Heteroatom Chemistry
Volume 11, Number 5, 2000

A Facile One-Pot Synthesis of Thiazo[2′,3′:2,1] Imidazo[**4,5-*b***]Pyrane; Thiazo[2′,3′:2,1]Imidazo [**4,5,*b***]Pyridine; Imidazo[2,1-b]Thiazole and 2-(2-Amino-4-Methylthiazol-5-yl)-1-Bromo-1,2-Ethanedione-1-Arylhydrazones

Samia M. Sayed,[1] Maghraby A. Selim,[2] Mohamed A. Raslan,[1] and Mohamed A. Khalil[1]

[1]*Department of Chemistry, Faculty of science, University of South Valley, 81528 Aswan, Egypt*

[2]*Department of Chemistry, Faculty of science, University of South Valley, Qena, Egypt*

Received 21 March 2000; revised 28 April 2000

ABSTRACT: *Thiazole* **1**, *when reacted with chloroacetyl chloride, afforded N-(5-acetyl-4-methylthiazol-2-yl) chloroacetamide* **2**. *It has been found that compound* **2** *reacted with α-cyanocinnamonitrile derivatives* **6a–c** *to afford reaction products* **8a–c**. *Also, compound* **2** *coupled smoothly with benzenediazonium chloride afforded the phenylhydrazone* **14**. *Coupling of the sulfonium bromide* **17** *with diazotized aromatic amines or N-nitrosoacetanilides afforded the arylhydrazones* **20a,b**. *Treatment of* **16** *with 2-cyanoethanethioamide afforded [4-(2-amino-4-methylthiazol-5-yl) thiazol-2-yl] acetonitrile* **22**. © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:362–369, 2000

INTRODUCTION

Thiazoles and their annelated derivatives are reported to exhibit diverse biological activities as antituberculous, [1] bacteriostatic, [2] and fungistatic [3] agents. Moreover, many derivatives of these systems are frequently present in the tuberculostically active drugs, [4,5] in addition to their use as mildew-preventing agents [3]. From the industrial point of view, these compounds are extensively used in the synthesis of cyanine and merocyanine dyes [6,7] together with the utility to protect light sensitive photographic films from harmful effect of UV radiations [8]. Furthermore, the interesting properties of thiazole derivatives [9–17] in relation to the various changes in the structures of these compounds is worth studying for the synthesis of some less toxic and more potent drugs. Thus, the introduce of other heterocyclic moieties (as the pyrane, pyridine, and/or thiazole ring) should certainly help to fulfill this objective. The aforementioned biological, pharmacological, and industrial importance of these derivatives prompted our interest for the synthesis of some new examples of this class of compounds. In continuation of our previous studies aiming at the synthesis of functionalized heterocycles [18–19], we report here the synthesis of the versatile, hitherto unreported *N*-(5-acetyl-4-methyl-thiazol-2-yl)chloroacetamide (**2**) and its utility in the synthesis of several derivatives of thiazo[2′,3′:2,1]imidazo-[**4,5,*b***]pyrane; thiazo[2′,3′:2,1]imidazo[**4,5,*b***]pyr-

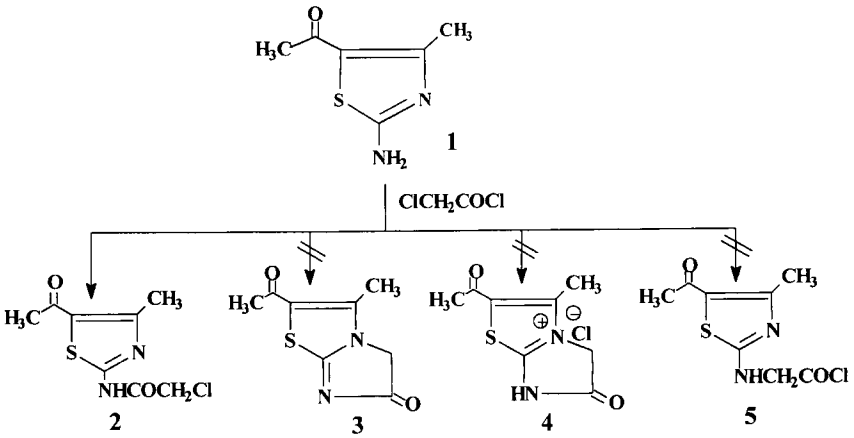
Correspondence to: Samia M. Sayed.

idine; imidazo[2,1-*b*]thiazole, and also, 2-(2-amino-4-methylthiazol-5-yl)-1-bromo-1,2-ethanedione-1-arylhydrazones.

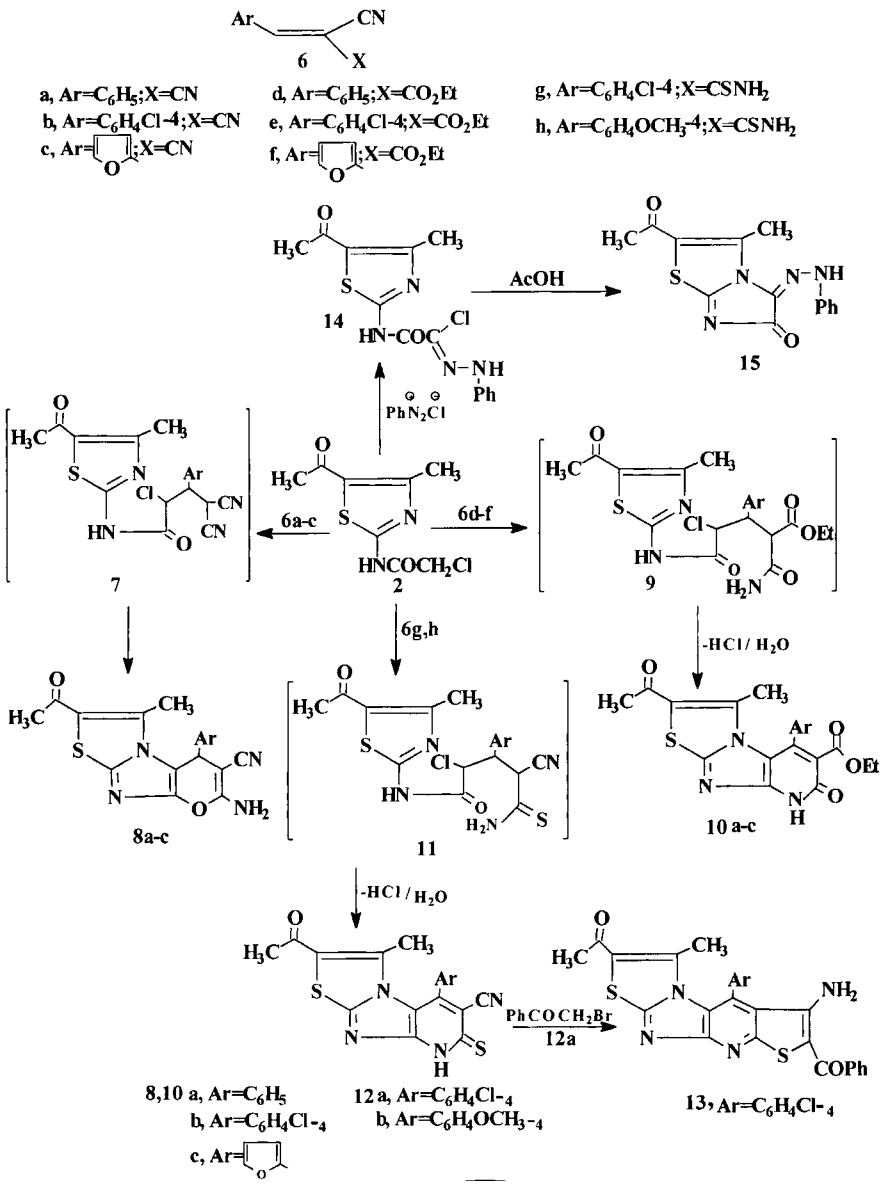
Thus, 5-acetyl-2-amino-4-methylthiazole **1** reacted with chloroacetyl chloride in an oil bath at 200°C for 30 minutes to afford a single product for which the four proposed structures **2–5** depicted in Scheme 1 seemed possible. However, the spectral data of the reaction product were compatible only with the structure of *N*-(5-acetyl-4-methyl-thiazol-2-yl) chloroacetamide (**2**). Its ^{1}H NMR spectrum revealed a singlet signal at δ 12.83 (exchangeable with D_2O) and at δ 4.45 due to NH and methylene protons, respectively, in addition to two singlet signals at δ 2.52 and 2.57 due to methyl and acetyl protons, respectively.

α,β-Unsaturated nitriles are highly reactive reagents and have been extensively utilized in heterocyclic synthesis [20]. Reactions of nucleophiles with these reagents normally take place at the β-carbon [21,22]. It has been found that **2** reacted with α-cyanocinnamonitrile derivatives **6a–c** in boiling pyridine to afford reaction products **8a–c.** These are assumed to be proceed via Michael addition of the methylene function in **2** to the activated double bond in **6a–c,** yielding the adducts **7** which then cyclize into stable compounds **8a–c** with loss of hydrogen chloride. Structures **8a–c** were established based on the elemental analyses and spectral data. The IR spectra of **8a–c** showed in each case, the appearance of amino and nitrile absorption bands at 3350–3190 and 2205–2215 cm^{-1}, respectively, in addition to absorption bands due to the carbonyl group. Moreover, its ^{1}H NMR spectrum revealed a broad signal at δ 6.42–6.79 (exchangeable with D_2O) and a singlet signal at δ 4.86–5.12 due to amino and pyrane 4-H protons, respectively, in addition to a multiplet due to aromatic protons. In contrast to the anticipated formation of imidazo[4,5-*b*]pyrane from the reaction of **2** with **6d–f,** the reaction of **2** with **6d–f** afforded thiazo [2′,3′:2,1] imidazo[4,5-*b*]pyridines **10a–c,** presumably via elimination of hydrogen chloride and water from the intermediates **9.** The structures **10a–c** assigned to the reaction products were amply supported by IR and ^{1}H NMR spectra. The IR spectra of **10a–c** showed, in each case, the absence of a cyano group and revealed the appearance of an NH absorption band near 3290 cm^{-1} and a carbonyl absorption band at 1680, 1720 cm^{-1}. The ^{1}H NMR spectrum of **10a,** for example, displayed a broad D_2O-exchangeable singlet signal at δ 10.38 due to an NH proton, in addition to a multiplet at δ 7.32–7.87 due to aromatic protons. These results provide firm support for structures **10a–c** for the reaction products (Scheme 2).

Similar to the behavior of **6a–c,** the thiocarboxaminocinnamonitriles **6g,h** reacted with **2** to yield products corresponding to equimolecular addition, cyclization, and water elimination affording **12a,b.** ^{1}H NMR of **12a,b,** in each case, showed disappearance of the pyrane H-4, in addition to the IR revealed absorption bands at 3295–3250 and 2210 cm^{-1} due to NH and cyano groups, respectively. Based on these findings, these compounds could be formulated as the thiazo[2′,3′:2,1]imidazo[4,5-*b*]pyridinehione derivatives **12a,b.** Moreover, the reaction products **12a,b** were proved to be stable under conditions that were expected to effect the opening of the thiopyrane ring [23]. The chemical confirmation of **12a** was achieved by its reaction with phenacyl bromide affording thieno[2″,3″:2′,3′]pyridino-[6′,5′:4,5]imidazo[2,1-*b*]thiazole derivatives **13.** The structure of **13** was supported based on its IR spectra, which revealed the absence of the cyano absorption band.



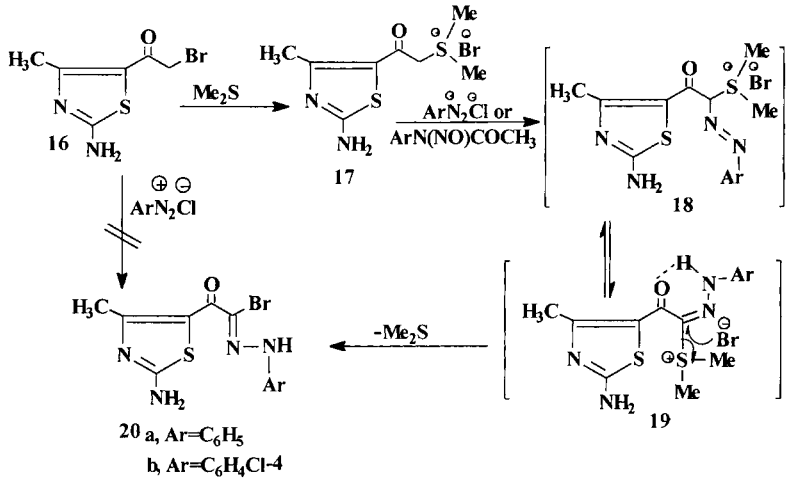
SCHEME 1



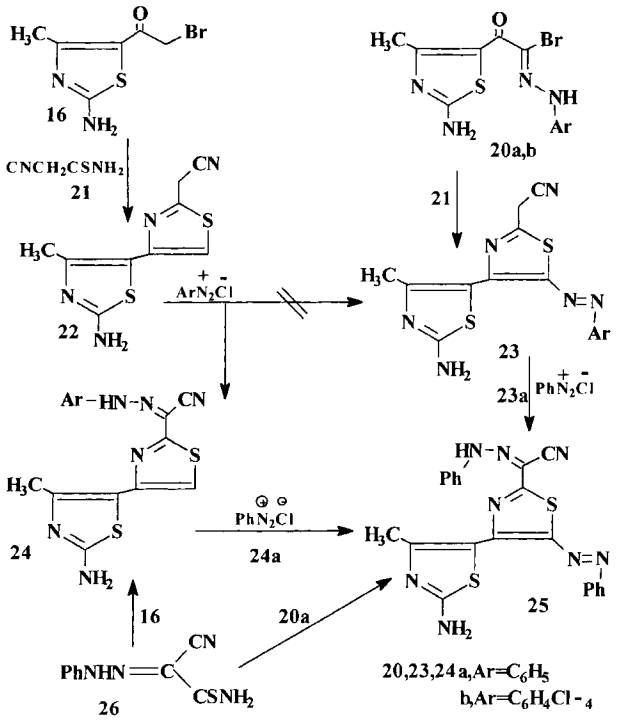
SCHEME 2

Compound **2** coupled smoothly with benzenediazonium chloride in ethanol buffered with sodium acetate at 0–5°C to afford the phenylhydrazone **14.** The structure of the phenylhydrazone **14** was established on the basis of its elemental analyses and spectral data as well as the chemical transformation depicted in Scheme 2. The ^{1}H NMR spectra of **14** displayed an exchangeable signal around δ 13.31–13.62 due to the NH proton. Its IR spectra showed also hydrazone N-H stretching 3180–3330 cm^{-1}. Cyclization of **14** via refluxing in acetic acid afforded the imidazo[2,1-*b*]thiazole **15** (see Experimental section).

Coupling of the sulfonium bromide **17** with diazotized aromatic amines in ethanol buffered with sodium acetate at 0–5°C, or with *N*-nitrosoacetanilides in ethanol at room temperature, afforded the arylhyrazones **20a,b** (Scheme 3). All attempts to prepare **20a,b** by direct coupling of **16** with diazotized aromatic amines or *N*-nitrosoacetanilides were unsuccessful. The structures of the arylhydrazones **20a,b** were established on the basis of their elemental analyses and spectral data, as well as their chemical transformations depicted in Scheme 4. The ^{1}H NMR spectra of **20a,b** displayed, in each case, an exchangeable signal around δ 11.31–11.82 due to the NH proton. Their IR spectra showed also in each case a conjugated carbonyl absorption band near 1660 cm^{-1}, and a hydrazone N-H stretching near



SCHEME 3



SCHEME 4

3280 cm^{-1}, in addition to an amino group at 3310 cm^{-1}.

Treatment of 2-bromoacetylthiazole **16** with 2-cyanoethanethioamide **21** in refluxing ethanol afforded a single product which analyzed correctly for $C_9H_8N_4S_2$. The structure of the latter product was identified as [4-(2-amino-4-methylthiazol-5-yl)thiazol-2-yl]acetonitrile **22** on the basis of its spectral data as well as its chemical transformation outlined in (Scheme 4).

Compound **22** coupled readily with diazotized aromatic amines in pyridine to afford colored products for which the two isomeric structures **23a,b** or **24a,b** seemed possible. However, the appearance of CN, NH_2, and NH bands at ca. 2215, 3330, and 3240 cm^{-1}, respectively, in the IR spectra of the isolated products and the lack of signals due to methylene protons in their ^1H NMR spectra provided a firm support for structure **24** and ruled out the other possible isomer **23.** The structure of **24** was further confirmed unequivocally by an independent synthesis by the reaction of **16** with 2-phenylhydrazono-2-cyanoethanethioamide **26** (Scheme 4).

On the other hand, compounds **23a,b** were readily obtained in high yields by cyclocondensation of the hydrazonoyl bromides **20a,b** with 2-cyanoethanethioamide **21** in refluxing ethanol. Treatment of either **23a** or **24a** with benzenediazonium chloride in pyridine-dimethylsulfoxide at 0–5°C, afforded [4-(2-amino-4-methyl thiazol-5-yl)-5-phenylazothiazol-2-yl](phenylhydrazono)acetonitrile **25.** Compound **25** was also obtained readily by an alternative route via cyclocondensation of the hydrazonyl bromide **20a** with 2-phenylhydrazono-2-cyanoethanethioamide **26** in refluxing ethanol.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were measured as KBr pellets on a Pye Unicam SP 3-300 spectrometer. ^1H NMR spectra were recorded in deuterated dimethylsulfoxide solution at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 Ev. Elemental analyses were car-

ried out at the Microanalytical Center of Cairo University. 5-Acetyl-2-amino-4-methyl thiazole (**1**) [19], 2-Bromoacetylthiazole (**16**) [19], *N*-nitrosoacetanilides [24], 2-Phenylhydrazono-2-cyanoethanethioamide (24) [25], and Cinnamonitrile derivatives (**6a–f**) [26,27] (were prepared as described in the literature).

*N-(5-aetyl-4-methyl thiazol-2-yl)chloroacetamide (**2**)*

A mixture of 5-acetyl-2-amino-4-methyl thiazole (**1**) (7.8 g, 50 mmol) and chloroacetyl chloride (6 mL, 54 mmol) was fused in an oil bath at 200°C for 30 minutes then left to cool. The solid product so formed was triturated with ethanol and collected by filtration, washed with ethanol, and then recrystallized.

Reaction of N-(5-aetyl-4-methyl thiazol-2-yl)chloroacetamide (**2**) *with* (**6a–h**)

General Procedure. A solution of **2** (2.32 g, 10 mmol) in pyridine (30 mL) was treated with (10 mmol) of each of (**6a–c, 6d–f**) and/or (**6g,h**) and the reaction mixture was heated under reflux for 4–6 hours (TLC control). The reaction mixture was cooled, poured onto ice/cold water, and acidified with concentrated HCl. The solid products obtained were filtered off, washed with water, then recrystallized from the proper solvents and identified as (**8a–c**), (**10a–c**), and (**12a,b**), respectively.

6-Acetyl-3-amino-2-benzoyl-5-methyl-4-phenylthieno[2″,3″:2′,3′]pyridino[5′,6′:5,4]-imidazo[2,1-b]thiazole (**13**)

A solution of **12a** (1.97 g, 5 mmol) in ethanol (30 mL) containing triethylamine (0.5 mL) was treated with phenacyl bromide (0.995 g, 5 mmol), and the reaction mixture was heated under reflux for 5 hours. The solid product obtained after cooling and acidification was filtered off and recrystallized from the proper solvent to give **13.**

Reaction of **2** *with Benzenediazonium Chloride*

To a cold solution of **2** (2.32 g, 10 mmol) in ethanol (50 mL) and sodium acetate trihydrate (5 g) was added benzenediazonium chloride solution (10 mmol) over a period of 30 minutes with stirring. After the addition was complete, the reaction mixture was stirred for a further 3 hours at 0–5°C and left to stand in an ice box for 12 hours, then it was diluted with water. The solid that formed was filtered off, washed with water, and dried. Recrystallization from acetic acid yielded the phenylhydrazone **14.**

2-Acetyl-3-methyl-5-oxo-4-phenylhydrazone imidazo[2,1-b]thiazole **15**

A solution of **14** (0.34 g, 1 mmol) in acetic acid (20 mL) was heated under reflux for 4 hours, left to cool, then diluted with water (20 mL). The separated solid was collected by filtration, washed with water, and dried; recrystallization from DMF afforded **15.**

1-(2-Amino-4-methylthiazol-5-yl)-1-ethanone-2-dimethylsulfonium Bromide **17**

2-Bromoacetylthiazole **16** (2.35 g, 10 mmol) was refluxed with dimethyl sulfide (1 mL) in absolute methanol (50 mL) for one hour. The reaction mixture was cooled, and the precipitated solid was filtered off, washed with dry ether, dried, and recrystallized from the proper solvent to afford the arylhydrazones **17**.

2-(2-Amino-4-methylthiazol-5-yl)-1-bromo-2-ethanone-1-arylhydrazones **20**

Method A: General Procedure. To a cold solution of **17** (2.35 g, 10 mmol) in ethanol (50 mL) and sodium acetate trihydrate (5 g) was added aryldiazonium chloride solution (10 mmol) over a period of 30 minutes with stirring. After the addition was complete, the reaction mixture was stirred for a further 5 hours at 0–5°C and left to stand in an ice box for 24 hours, then it was diluted with water. The solid that formed was filtered off, washed with water, and dried. Recrystallization from acetic acid yielded the arylhydrazone **20.**

Method B: General Procedure. A mixture of the sulfonium bromide **17** (2.97 g, 10 mmol) and the appropriate *N*-nitosoacetanilide derivative (10 mmol) in ethanol (50 mL) was stirred at room temperature for 12 hours, then it was collected by filtration, washed with water, and dried. Recrystallization from dioxane afforded products identical in all respects (m.p., mixed m.p., and spectra) with those obtained previously by method A.

[4-(2-Amino-4-methyl thiazol-5-yl)thiazol-2-yl]acetonitrile **22**

A mixture of 2-bromoacetylthiazole **16** (2.35 g, 10 mmol) and 2-cyanoethanethioamide **21** (1 g, 10 mmol) in ethanol (40 mL) was refluxed for 3–5 hours and cooled. The solid that precipitated was filtered off, washed with water, and dried. Recrystallization from DMF afforded **22.**

TABLE 1 Analytical Data and Physical Characteristic of New Compounds

Compound	Molecular Formula (*MW*)	*m.p.* (°C)	Color[a]	*Yield* (%)	*Elemental Analysis* (*Calcd.*)					
					C	*H*	*N*	*S*	*Cl*	*Br*
2	$C_8H_9N_2O_2SCl$ (232.68)	180–182	colorless	83	41.22 (41.30)	3.93 (3.90)	12.12 (12.04)	13.81 (13.78)	15.21 (15.24)	
8a	$C_{18}H_{14}N_4O_2S$ (350.39)	134–135	buff	62	61.23 (61.70)	4.11 (4.03)	15.08 (15.99)	9.18 (9.15)		
8b	$C_{18}H_{13}N_4O_2SCl$ (384.84)	250–252	white	66	56.14 (56.18)	3.48 (3.40)	14.64 (14.56)	8.41 (8.33)	9.24 (9.21)	
8c	$C_{16}H_{12}N_4O_3S$ (340.35)	164–165	violet	71	56.44 (56.46)	3.49 (3.55)	16.38 (16.46)	9.46 (9.42)		
10a	$C_{20}H_{17}N_3O_4S$ (395.35)	235–236	pale yellow	46	60.73 (60.75)	4.38 (4.33)	10.59 (10.63)	8.15 (8.11)		
10b	$C_{20}H_{16}N_3O_4SCl$ (429.88)	265–267	pale brown	52	55.78 (55.88)	3.83 (3.75)	9.68 (9.77)	7.41 (7.46)	8.31 (8.25)	
10c	$C_{18}H_{15}N_3O_5S$ (385.39)	210–212	pale red	58	56.22 (56.10)	3.96 (3.92)	10.89 (10.90)	8.26 (8.32)		
12a	$C_{18}H_{11}N_4OS_2Cl$ (398.89)	160–161	brown	53	54.10 (54.20)	3.10 (2.78)	13.96 (14.05)	15.68 (16.07)	8.93 (8.89)	
12b	$C_{19}H_{14}N_4O_2S_2$ (394.64)	200–201	red	51	57.79 (57.85)	3.49 (3.58)	13.96 (14.20)	16.38 (16.25)		
13	$C_{26}H_{17}N_4O_2S_2Cl$ (517.02)	>300	brown[c]	38	60.69 (60.40)	3.62 (3.31)	10.96 (10.84)	12.36 (12.40)	6.89 (6.86)	
14	$C_{14}H_{13}N_4O_2SCl$ (336.79)	156–157	yellow[b]	58	49.89 (49.93)	3.82 (3.89)	16.59 (16.64)	9.66 (9.52)		
15	$C_{14}H_{12}N_4O_2S$ (300.33)	>300	brown[b]	52	55.91 (55.99)	3.98 (3.75)	18.61 (18.65)	10.73 (10.67)		
17	$C_8H_{13}N_2OS_2Br$ (296.78)	210–212	pale red	86	32.28 (32.38)	4.39 (4.42)	9.39 (9.43)	21.68 (21.61)		26.73 (26.77)
20a	$C_{12}H_{11}N_4OSBr$ (338.76)	166–167	brown	36	42.51 (42.55)	3.19 (3.27)	16.48 (16.54)	9.52 (9.46)		23.53 (23.45)
20b	$C_{12}H_{10}N_4OSBrCl$ (373.20)	208–210	brown	31	21.11 (21.29)	2.89 (2.70)	14.94 (15.01)	8.66 (8.59)	9.49 (9.50)	21.33 (21.29)
22	$C_9H_8N_4S_2$ (236.31)	156–157	brown	69	45.69 (45.74)	3.63 (3.41)	23.64 (23.71)	27.26 (27.13)		
23a	$C_{15}H_{12}N_6S_2$ (340.42)	>300	brown[b]	65	52.82 (52.92)	3.48 (3.55)	24.76 (24.69)	18.89 (18.84)		
23b	$C_{15}H_{11}N_6S_2Cl$ (374.86)	>300	brown[b]	67	48.12 (48.06)	2.91 (2.96)	22.52 (22.42)	17.16 (17.11)	9.39 (9.46)	
24a	$C_{15}H_{12}N_6S_2$ (340.41)	180–181	brown[b]	51	52.84 (52.92)	3.59 (3.55)	24.61 (24.69)	18.93 (18.84)		
24b	$C_{15}H_{11}N_6S_2Cl$ (374.86)	220–222	brown[b]	48	47.98 (48.06)	2.91 (2.96)	22.46 (22.42)	17.02 (17.11)	9.41 (9.46)	
25	$C_{21}H_{16}N_8S_2$ (444.53)	>300	brown[b]	50	56.69 (56.74)	3.76 (3.63)	25.10 (25.21)	14.61 (14.42)		

[a]From EtOH unless otherwise stated.
[b]From DMF.
[c]From DMF-EtOH.

*5-Arylazo-[4-(2-amino-4-methylthiazol-5-yl)thiazol-2-yl]acetonitrile (***23a,b***)*

General Procedure. To a solution of the appropriate hydrazonoyl bromide (**20a,b**) (5 mmol) in ethanol (30 mL) was added 2-cyanoethanethioamid (**21**) (0.5 g, 5 mmol). The reaction mixture was refluxed for 2 hours, whereupon the solid reactants went into solution and a new brown-red product was precipitated while still hot. The mixture was cooled and the solid formed was collected by filtration, washed with water, dried and finally recrystallized from DMF to afforded (**23a,b**).

[4-(2-Amino-4-methylthiazol-5-yl)thiazol-2-yl]phenylhydrazonoacetonitriles **24a,b**

Method A: General Procedure. To a cold solution of **22** (2.36 g, 10 mmol) in pyridine (50 mL) was added the appropriate aromatic diazonium salt solution (20 mmol) portionwise over 30 minutes with constant stirring. After complete addition, the reac-

TABLE 2 Spectral Data of Newly Synthesized Compounds.

Compound	*^{1}H NMR (δ:ppm)*	*Mass Spectra m/e* (%)	*IR* (cm^{-1})
2	2.52 (s, 3H); 2.57 (s, 3H); 4.45 (s, 2H); 12.83 (s, 1H)	232 (M^+, 49.6); 228 (100); 212 (34.8); 152 (80.7); 138 (89.6); 76 (12.2)	3330 (NH); 1704, 1680 (CO), 1630 (C = N)
8a	2.47 (s, 3H); 2.59 (s, 3H); 4.86 (s, 1H); 6.79 (br, 2H); 7.39–7.55 (m, 5H)	351 ($M^+ + 1$, 64.4); 350 (M^+, 83.6); 335 (26.3); 260 (18.4); 192 (9.7); 141 (43.1); 91 (100); 58 (20.6)	3328, 3205 (NH_2); 3070 (CH aromatic); 2215 (CN), 1715 (CO); 1646 (C = N)
8b	2.46 (s, 3H); 2.61 (s, 3H); 5.12 (s, 1H); 6.48 (brs, 2H); 7.21–7.63 (m, 4H)		3350, 3190 (NH_2); 2205 (CN); 1718 (CO); 1630 (C = N)
8c	2.49 (s, 3H); 2.6 (s, 3H); 4.96 (s, 1H); 6.42 (brs, 2H); 6.76–6.83 (m, 1H); 7.87 (d, 1H)		3340, 3205 (NH_2; CH aromatic); 2210 (CN); 1723 (CO); 1638 (C = N)
10a	1.21 (t, 3H); 2.33 (s, 3H); 2.52 (s, 3H) 4.31 (q, 2H); 7.32–7.87 (m, 5H); 10.38 (s, 1H)		3485–3290 (OH, NH); 3075 (CH aromatic); 1720, 1680 (CO); 1630 (C = N)
10b	1.17 (t, 3H); 2.33 (s, 3H); 2.48 (s, 3H); 4.28 (q, 2H); 7.61–8.09 (m, 4H); 10.21 (br, 1H)		3460–3180 (OH, NH); 1712, 1682 CO); 1638 (C = N)
10c	1.24 (t, 3H); 2.42 (s, 3H); 2.52 (s, 3H); 4.21 (q, 2H); 7.08 (m, 1H); 7.50–7.55 (m, 1H); 7.97–8.10 (m, 1H); 10.38 (br, 1H)		3385–3250 (OH, NH); 1718, 1685 (CO); 1635 (C = N)
12a	2.48 (s, 3H); 2.57 (s, 3H); 7.39–8.00 (m, 5H); 14.15 (brs, 1H)	3.98 (M^+, 3.6); 371 (1.2); 327 (13.8); 300 (10.6); 264 (11.4); 141 (47.1); 86(100); 71 (18.3)	3295 (NH); 2210 (CN); 1716, 1681 (CO); 1630 (C = N)
12b	2.52 (s, 3H); 2.59 (s, 3H); 7.41–8.11 (m, 4H); 13.98 (brs, 1H)		3250 (NH); 2210 (CN); 1705, 1685 (CO); 1640 (C = N)
13	2.52 (s, 3H); 2.61 (s, 3H); 7.11–8.32 (m, 11H)		3410–3215 (NH_2), 3050 (CH aromatic); 1713–1695 (CO)
14	2.38 (s, 3H); 2.58 (s, 3H); 6.83–7.95 (m, 5H); 13.31 (s, 1H); 13.62 (s, 1H)	337 (M^+, 19.2); 301 (1.3); 227 (49.9); 213 (30.9); 172 (2.8); 138 (100); 111 (15.4); 76 (43.1); 41 (46.0)	3330, 3180 (NH); 1718, 16882 (CO); 1628 (C = N)
15	2.46 (s, 3H); 2.59 (s, 3H); 7.1–7.83 (m, 5H); 12.75 (br, 1H)	301 (M^+, 1.3); 229 (19.0); 214 (11.5); 178 (7.7); 153 (100); 111 (15.4); 77 (35.9); 65 (11.3)	3282 (NH); 1693, 1680 (CO); 1599 (C = N)
17	Insufficient soluble in the usual NMR solvents		3426; 3278 (NH_2); 1700 (CO); 1622 (C = N)
20a	2.48 (s, 3H); 7.15–8.31 (m, 5H); 8.45 (br, 2H); 11.31 (br, 1H)		3310; 3280 (NH_2, NH); 1660 (CO); 1600 (C = N)
20b	2.39 (s, 3H); 7.19–8.1 (m, 4H); 8.52 (br, 2H); 11.82 (br, 1H)		3326; 3278 (NH_2, NH); 1663 (CO); 1612 (C = N)
22	2.42 (s, 3H); 4.42 (s, 2H); 7.95 (br, 1H); 8.45 (br, 2H)		3380; 3310 (NH_2); 2203(CN); 1600 (C = N)
23a	2.51 (s, 3H); 4.51 (s, 2H); 7.12–8.12 (m, 5H); 8.52 (br, 2H)		3330; 3210 (NH_2); 2189 (CN); 1652 (C = N)
23b	2.49 (s, 3H); 4.56 (s, 2H); 7.62–8.43 (m, 6H)		3380; 3180 (NH_2); 2196 (CN); 1635 (C = N)
24a	2.51 (s, 3H); 7.13–8.22 (m, 6H); 8.53 (br, 2H); 13.57 (br, 1H)		3340; 3243 (NH_2, NH); 2216 (CN); 1599 (C = N)
24b	2.49 (s, 3H); 7.19–8.11 (m, 5H); 8.51 (br, 2H); 13.86 (br, 1H)		3330; 3240 (NH_2, NH); 2215 (CN); 1605 (C = N)
25	2.54 (s, 3H); 6.98–8.11 (m, 10H); 8.68 (br, 2H); 12.9 (br, 1H)		3410; 3235 (NH_2, NH); 2198 (CN); 1610 (C = N)

tion mixture was stirred further for 1 hour at 0–5°C and left to stand in an ice box for 24 hours, then diluted with water. The formed precipitate was collected by filtration, washed, dried, and finally recrystallized from DMF to afford the corresponding arylhydrazones **24a,b.**

Method B. A mixture of **16** (0.46 g, 2 mmol) and 2-phenylhydrazono-2-cyanoethane-thioamide **26** (0.47 g, 2 mmol) in ethanol (30 mL) was refluxed for 1 hour and then allowed to cool. The precipitated product was collected by filtration, washed with water, and dried. Recrystallization from DMF afforded a product identical in all respects (m.p., mixed m.p., and spectra) with compound **24a,b.**

[(4-(2-Amino-4-methylthiazol-5-yl)-5-phenylazothiazol-2-yl](phenylhydrazono) acetonitrile **25**

Method A. To a cold solution of **23a** (1.7 g, 5 mmol) in pyridine dimethylsulfoxide (1:2, 30 mL) was added benzendiazonium chloride (5 mmol) [prepared by diazotization of aniline (0.5 g) in concentrated HCl (5 mL) with sodium nitrite (0.35 g) at 0–5°C] portionwise over 30 minutes with constant stirring. After complete addition, the reaction mixture was stirred for a further 3 h at 0–5°C. The solid product was filtered off, washed with water, dried, and finally recrystallized from DMF to afford compound (**25**).

Method B. The same product was obtained by coupling of **24a** (0.34 g, 1 mmol) with benzenediazonium chloride (1 mmol) as described in method A.

Method C. A mixture of **20a** (0.34 g, 1 mmol) and **26** (0.2 g, 1 mmol) in ethanol (25 mL) was refluxed for 1 hour and then cooled. The solid so formed was filtered off, washed with water and dried. Recrystallization from DMF afforded a product identical in all respects (m.p., mixed m.p., and spectra) with compound **25** obtained by method A.

REFERENCES

[1] Mizzoni, R. M.; Eisman, P. C. J Am Chem Soc 1958, 80, 3471.
[2] Wieniowski, W. Roczniki Chem 1958, 32, 545; Chem Abstr 1959, 53, 1461.
[3] Brown, F. C.; Bradsher, C. K. Nature, 1951, 168, 171.
[4] Froelich, F. J Am Chem Soc 1954, 76, 3099.
[5] Metzgr, J. V. In Comprehensive Heterocyclic Chemistry; ed. Katritzky, A., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; pp. 6, 328.
[6] Anderson, G. The Chemistry of Carbon Compounds; Elsevier Publishing Co.; Amsterdam, 1958; Volume IV, p. 1053.
[7] Brooker, L. G. S. The Theory of Photographic Process; Macmillan: New York, 1954; p. 371.
[8] Sawedy, G. W. U.S. Patent 2,808,330, 1958; Chem Abstr 1958, 52, 2624.
[9] Mostafa, A.; Asker, W.; Khottab, S.; Abou Elazaym, K. J Am Chem Soc 1960, 82, 2029.
[10] Metzger, J. V., Ed. Thiazole and Its Derivatives; John Wiley: New York, 1979; 39.
[11] Shadha, V. K.; Chaudharv, H. S.; Piyari, H. K. Indian J Chem 1969, 7, 769.
[12] Kuhia, D. E. U.S. Patent 3,860,718, 1975; Chem Abstr 1975, 82, 140133.
[13] D'Amico, J. J. U.S. Patent 3,225,059, 1966; Chem Abstr 1966, 64, 8193.
[14] School, H. J.; Klaule, E.; Grewe, F.; Hammann, I.; Ger Offen 348,2062, 1972; Chem Abstr 1977, 77, 114391.
[15] Hasegawa, G. Kotani, A. Jap Patent 7,495,997, 1975; Chem Abstr 1975, 82, 156299.
[16] Chabrier, P.; Pullu, L. Comp Rend 1945, 220, 363.
[17] Cingolani, G. M.; Gualtieri, F.; Pigini, M. J. Med Chem 1969, 12, 531.
[18] Elnagdi, M. H.; Selim, M. A.; Abd El-latif, F. M.; Sayed, S. M. Asw Sci Tech Bull 1998, 19, 1.
[19] Sayed, S. M.; Raslan, M. A.; Khalil, M. A.; Dawood, K. M. Heteroat Chem 1999, 10, 5.
[20] Elnagdi, M. H.; Sherif, S. M.; Mohareb, R. M. Heterocycles 1987, 26, 497, and references cited therein.
[21] Hafez, E. A.; Abdel-Galil, F. M.; Sherif, S. M.; Elnagdi, M. H. J Heterocycl Chem 1986, 23, 1375.
[22] Higashiyama, K.; Otomasu, H. Chem Pharm Bull 1980, 28, 648.
[23] Elgemie, G. E. H.; Sallam, M. M. M.; Sherief, S. M.; Elnagdi, M. H. Heterocycles 1985, 23, 3107.
[24] Sawhney, H. S.; Singh, J. Indian J Chem 1970, 8, 882.
[25] Mansour, S. A.; Eldeib, W. M.; Abdou, S. E.; Daboun, H. A. Sulfur Lett 1987, 6, 181.
[26] Brumskill, J. S. A.; Deand, A.; Ewing, D. F. J Chem Soc Perkin Trans 1 1978, 629.
[27] Freeman, F.; Chem Rev 1980, 80, 329.