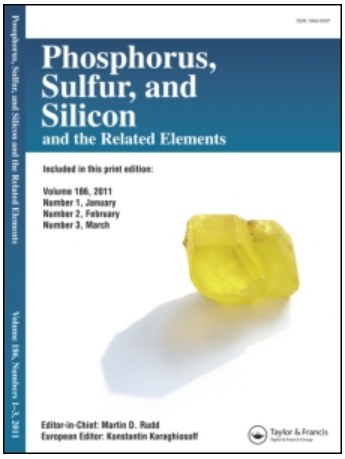


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Novel Synthesis of Thieno[2,3-c]Pyridazine and Pyrimido[4',5':4,5]thieno[2,3-c]pyridazine Derivatives

A. M. Kamal El-Dean[a]; M. S. A. El-Gaby[b]; A. M. Gaber[a]; H. A. Eyada[c]; A. S. N. Al-Kamali
[a] Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt [b] Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut, Egypt [c] Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt

Online publication date: 21 December 2010

To cite this Article El-Dean, A. M. Kamal , El-Gaby, M. S. A. , Gaber, A. M. , Eyada, H. A. and Al-Kamali, A. S. N.(2005) 'Novel Synthesis of Thieno[2,3-c]Pyridazine and Pyrimido[4',5':4,5]thieno[2,3-c]pyridazine Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 2, 413 — 424
To link to this Article: DOI: 10.1080/104265090509216
URL: http://dx.doi.org/10.1080/104265090509216

Phosphorus, Sulfur, and Silicon, 180:413–424, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090509216

Taylor & Francis
Taylor & Francis Group

Novel Synthesis of Thieno[2,3-c]Pyridazine and Pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine Derivatives

A. M. Kamal El-Dean
Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt

M. S. A. El-Gaby
Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut, Egypt

A. M. Gaber
Department of Chemistry, Faculty of Science, Assiut University, Assiut, Egypt

H. A. Eyada
Department of Chemistry, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt

A. S. N. Al-Kamali

Novel series of thieno[2,3-c]pyridazines and pyrimido[4′,5′:4,5] thieno-[2,3-c]pyridazines have been synthesized from the readily accessible 4-cyano-5,6-dimethylpyridazin-3(2H)-thione **3b**.

Keywords Pyridazine; pyrimidine; thieno[2,3-c]pyridazine

INTRODUCTION

The pyridazine ring is found in many pharmaceuticals, herbicides, insecticides and fungicides.[1,2] Also, thienopyridazine derivatives are important compounds due to their broad range of biological and pharmacological effects.[3–5] In addition, fused pyrimidines are found in a broad variety of pharmaceuticals, agrochemicals, and veterinary products.[6] In continuation of our work on pyridazine chemistry[7–9], we reported the synthesis of some novel pyridazine, thieno[2,3-c]pyridazine and

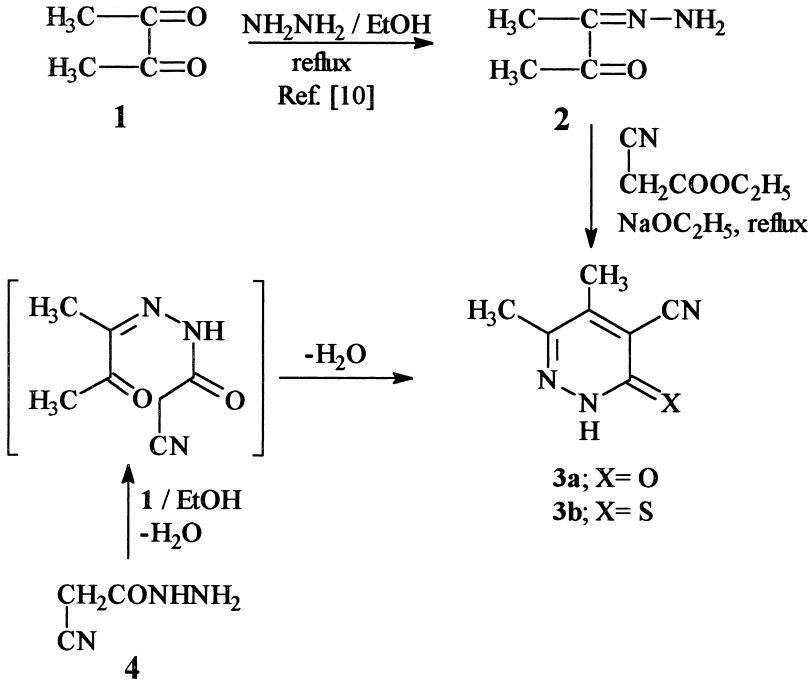
Address correspondence to Mohamed S. A. El-Gaby, Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut 71524, Egypt. E-mail: m_elgaby@hotmail.com

pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine derivatives starting from the readily accessible 4-cyano-5,6-dimethylpyridazin-3(2*H*)-thione **3b**.

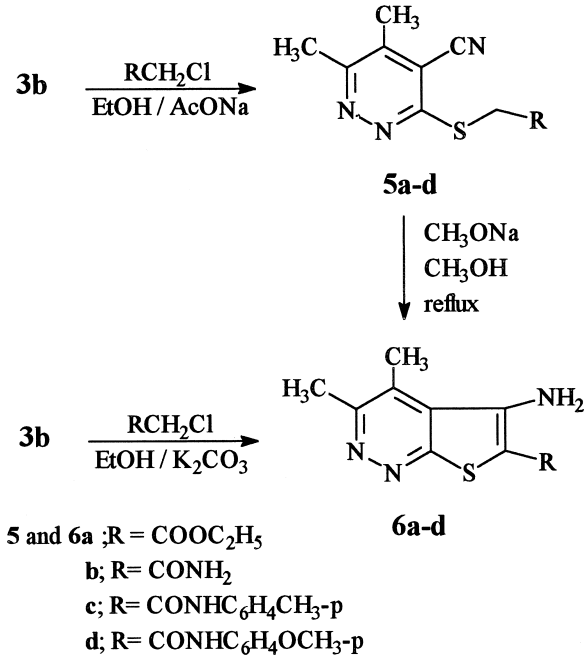
RESULTS AND DISCUSSION

Druey and Schmidt[10] reported the synthesis of 4-cyano-5,6-dimethylpyridazin-3(2*H*)-one **3a** by treatment of diacetyl **1** with hydrazine hydrate in refluxing ethanol to yield monohydrazone **2** followed by cyclocondensation with ethyl cyanoacetate in the presence of sodium ethoxide, Scheme 1. Our investigation describes the synthesis of pyridazinone **3a** via a one-pot reaction of diacetyl **1** and cyanoacetic acid hydrazide **4** in ethanol at room temperature in quantitative yield (94%). Thiation of compound **3a** with phosphorus pentasulfide under reflux in pyridine afforded the pyridazinethione **3b**. The latter compound was used as a key intermediate for the synthesis of thieno[2,3-c]pyridazine and pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine derivatives.

The cyclocondensation of compound **3b** with ethyl chloroacetate was performed in ethanol in the presence of catalytic amount of potassium



SCHEME 1



SCHEME 2

carbonate and yielded the novel thieno[2,3-c]pyridazine derivative **6a** in good yield (87%), Scheme 2. The structure of compound **6a** was supported by its analytical and spectral data. The infrared spectrum of compound **6a** displayed absorption at 3440, 3330 cm^{-1} for NH_2 stretching, at 1665 cm^{-1} for C=O stretching with lack of the characteristic absorption due to the C≡N stretching. In the ^{1}H-NMR spectrum ($CDCl_3$) of compound **6a** triplet at $\delta = 1.4$ ppm, quartet at $\delta = 4.4$ ppm assigned for ethoxycarbonyl moiety in addition to amino and $2CH_3$ protons. In a similar manner, compound **3b** was cyclized with chloroacetamide and *N*-substituted chloroacetamide and furnished the corresponding thienopyridazines **6b** and **6c**,**d**, respectively. The mass spectrum of compound **6c** revealed a molecular ion peak at m/z = 312 (8.12%) with base peak at m/z = 106.8. The formation of thienopyridazine **6** is assumed to proceed through initial alkylation of compound **3b** to form the intermediate **5** which readily undergo intramolecular cyclization under the reaction condition to yield **6**, Scheme 2. The intermediate compounds **5a–d** were isolated by refluxing of compound **3b** with α-halocarbonyl compounds in ethanol in the presence of fused sodium acetate. Compounds **6a–d** were

also independently synthesized via another pathway by cyclization of compound **5** with sodium methoxide in methanol under reflux.

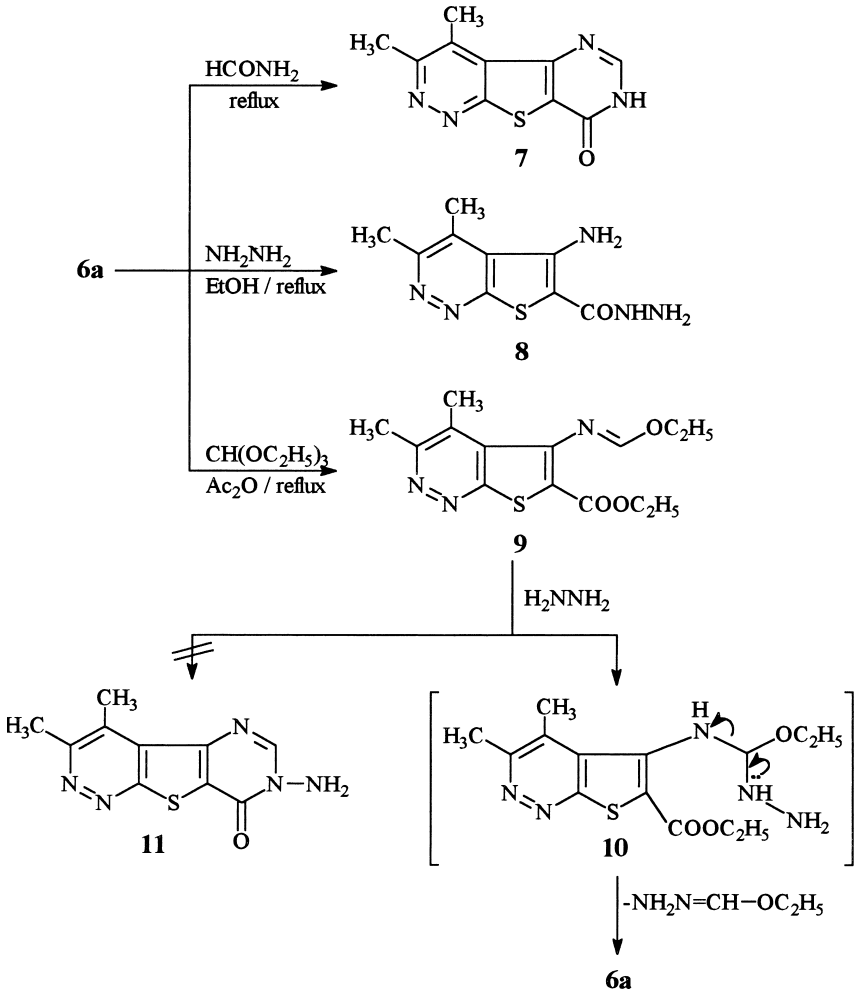
Cyclization of compound **6a** with formamide under reflux afforded pyrimido[4′,5′:4,5]thieno[2,3-c]pyridazine derivative **7**. The carbohydrazide derivative **8** was obtained by refluxing of compound **6a** with hydrazine hydrate under reflux in ethanol. The reaction of compound **6a** with triethyl orthoformate in the presence of acetic anhydride provided the ethoxymethyleneamino derivative **9**. Treatment of compound **9** with hydrazine hydrate in benzene at room temperature led to the formation of amino derivative **6a** and the cyclized product **11** was not formed (mp, mmp, and TLC). The formation of compound **6a** from **9** was assumed to proceed via the addition of hydrazine at the imino function group to form intermediate **10** followed by elimination of ethyl formate hydrazone,[11] (Scheme 3).

The carbonylazide **12** was formed by treatment of carbohydrazide **8** with sodium nitrite in glacial acetic acid at room temperature. The infrared spectrum of compound **12** revealed the presence of absorption band characteristic for azide group at 2130 cm^{-1}. Compound **12** underwent intramolecular cyclization in refluxing *m*-xylene into imidazo[4′,5′:4,5]-thieno[2,3-c]pyridazine derivative **14**. The formation of compound **14** is assumed to proceed via Curtius rearrangement[12] of compound **12** into isocyanate **13** followed by nucleophilic addition of the NH_2 function of **13** to the N=C=O to yield the novel condensed imidazole **14** (Scheme 4).

Cyclocondensation of compound **8** with excess triethyl orthoformate produced the ethoxymethylene derivative **15** (Scheme 5). In a similar manner, compound **8** was cyclized with acetic anhydride under reflux and furnished the diacetylamino derivative **16**. Formylamino derivative **17** was achieved by refluxing of compound **8** in formic acid. Condensation of compound **8** with aromatic aldehydes in refluxing ethanol yielded the corresponding azomethines **18a**,**b** which on refluxing with triethyl orthoformate gave the pyrimidothienopyridazines **19a**,**b**. Cyclocondensation of carbohydrazide group in compound **8** with acetylacetone in ethanol under reflux gave the novel pyrazole derivative **20** (Scheme 5).

EXPERIMENTAL

Melting points are determined on a Fisher-John melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer using KBr pellets. ^{1}H-NMR spectra were measured on a Varian 390-90 MHz NMR spectrometer using TMS as internal standard and mass spectra on a Jeol-JMS-600 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 C

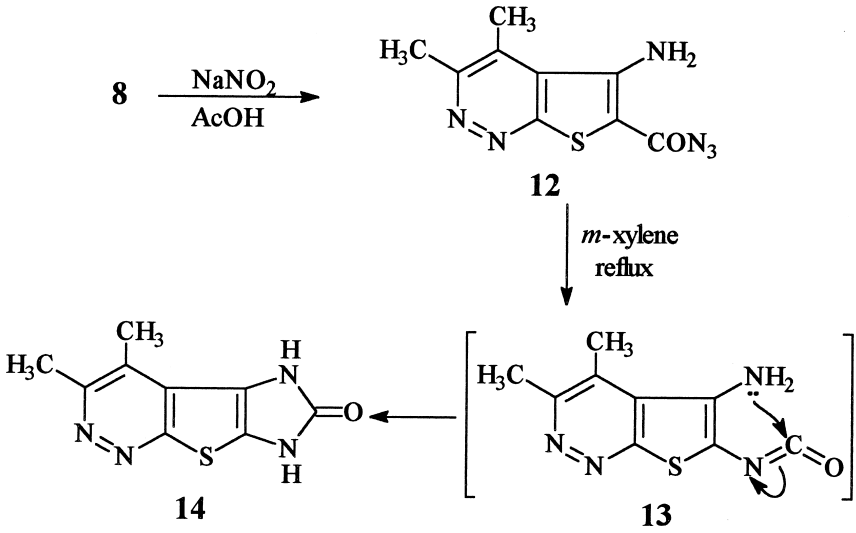


SCHEME 3

microanalyzer. The physical and spectral data are shown in Tables I and II, respectively.

4-Cyano-5,6-dimethylpyridazin-3(2H)-one (3a)

A mixture of diacetyl **1** (0.01 mole) and cyanoacetic acid hydrazide **4** (0.01 mole) in ethanol (30 mL) was stirred at room temperature for 3 h. The solid product was collected by filtration and recrystallized to give **3a**.



SCHEME 4

4-Cyano-5,6-dimethylpyridazin-3(2H)-thione (3b)

A mixture of compound **3a** (0.01 mole) and phosphorus pentasulfide (0.012 mole) in pyridine (15 mL) was refluxed for 2 h, then allowed to cool and poured into cold water (100 mL). The solid product was collected by filtration and recrystallized to give **3b**.

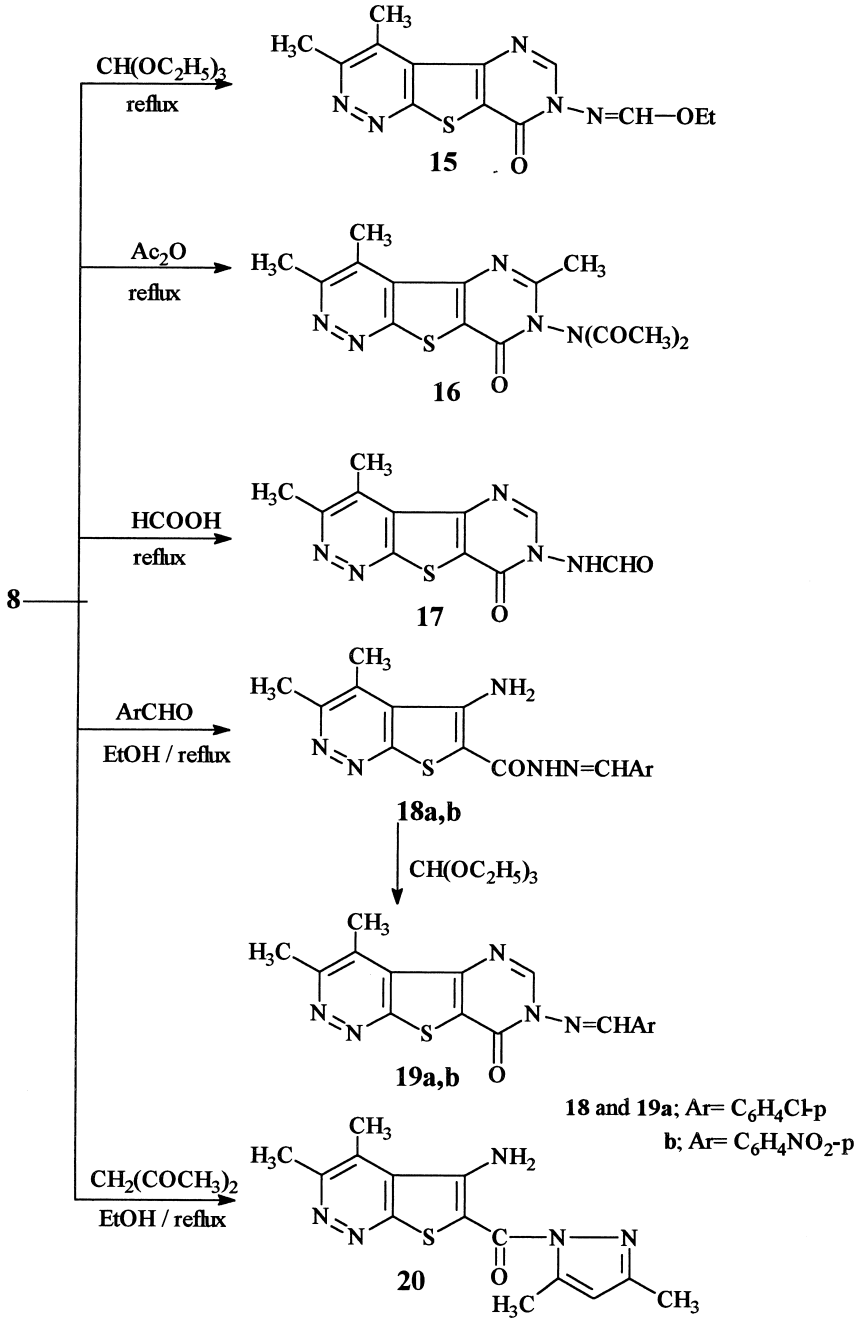
4-Cyano-5,6-dimethyl-3-substituted Mercapto-pyridazines (5a–d): General Procedure

A mixture of compound **3b** (0.01 mole), fused sodium acetate (0.012 mole), and α-halocarbonyl compound (0.01 mole) in ethanol (30 mL) was heated under reflux for 2 h, allowed to cool, and poured into water (100 mL). The solid product was collected by filtration and recrystallized to give **5**.

5-Amino-3,4-dimethyl-6-R-thieno[2,3-c]pyridazines (6a–d): General Procedure

Method A

A mixture of compound **3b** (0.01 mole), α-halocarbonyl compound (0.01 mole) and potassium carbonate (0.012 mole) in ethanol (30 mL)



SCHEME 5

TABLE I Physical Data of the Synthesized Compounds

Compd. no.	M.P. (°C)	Yield (%) (color)	Solvent cryst.	Molecular formula (mol. wt.)	Elemental analyses [calcd./found]			
					C%	H%	N%	S%
3a	210	94 (White)	Ethanol	$C_7H_7N_3O$ (149.15)	56.37 56.20	4.73 4.80	28.17 28.20	
3b	213	90 (Yellow)	Ethanol	$C_7H_7N_3S$ (165.21)	50.89 50.80	4.27 4.10	25.44 25.50	19.41 19.30
5a	120	66 (Brown)	Ethanol	$C_{11}H_{13}N_3O_2S$ (251.31)	52.57 52.37	5.21 5.25	16.72 16.60	12.76 12.80
5b	218	66 (White)	Ethanol	$C_9H_{10}N_4OS$ (222.27)	48.63 48.50	4.53 4.60	25.21 25.30	14.43 14.20
5c	120	52 (White)	Ethanol	$C_{16}H_{16}N_4OS$ (312.40)	61.52 61.61	5.16 5.20	17.93 18.00	10.26 10.29
5d	174	64 (White)	Ethanol	$C_{16}H_{16}N_4O_2S$ (328.40)	58.52 58.33	4.91 4.90	17.06 17.20	9.76 9.80
6a	240	87 (Brown)	Ethanol	$C_{11}H_{13}N_3O_2S$ (251.31)	52.57 52.60	5.21 5.01	16.72 16.80	12.76 12.80
6b	250	93 (Yellow)	Ethanol	$C_9H_{10}N_4OS$ (222.27)	48.58 48.60	4.49 4.49	25.19 25.30	14.43 14.51
6c	330	86 (Yellow)	Ethanol	$C_{16}H_{16}N_4OS$ (312.40)	61.45 61.32	5.12 5.10	17.93 18.18	10.24 10.52
6d	318	89 (Yellow)	Ethanol	$C_{16}H_{16}N_4O_2S$ (328.40)	58.46 58.72	4.87 4.80	17.06 16.88	9.76 10.00
7	>360	66 (White)	Acetic acid	$C_{10}H_8N_4OS$ (232.26)	51.66 51.66	3.44 3.52	24.12 24.00	13.80 14.00
8	>300	75 (Yellow)	Ethanol	$C_9H_{11}N_5OS$ (237.28)	45.52 45.61	4.63 4.68	29.51 29.33	13.48 13.62
9	140	83 (White)	Ethanol	$C_{14}H_{17}N_3O_3S$ (307.36)	54.66 54.90	5.53 5.50	13.67 13.72	10.43 10.51
12	190	71 (Yellow)	Chloro-form	$C_9H_8N_6OS$ (248.27)	43.50 43.60	3.25 3.33	33.85 34.00	12.88 12.85
14	>300	90 (Yellow)	Ethanol	$C_9H_8N_4OS$ (220.25)	49.03 49.12	3.63 3.52	25.42 25.60	14.52 14.71
15	228	76 (White)	Ethanol	$C_{13}H_{13}N_5O_2S$ (303.34)	51.42 51.23	4.28 4.30	23.09 23.20	10.54 10.62
16	276	75 (Red)	Ethanol	$C_{15}H_{15}N_5O_3S$ (345.38)	52.16 52.31	4.34 4.40	20.28 20.33	9.28 9.15
17	268	66 (White)	Ethanol	$C_{11}H_9N_5O_2S$ (275.29)	47.95 48.21	3.26 3.25	25.44 25.66	11.62 11.72
18a	>330	80 (Yellow)	Acetic acid	$C_{16}H_{14}ClN_5OS$ (359.84)	53.35 53.33	3.89 3.80	19.46 19.52	8.89 8.70
18b	>340	88 (Orange)	Acetic acid	$C_{16}H_{14}N_6O_3S$ (370.39)	51.83 51.77	3.78 3.90	22.69 22.62	8.64 8.52
19a	278	83 (Yellow)	Acetic acid	$C_{17}H_{12}ClN_5OS$ (369.83)	55.16 55.15	3.24 3.31	18.94 19.02	8.65 8.81
19b	300	90 (Brown)	Acetic acid	$C_{17}H_{12}N_6O_3S$ (380.38)	53.61 53.82	3.16 3.22	22.09 21.88	8.41 8.40
20	220	65 (Yellow)	Ethanol	$C_{14}H_{15}N_5OS$ (301.37)	55.74 56.01	4.97 4.80	23.27 23.31	10.62 10.71

TABLE II Spectral Data of the Synthesized Compounds

Compd no.	IR/ν_{max} (cm^{-1})	^{1}HNMR (δ/ppm)
3a	3400 (NH), 2200 (C≡N), 1660 (C=O).	DMSO-d_6; 2.3, 2.4 (2s, 6H, $2CH_3$), 10.8 (hump, 1H, NH).
3b	3300 (NH), 2200 (C≡N).	
5a	2220 (C≡N), 1730 (C=O).	$CDCl_3$; 1.35 (t, 3H, CH_3), 2.55, 2.77 (2s, 6H, $2CH_3$), 4.1–4.4 (m, 4H, $2CH_2$).
5b	3380, 3280 (NH_2), 2220 (C≡N), 1650 (C=O).	
5c	3250 (NH), 2220 (C≡N), 1670 (C=O).	DMSO-d_6; 2.3, 2.5, 2.65 (3s, 9H, $3CH_3$), 4.38 (s, 2H, CH_2), 7.2, 7.5 (2d, 4H, Ar-H), 10.7 (s, 1H, NH).
5d	3290 (NH), 2220 (C≡N), 1670 (C=O).	$CDCl_3$; 2.34, 2.6 (2s, 6H, $2CH_3$), 3.62 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 6.6, 7.3 (2d, 4H, Ar-H), 9.2 (s, 1H, NH).
6a	3440, 3330 (NH_2), 1665 (C=O).	$CDCl_3$; 1.4 (t, 3H, CH_3), 2.7, 3.3 (2s, 6H, $2CH_3$), 4.4 (q, 2H, CH_2), 6.8 (s, 2H, NH_2).
6b	3410, 3340, 3180 (NH_2, NH), 1650 (C=O).	DMSO-d_6; 2.78, 3.4 (2s, 6H, $2CH_3$), 6.45 (s, 2H, NH_2), 7.5 (s, 2H, NH_2).
6c	3400, 3300, 3120 (NH_2, NH), 1620 (C=O).	
6d	3390, 3280, 3100 (NH_2, NH), 1600 (C=O).	
7	3420 (NH), 1665 (C=O).	
8	3420, 3300, 3200 (NH_2, NH), 1670 (C=O).	
9	1680 (C=O).	CF_3COOD; 1.2–1.6 (m, 6H, $2CH_3$), 3.05, 3.1 (2s, 6H, $2CH_3$), 4.3–4.6 (m, 4H, $2CH_2$).
12	3420, 3320 (NH_2), 2130 (N_3).	DMSO-d_6; 2.8, 3.4 (2s, 6H, $2CH_3$), 5.2 (s, 2H, NH_2).
14	3240, 3200 (NH), 1700 (C=O).	
15	1670 (C=O), 1580 (C=N).	CF_3COOD; 1.4 (t, 3H, CH_3), 3.2, 3.45 (2s, 6H, $2CH_3$), 4.2 (q, 2H, CH_2), 8.3 (s, 1H, CH-pyrimidine).
16	1760 (2C=O), 1680 (C=O).	CF_3COOD; 2.35, 2.8, 2.9, 3.2, 3.5 (5s, 15H, $5CH_3$).
17	3280 (NH), 1690, 1670 (2C=O).	CF_3COOD; 3.2, 3.45 (2s, 6H, $2CH_3$), 8.68 (s, 1H, CH-pyrimidine), 8.9 (s, 1H, CHO).
18a	3470, 3300, 3190 (NH_2, NH), 1620 (C=O).	
18b	3480, 3290, 3185 (NH_2, NH), 1670 (C=O).	DMSO-d_6; 2.78, 3.4 (2s, 6H, $2CH_3$), 6.45 (s, 2H, NH_2), 7.2, 8.1 (2d, 4H, Ar-H), 8.4 (s, 1H, CH=N), 11.3 (s, 1H, NH).
19a	1670 (C=O).	CF_3COOD; 3.2, 3.5 (2s, 6H, $2CH_3$), 7.7, 8.1 (2d, 4H, Ar-H), 8.1 (s, 1H, CH=N), 9.2 (s, 1H, CH-pyrimidine).
19b	1672 (C=O).	CF_3COOD; 3.4, 3.65 (2s, 6H, $2CH_3$), 8.1, 8.7 (2d, 4H, Ar-H), 9.1 (s, 1H, CH=N), 9.7 (s, 1H, CH-pyrimidine).
20	3380, 3280 (NH_2), 1660 (C=O).	2.7, 3.0, 3.1, 3.4 (4s, 12H, $4CH_3$), 5.9 (s, 2H, NH_2), 6.2 (s, 1H, CH-pyrazole).

was heated under reflux for 3 h, then allowed to cool. The solid product was collected by filtration and recrystallized to give **3**.

Method B

A sample of compound **5** (0.01 mole) in sodium methoxide (0.23 Na/30 mL methanol) was heated under reflux for 2 h, then allowed to cool. The solid product was collected by filtration, washed with water, and recrystallized to give **6**.

MS (**6b**): 222 (M^+; 13%), 221 (M − 1; 79%), 223 (M + 1; 4.8%), 205 (15%), 204 (base peak; 100%), 148 (42%), 149 (8.2%), 135 (12%), 108 (14%), 94 (4.6%), 65 (8.0%) and 43 (4%).

MS (**6c**): 312 (M^+; 8.2%), 313 (M + 1; 2.7%), 314 (M + 2; 0.6%), 231 (0.5%), 205 (20%), 179 (0.2%), 149 (2.6%), 106 (base peak; 100%), 93 (2.4%) and 76 (0.4%).

3,4-Dimethylpyrimido[4′,5′:4,5]thieno[2,3-c]pyridazin-8(7H)-one (7)

A sample of compound **6a** (0.01 mole) in formamide (10 mL) was heated under reflux for 2 h. The solid product which produced on heating was collected and recrystallized to give **7**.

MS (**7**): 232 (M^+; 16%), 231 (M − 1; base peak), 204 (4.8%), 202 (74%), 174 (17%), 135 (5%), 107 (6%), 78 (0.3%) and 42 (5.3%).

5-Amino-3,4-dimethylthieno[2,3-c]pyridazine-6-carbohydrazide (8)

A mixture of compound **6a** (0.01 mole) and hydrazine hydrate (99%; 0.01 mole) in ethanol (30 mL) was heated under reflux for 5 h, then allowed to cool. The solid product was collected by filtration and recrystallized to give **8**.

MS (**8**): 237 (M^+; 13.4%), 206 (17%), 79 (base peak; 100%), 52 (72%), 50 (67%) and 40 (18%).

5-Ethoxymethyleneamino-3,4-dimethyl-thieno[2,3-c]pyridazine-6-ethoxycarbonyl (9)

A mixture of compound **6a** (0.01 mole), triethyl orthoformate (2 mL) and acetic acid (10 mL) was heated under reflux for 4 h, then allowed to cool. The product was collected by filtration and recrsytallized to give **9**.

5-Amino-3,4-dimethyl-thieno[2,3-c]pyridazine-6-carboazide (12)

To an ice-cooled solution of compound **8** (0.01 mole) in acetic acid (10 mL), sodium ntirite solution (0.01 mole in 3 mL H_2O) was added dropwise for ten min. The stirring was continued for additional 1 h, then allowed to stand for 2 h. The solid product was collected to give **12**.

3,4-Dimethyl-5,7-dihydroimidazo[4′,5′:4,5]thieno[2,3-c]-pyridazin-6-one (14)

A sample of carboazide derivative **12** (1 g) in dry *m*-xylene (20 mL) was heated under reflux until the nitrogen gas was ceased and then allowed to cool. The solid product was collected by filtration and recrystallized to give **14**.

7-Ethoxymethyleneamino-3,4-dimethylpyrimido[4′,5′:4,5]-thieno-[2,3-c]pyridazin-8-one (15)

A sample of compound **8** (0.01 mole) in triethyl orthoformate (5 mL) was heated under reflux for 5 h, then allowed to cool and poured into cold water (100 mL). The solid product was collected by filtration and recrystallized to give **15**.

7-Diacetylamino-3,4,6-trimethylpyrimido[4′,5′:4,5]thieno-[2,3-c]-pyridazin-8-one (16)

A sample of compound **8** (0.01 mole) in acetic anhydride (10 mL) was heated under reflux for 3 h, then allowed to cool and poured into cold water (100 mL). The solid product was collected by filtration and recrystallized to give **16**.

7-Formylamino-3,4-dimethylpyrimido[4′,5′:4,5]thieno[2,3-c]-pyridazin-8-one (17)

A sample of compound **8** (0.01 mole) in formic acid (10 mL) was heated under reflux for 5 h, then allowed to cool and poured into cold water (100 mL). The solid product was collected by filtration and recrystallized to give **17**.

5-Amino-6-arylidenecarbohydrazone-3,4-dimethyl-thieno-[2,3-c]-pyridazines (18a,b): General Procedure

A mixture of compound **8** (0.01 mole) and appropriate aldehyde (0.01 mole) in ethanol (30 mL) was heated under reflux for 4 h, then allowed to cool. The solid product was collected by filtration and recrystallized to give **18**.

7-Arylideneamino-3,4-dimethylpyrimido[4′,5′:4,5]thieno-[2,3-c]-pyridazin-8-one (19a,b): General Procedure

Few drops of acetic acid was added to a refluxed mixture of compound **18** (0.01 mole) and triethyl orthoformate (4 mL). The reaction mixture was heated under reflux for 2 h, then allowed to cool. The solid product was collected by filtration and recrystallized to give **19**.

(5-Amino-3,4-dimethyl-thieno[2,3-c]pyridazin-6-yl)-(3,5-dimethyl-pyrazol-1-yl)-ketone (20)

A mixture of carbohydrazide **8** (0.01 mole) and acetylacetone (0.01 mole) in ethanol (30 mL) was heated under reflux for 6 h, then allowed to cool. The solid product was collected by filtration and recrystallized to give **20**.

REFERENCES

[1] G. Heinisch and H. Kopelent-Frank, in *Progress in Medicinal Chemistry*, *Vol. 27*, G. P. Ellis and G. B. West, eds. (Elsevier Science Publishers, 1990) pp. 1–49.
[2] G. Heinisch and H. Kopelent-Frank, in *Progress in Medicinal Chemistry*, *Vol. 27,* G. P. Ellis and G. B. West, eds. (Elsevier Science Publishers, 1990) pp. 141–183.
[3] M. S. Abbady and Sh. M. Radwan, *Phosphorus, Sulfur, and Silicon*, **86,** 203 (1994).
[4] V. Dal Piaz, M. P. Giovannoni, and C. Castellana, *J. Med. Chem.*, **40,** 1417 (1997).
[5] R. S. Vartanyan, Zh.V. Kazaryan, M. A. Sheiranyan, A. S. Agaronyan, and N. O. Stepanyan, *Khim-Farm. Zh.*, **30,** 29 (1996).
[6] D. J. Brown, Fused Pyrimidines, Part III. Pteridines. In the *Chemistry of Heterocyclic Compounds*, E. C. Taylor, eds. (Wiley-Interscience, New York, 1988).
[7] A. M. Kamal El-Dean and Sh. M. Radwan, *Pharmazie*, **53,** 839 (1998).
[8] A. M. Kamal El-Dean, Sh. M. Radwan, and M. I. Abdel-Moneam, *Afinidad*, **466,** 387 (1996).
[9] M. S. A. El-Gaby, A. M. Kamal El-Dean, A. M. Gaber, H. A. Eyada, and A. S. N. Al-Kamali, *Bull. Korean Chem. Soc.*, **24,** 1181 (2003).
[10] J. Druey and P. Schmidt, *Swiss*, **320,** 131 (1957).
[11] S. M. Hassan, H. A. Emam, and M. M. Abdellah, *J. Chem. Research (S)*, 554 (2000); *J. Chem. Research (M)*, 1301 (2000).
[12] I. M. A. Awad, A. E. Abdel-Rahman, and E. A. Bakhit, *Collect. Czech. Chem. Commun.*, **56,** 1749 (1991).