetophenone,

TABLE II Characterization Data of the Newly Synthesized Compounds

Compd. no.	Mp., °C Solvent	Yield % Colour	Mol. Formula Mol. Wt.	% Analyses, Calcd./Found C	H	N	S
3	>300	90	$C_{20}H_{12}N_2OS$	73.15	3.68	8.53	9.76
	EtOH	Yellow	328.39	73.24	3.86	8.35	10.23
4a	>300	80	$C_{21}H_{14}N_2OS$	73.66	4.11	8.18	9.36
	Dioxan	Yellow	342.41	73.54	4.12	18.23	9.57
4b	260–62	80	$C_{23}H_{16}N_2O_2S$	71.86	4.19	7.28	8.34
	Dioxan	Yellow	384.46	71.58	4.18	7.15	8.43
5a	270–71	75	$C_{23}H_{16}N_2O_2S$	71.86	4.19	7.28	8.34
	Dioxan	Yellow	384.46	71.68	4.28	7.46	8.43
5b	260–62	80	$C_{24}H_{18}N_2O_3S$	69.55	4.38	6.76	7.74
	Dioxan	Yellow	414.49	69.64	4.50	6.80	7.85
5c	>300	80	$C_{28}H_{18}N_2O_2S$	75.32	4.06	6.27	7.18
	Dioxan	Orange	446.53	75.23	4.18	6.42	8.32
5d	>300	85	$C_{22}H_{13}N_3OS$	71.92	3.57	11.44	8.73
	Dioxan	Yellow	367.43	72.12	3.75	11.21	8.64
6	290	90	$C_{22}H_{16}N_4O_2S$	65.99	4.03	13.99	8.01
	Dioxan	White	400.64	66.21	3.88	14.12	7.75
8a	270	80	$C_{33}H_{24}N_6O_2S$	69.70	4.25	14.78	5.64
	Dioxan	Yellow	568.66	69.51	4.32	14.87	5.46
8b	160	80	$C_{34}H_{26}N_6O_2S$	70.09	4.50	14.42	5.50
	EtOH	Yellow	582.69	70.24	4.23	14.34	5.74
8c	200	75	$C_{33}H_{23}N_6O_2SF$	67.56	3.95	14.33	5.47
	EtOH	Yellow	586.65	67.34	4.13	14.20	5.70
9	>300	90	$C_{24}H_{18}N_4O_3S$	65.13	4.10	12.66	7.25
	Dioxan	White	442.62	65.23	3.89	12.43	7.42
12a	>300	80	$C_{32}H_{22}N_6O_3S$	67.36	3.89	14.73	5.62
	Dioxan	Yellow	570.63	67.23	3.98	14.85	5.72
12b	240	80	$C_{33}H_{24}N_6O_3S$	67.79	4.14	14.37	5.48
	EtOH	White	584.66	67.57	4.00	14.31	5.64
13a	290	80	$C_{31}H_{22}N_8O_2S$	65.25	3.89	19.64	5.62
	Dioxan	Yellow	570.64	65.12	4.11	19.52	5.45
13b	170	90	$C_{32}H_{24}N_8O_2S$	65.74	4.14	19.17	5.48
	Dioxan	Yellow	584.66	65.85	2.24	19.329	5.62
13c	190	85	$C_{31}H_{21}N_8O_2FS$	63.26	3.60	19.04	5.45
	Dioxan	Yellow	588.63	63.41	3.65	28.88	5.54
14	> 300	Colorless	$C_{22}H_{13}N_5O_2S$	64.22	3.18	17.02	7.80
	EtOH	90	411.44	64.42	3.20	16.91	7.62
15	>300	90	$C_{23}H_{13}N_3O_2S$	69.86	3.31	10.63	8.11
	Dioxan	Yellow	395.44	69.75	3.42	10.45	8.53
16	>300	80	$C_{23}H_{14}N_4OS$	70.03	3.58	14.20	8.13
	Dioxan	Yellow	394.46	70.25	3.75	14.37	7.95
17	220-21	90	$C_{25}H_{17}N_3O_2S$	70.91	4.05	9.92	7.57
	EtOH	White	423.50	70.85	4.21	10.24	7.73

TABLE II Characterization Data of the Newly Synthesized Compounds *(Continued)*

Compd. no.	Mp., °C Solvent	Yield % Colour	Mol. Formula Mol. Wt.	% Analyses, Calcd./Found C	H	N	S
18	>300	90	$C_{23}H_{12}N_3OSCl$	66.75	2.92	10.15	7.75
	Dioxan	Black	413.89	66.65	2.84	10.34	7.91
19a	280	80	$C_{23}H_{15}N_5OS$	67.47	3.69	17.10	7.83
	EtOH	Brown	409.47	67.65	3.81	17.23	7.85
19b	240-43	80	$C_{29}H_{18}N_4OS$	74.02	3.86	11.91	6.81
	AcOH	Brown	470.56	74.18	3.68	12.26	6.64
19c	260	80	$C_{30}H_{20}N_4OS$	74.36	4.16	11.56	6.61
	EtOH	Brown	484.58	74.53	4.28	11.35	6.42
19d	> 300	80	$C_{29}H_{17}N_3OS_2$	71.44	3.51	8.62	13.15
	EtOH	Brown	487.61	7.24	3.62	8.75	13.00
19e	> 300	80	$C_{29}H_{17}N_3O_3S_2$	67.04	3.30	8.09	12.34
	EtOH	Brown	519.61	67.21	3.51	7.85	12.42
20	> 300	80	$C_{23}H_{12}N_6OS$	65.70	2.88	19.99	7.63
	EtOH	Brown	420.46	65.60	3.00	20.12	7.85
22	140-41	70	$C_{18}H_{12}N_2O_2S$	67.48	3.78	8.74	10.01
	EtOH	Brown	320.37	67.65	3.87	8.65	9.89
27a	210-12	70	$C_{22}H_{15}N_3O_4S$	63.30	3.62	10.07	7.68
	EtOH	Yellow	417.45	63.15	3.52	40.21	7.86
27b	190-91	70	$C_{26}H_{16}N_4O_3S$	67.23	3.47	12.06	6.90
	EtOH	Yellow	464.51	67.42	3.37	11.89	6.81
27c	200-202	70	$C_{21}H_{13}N_3O_3S$	65.11	3.38	10.85	8.28
	EtOH	Red	387.42	65.00	3.41	10.99	8.41
27d	180-81	80	$C_{26}H_{15}N_3O_3S$	69.48	3.36	9.35	7.13
	EtOH	Red	449.49	69.51	3.27	9.53	7.25
27e	220-22	70	$C_{28}H_{15}N_3O_4S$	68.70	3.09	8.58	6.55
	EtOH	Red	489.51	68.64	2.95	8.74	6.72
28	160-61	70	$C_{13}H_9NO_2S_2$	56.71	3.29	5.09	23.29
	EtOH	Brown	275.35	65.84	3.40	5.18	23.42

and chloroacetonitrile (10 mmol each) was added, and stirring was continued for 2 h. The resulting solid was collected and recrystallized from the proper solvent to give **5b–d**, respectively (Tables II and III).

Synthesis of N-Amino(3-amino-6-benzofuran-2-yl-4-phenylthieno[2,3-b]pyridine-2-yl)carboxamide (6)

A mixture of compound **5b** (1.8 g, 10 mmol) and hydrazine hydrate (4 mL, 85% solution, 4 mmol) in absolute ethanol (20 mL) for 2 h was heated under reflux. The reaction mixture was cooled, and the resulting

TABLE III Spectral Data of Some Newly Synthesized Compounds

Compound No.	Spectral data
3	IR: 3342 (NH), 2217 (CN) ^{1}H NMR: 6.67–7.42 (m, 10H, aromatic proton), 8.21 (s, 1H, 5-H of the pyridinethione ring), 14.10 (b, 1H, SH).
4a	IR: 2198 (CN) ^{1}H NMR: 2.47 (s, 3H, CH_3), 6.67–8.02 (m, 10H, aromatic proton), 8.21 (s, 1H, 5-H of the pyridinethione ring).
4b	IR: 2190 (CN), 1655 (CO) ^{1}H NMR: 2.33 (s, 3H, CH_3CO), 4.15 (s, 2H, SCH_2), 7.25–7.75 (m, 10H, aromatic proton), 8.17 (s, 1H, 5-H of the pyridinethione ring).
5a	IR: 3316, 3124 (NH_2), 1596 (CO) ^{1}H NMR: 2.38 (s, 3H, CH_3CO), 6.45 (br, 2H, NH_2), 7.16–7.73 (m, 10H, aromatic protons), 7.82 (s, 1H, 5-H of the thienopyridine ring). MS: 386 (8), 385 (28), 384 (100), 340 (29), 279 (4), 191 (10), 170 (4), 89 (8), 77 (11)
5b	IR: 3481, 3351 (NH_2), 1731 (CO) ^{1}H NMR: 1.29 (t, 3H, $J = 7$ Hz, CH_3), 4.24 (q, 2H, $J = 7$ Hz, CH_2), 6.21 (br, 2H, NH_2), 7.12–7.87 (m, 10H, aromatic protons), 7.99 (s, 1H, 5-H of the thienopyridine ring).
5c	IR: 3408, 3300 (NH_2), 1685 (CO). ^{1}H NMR: 16.21 (br, 2H, NH_2), 7.52–7.87 (m, 15H, aromatic protons), 7.99 (s, 1H, 5-H of the thienopyridine ring).
5d	IR: 3496, 3300 (NH_2), 2198 (CN) ^{1}H NMR: 6.57 (br, 2H, NH_2), 7.12 (m, 10H, aromatic protons), 8.31(s, 1H, 5-H of the thienopyridine ring).
6	IR: 3414, 3199 (NH_2, NH), 1650 (CO) ^{1}H NMR: 4.38 (br, 2H, N-NH_2), 6.70 (br, 2H, NH_2), 7.15–7.78 (m, 10H, aromatic protons), 8.29 (s, 1H, 5-H of the thienopyridine ring), 9.39 (br, 1H, NH).
8a	IR: 3445, 3257 (NH_2), 1640 (CO) ^{1}H NMR: 2.80 (s, 6H, 3-,5-CH_3 of pyrazole), 6.81 (br, 2H, NH_2), 7.12–7.84 (m, 15H, aromatic protons), 8.31 (s, 1H, 5-H of the thienopyridine ring).
8b	IR: 3445, 3257 (NH_2), 1640 (CO) ^{1}H NMR: 2.34 (s, 3H, CH_3), 2.80 (s, 6H, 3-,5-CH_3 of pyrazole), 6.81 (br, 2H, NH_2), 7.12–7.84 (m, 14H, aromatic protons), 8.31 (s, 1H, 5-H of the thienopyridine ring).
8c	IR: 3445, 3257 (NH_2), 1640 (CO) ^{1}H NMR: 2.80 (s, 6H, 3-,5-CH_3 of pyrazole), 6.81 (br, 2H, NH_2), 7.12–7.84 (m, 14H, aromatic protons), 8.31 (s, 1H, 5-H of the thienopyridine ring).
9	IR: 3414, 3199 (NH_2, NH), 1650 (CO) MS: 442 (12%), 341 (100%), 240 (16%).

TABLE III Spectral Data of Some Newly Synthesized Compounds *(Continued)*

Compound No.	Spectral data
12a	IR: 3445, 3257 (NH_2), 1720, 1640 (CO's) ^{1}H NMR: 1.24 (s, 3H, 3-CH_3 of pyrazole), 6.81 (br, 2H, NH_2), 7.12–7.84 (m, 15H, aromatic protons), 8.31 (s, 1H, 5-H of the thienopyridine ring), 11.23 (s, 1H, br., NH).
12b	IR: 3445, 3257 (NH_2), 1717, 1640 (CO's) ^{1}H NMR: 1.24 (s, 3H, 3-CH_3 of pyrazole), 2.41 (s, 3H, CH_3), 6.81 (br, 2H, NH_2), 7.12–7.84 (m, 14H, aromatic protons), 8.31 (s, 1H, 5-H of the thienopyridine ring), 11.23 (s, 1H, br., NH).
13a	IR: 3458, 3216 (NH_2), 1651 (CO) ^{1}H NMR: 6.79 (br, 2H, NH_2), 6.98 (br, 4H, 2 NH_2), 7.14–7.93 (m, 15H, aromatic protons), 8.01 (s, 1H, 5-H of the thienopyridine ring).
13b	IR: 3458, 3216 (NH_2), 1651 (CO) ^{1}H NMR: 2.41 (s, 3H, CH_3), 6.79 (br, 2H, NH_2), 6.98 (br, 4H, 2 NH_2), 7.14–7.93 (m, 14H, aromatic protons), 8.01 (s, 1H, 5-H of the thienopyridine ring).
13c	IR: 3458, 3216 (NH_2), 1651 (CO) ^{1}H NMR: 6.79 (br, 2H, NH_2), 6.98 (br, 4H, 2 NH_2), 7.14–7.93 (m, 14H, aromatic protons), 8.01 (s, 1H, 5-H of the thienopyridine ring).
14	IR: 3458, 3216 (NH_2), 2119 (azido group), 1692 (CO). ^{1}H NMR: 6.79 (br, 2H, NH_2), 7.14–8.21 (m, 11H, aromatic protons).
15	IR: 3423 (NH), 1660 (CO) ^{1}H NMR: 7.02–7.99 (m, 10H, aromatic protons), 8.25 (s, 1H, 5-H of the thienopyridine ring), 8.57 (s, 1H, Proton on C-2 of pyrimidine ring), 12.56 (s, 1H, NH of pyrimidine ring).
16	IR: 3458, 3216 (NH_2) ^{1}H NMR: 6.79 (br, 2H, NH_2), 7.14–7.93 (m, 11H, aromatic protons), 8.01 (s, 1H, 5-H of the thienopyridine ring).
17	IR: 2248 (CN) ^{1}H NMR: 1.22 (t, 3H, $J = 7.5$ Hz, CH_3), 4.33 (q, 2H, $J = 7.5$ Hz, CH_2), 6.73–7.98 (m, 10H, aromatic protons), 8.11 (s, 1H, 5-H of the thienopyridine ring), 8.66 (s, 1H, CH═N).
18	^{1}H NMR: 7.05–7.89 (m, 10H, aromatic protons), 8.17 (s, 1H, 5-H of the thienopyridine ring), 9.66 (s, 1H, Proton on C-2 of pyrimidine ring).
19a	IR: 3414, 3199 (NH_2, NH) ^{1}H NMR: 4.38 (br, 2H, N-NH_2), 7.15–7.78 (m, 11H, aromatic protons), 8.29 (s, 1H, 5-H of the thienopyridine ring), 9.39 (br, 1H, NH).
19b	IR: 3340 (NH) ^{1}H NMR: 7.15–7.78 (m, 15H, aromatic protons), 8.29 (s, 1H, 5-H of the thienopyridine ring), 8.69 (s, 1H, Proton on C-2 of pyrimidine ring), 9.39 (br, 1H, NH). MS: 408 (31), 407 (52), 361 (47), 307 (47), 250 (57), 225 (50), 174 (65), 110 (39), 77 (55).

(Continued on next page)

TABLE III Spectral Data of Some Newly Synthesized Compounds *(Continued)*

Compound No.	Spectral data
19c	IR: 3340 (NH) ^{1}H NMR: 2.42 (s, 3H, CH_3), 7.15–7.78 (m, 14H, aromatic protons), 8.29 (s, 1H, 5-H of the thienopyridine ring), 8.69 (s, 1H, Proton on C-2 of pyrimidine ring), 9.39 (br, 1H, NH).
20	IR: 3072 (CH), 1640 (C═N) ^{1}H NMR: 7.14–7.93 (m, 11H, aromatic protons), 9.26 (s, 1H, 2-H of the pyrimidine ring).
22	IR: 3386 (NH) and 2198 (CN). ^{1}H NMR: 7.31–8.10 (m, 11H) and 12. 53 (s, br., 1H).
27a	IR: 2190 (CN) and 1720–1680 (CO). ^{1}H NMR: 1.36 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 4.2 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 7.10–7.92 (m, 10H). ^{13}C NMR: 13.8 ($\underline{CH_3}CH_2O$), 60.7 ($CH_3\underline{CH_2}O$), 87.2, 111.6, 115.9, 116.3, 116.7, 118.8, 121.0, 123.3, 124.7, 129.6, 131.4, 146.4, 154, 155.2, 195.2, 161.0, 161.7, 175 (CO).
27b	IR: 3220 (NH), 2190 (CN) and 1680, 1665 (CO). ^{1}H NMR: 7.10–7.92 (m, 15H, aromatic protons), 9.31 (s, br., 1H, NH)
27c	IR: 2190 (CN) and 1665, 1655 (CO). ^{1}H NMR: 2.11 (s, 3H, CH_3), 7.10–7.92 (m, 10H, aromatic protons).
27d	IR: 2190 (CN) and 1665, 1660 (CO). ^{1}H NMR: 7.10–7.92 (m, aromatic protons).
27e	IR: 2364 (CS), 2190 (CN) and 1665, 1655 (CO). ^{1}H NMR: 7.10–8.24 (m, aromatic protons).
28	IR: 2190 (CN) and 1665 (CO). ^{1}H NMR: 2.47 (s, 3H, SCH_3), 6.65–7.59 (m,5H, aromatic protons), 12.10 (s, 1H, SH).

solid was collected and washed with ethanol/water and recrystallized from dioxan to give **6** (Tables II and III).

Synthesis of N-[2-(N-amino(3-aminocarbamoyl)-6-benzofuran-2-yl-4-phenylthieno[2,3-b]pyridine-2-yl]acetamide (9)

Method A

A mixture of compound **6** (0.9 g, 5 mmol) and the appropriate of arylazoacetylacetone **7a–c** (5 mmol) was heated under reflux in acetic acid (10 mL) with stirring for 10 h. The reaction mixture was cooled to room temperature, and the separated solid was filtered, washed with water, dried, and recrystallized from the proper solvent to give **9** (Tables II and III).

Method B

A mixture of compound **6** (0.9 g, 5 mmol), acetic anhydride (5 mL), and acetic acid (10 mL) was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and poured onto ice (50 g), and the separated solid was filtered, washed with water, dried, and recrystallized from the proper solvent to give product identical in all aspects (mp., mixed mp. and spectra) with **9** (Tables II and III).

Synthesis of 3-Amino-6-benzofuran-2-yl-4-phenylthieno[2,3-b]-2-pyridyl-4-arylazo-3,5-disubstituted-1-pyrazolylmethanone (8, 12 , 13a–c)

A mixture of compound **6** (0.9 g, 5 mmol) and the appropriate amounts of arylazoacetylacetone **7a–c**, ethyl arylazoacetoacetate **10a,b,** and arylazomalononitrile **11a–c** (5 mmol) was heated under reflux in ethanol (10 mL) containing triethylamine (0.75 g, 5 mmol) with stirring for 10 h. The reaction mixture was cooled to room temperature, and the separated solid was filtered, washed with water, dried, and recrystallized from the proper solvent to give (**8, 12,** and **13a–c)** (Tables II and III).

Synthesis of 3-Amino-6-benzofuran-2-yl-4-phenylthieno[2,3-b]pyridine-2-carbonylazide (14)

A saturated solution of sodium nitrite was added to a stirred solution of **6** (0.9 g, 5 mmol) in acetic acid (10 mL) at room temperature for 20 min. The resulting solution was collected, washed with water, and recrystallized from ethanol to give **14** (Tables II and III).

Synthesis of 7-Benzofuran-2-yl-9-phenyl-3-hydropyrimidino[4′,5′:4,5]thieno[2,3-b]pyridine-4-one (15)

A mixture of **5d** (1.8 g, 10 mmol) and formic acid (99%, 20 mL) was heated under reflux for 7 h. After cooling, the reaction mixture was poured over ice (100 g), and the resulting solid was collected and recrystallized from *N*,*N*-dimethylformamide to give **15** (Tables II and III).

Synthesis of 4-Amino-7-benzofuran-2-yl-9-phenyl-3-hydropyrimidino[4′,5′:4,5]-thieno[2,3-b]pyridine (16)

Compound **5d** (1.8 g, 10 mmol) was heated with formamide (20 mL) at 180°C for 2 h. After cooling, the reaction mixture was poured over ice,

and the formed solid was collected by filtration and recrystallized from *N*,*N*-dimethylformamide to give **16** (Tables II and III).

Synthesis of 7-Benzofuran-2-yl-4-chloro-9-phenyl-3-hydropyrimidino[4′,5′:4,5]-thieno[2,3-b]pyridine (18)

Compound **15** (0.9 g, 5 mmol) reacted with $POCl_3$ (20 mL) under reflux for 5 h. The reaction mixture was poured over ice (100 g), and the resulting solid was collected by filtration and recrystallized from ethanol to give **18** (Tables II and III).

Synthesis of 3-(1-Aza-2-ethoxyvinyl)-6-benzofuran-2-yl-4-phenylthieno[2,3-b]-pyridin-2-carbonitrile (17)

A mixture of **5d** (1.8 g, 10 mmol) and triethylorthoformate (20 mL) with a catalytic amount of acetic acid were heated under reflux at 140°C for 6 h. The resulting dark brown solution was allowed to cool to room temperature and was evaporated under vacuum. N-Hexane was added to the residue, and the separated solid was filtered, washed with n-hexane, and recrystallized from ethanol to give **17** (Tables II and III).

Synthesis of 7-Benzofuran-2-yl-9-phenylpyrimidino[4′,5′:4,5]thieno[2,3-b]pyridine-4-ylhydrazine (19a), (7-Benzofuran-2-yl-9-phenylpyrimidino[4′,5′:4,5]thieno-[2,3-b]pyridine-4-yl)phenylamine (19b), (7-Benzofuran-2-yl-9-phenylpyrimidino-[4′,5′:4,5]thieno[2,3-b]pyridine-4-yl)(4-methylphenyl)amine (19c), 7-Benzofuran-2-yl-9-phenyl-4-phenylthiopyrimidino[4′,5′:4,5]thieno[2,3-b]pyridine (19d), and 7-Benzofuran-2-yl-9-phenyl-4-(phenylsulfonyl)pyrimidino[4′, 5′:4,5]thieno[2,3-b]-pyridine (19e)

Compound **18** (1.7 g, 5 mmol) was dissolved in ethanol (10 mL) containing the appropriate amounts of hydrazine hydrate, aniline, p-toluidine, sodium thiophenolate, or sodium benzenesulfinate (10 mmol) was heated under reflux for 4 h. Ethanol was removed under vacuum. The crude product residue was tritrated with hexane and recrystallized from the proper solvent to give **19a–e**, respectively (Tables II and III).

Alternative Method for 19d

Hydrogen peroxide (5 mL, 30%) was added to a solution of **19d** (0.5 g) in acetic acid (15 mL) while stirring at room temperature. Stirring was

continued for 24 h and then poured over water (50 mL). The crude product was collected and recrystallized from ethanol to give **19d**.

Synthesis of 8-Benzofuran-2-yl-10-phenyl-2a-hydro-12,3,4-tetrazolo[1",5":6′,1′]-pyrimidino[4′,5′:4,5]thieno[2,3-b]pyridine (20)

A saturated solution of sodium nitrite was added to a stirred solution of **6** (0.9 g, 5 mmol) in acetic acid (10 mL) at room temperature for 20 min. The resulting solution was collected, washed with water, and recrystallized from ethanol to give **20** (Tables II and III).

Synthesis of 2-Benzofuran-2-yl-3-(phenylamino)-3-thioxopropanenitrile (22)

Phenyl isothiocyanate (0.65 g [0.6 mL], 5 mmol) was added to a mixture of **21** (0.9 g, 5 mmol) and potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (15 mL) while stirring at room temperature until the potassium hydroxide dissolved completely, and then the reaction mixture was stirred for a further 1 h. The reaction mixture was poured onto water (30 mL) and acidified with dilute hydrochloric acid. The resulting solid was collected and recrystallized from dioxan to give thioanilide **22** (Tables II and III).

Synthesis of 2,3-Dihydro-1,3,4-thiadiazoles 27a–e

Method A

Phenyl isothiocyanate (0.65 g [0.6 mL], 5 mmol) was added to a mixture of benzofuran-2-oylacetonitrile (0.9 g, 5 mmol) **21** and potassium hydroxide (0.28 g, 5 mmol) in *N*,*N*-dimethylformamide (15 mL) while stirring at room temperature until the potassium hydroxide dissolve completely, and the reaction mixture was continued stirring for further 30 min. The appropriate hydrazonoyl halides **23a–e** (5 mmol) were added, and stirring was continued for 3 h. The resulting solid was collected and recrystallized from the appropriate solvent to afford **27a–e** (Tables II and III).

Method B

Triethylamine (0.5 g, [0.75 mL], 5 mmol) was added dropwise to a mixture of the appropriate hydrazonoyl halides **23a–e** and **28** (5 mmol) in ethanol (20 mL) while stirring. Stirring was continued for 1 h, and the resulting solid was collected and recrystallized. The product is identical

in all aspects (mp., mixed mp. and spectra) with those obtained in method A.

Synthesis of 2-(Benzofuran-2-ylcarbonyl)-3-mercapto-3-methylsulfanylacrelonitrile (28)

A mixture of **21** (0.9 g, 5 mmol), potassium hydroxide (0.28 g (5 mmol), and carbon disulfide (0.47 g, 5 mmol) in *N*,*N*,-dimethylformamide (15 mL) was stirred for 6h at room temperature. Iodometane (0.71 g, 5 mmol) was added dropwise to the above mixture and stirred for 1 hr. The resulting solid was collected and crystallized from ethanol to give **28** (Tables II and III).

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